COMPREHENSIVE MEDICAL REFERENCE & REVIEW FOR MCCQE AND USMLE II

Editors-in-Chief: Tina Binesh Marvasti & Sydney McQueen
Production Managers: Ilya Mukovozov & Kirill Zaslavsky
Thirty-fourth Edition

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FEEDBACK AND ERRATA
We are constantly trying to improve the Toronto Notes and welcome your feedback. If you have found an error in this edition please do not hesitate to contact us. As well, we look forward to receiving any comments regarding any component of the Toronto Notes package and website.

Please send your feedback to: torontonotes.production@gmail.com

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Dedicated to all
past and present contributors
and
supporters of Toronto Notes
who have made the production of the 2018 edition possible!

The Toronto Notes for Medical Students is dedicated to helping fund many charitable endeavours and medical student initiatives at the University of Toronto’s Faculty of Medicine and beyond. Programs that have received Toronto Notes for Medical Students funding include:

**Community Affairs Projects**
- Saturday Program for Inner City High School and Grade 8 students
- St. Felix Mentorship Program for Inner City children
- Parkdale Mentorship Program for Grade 10-12 students
- WoodGreen Community Centre
  - Let's Talk Science
  - Growing Up Healthy

**Annual Faculty Showcase Events**
- Daffodil, in support of the Canadian Cancer Society
- Earhtones Benefit Concert
- Convocation and Ceremonies

**Scholarships and Bursaries**
- Nishant Fozdar Memorial Award
- Graduating Medical Class Scholarships and Bursaries

**Medical School Clubs**
- Books with Wings
- Women in Medicine
- University of Toronto International Health Program
- Complementary and Alternative Medicine
- Peer Support for Students
- History of Medicine Society
- Faculty of Medicine Yearbook

**Other Events**
- Save a Child's Heart
- Australian Medical School Association Conference
- Medical Student Research Day
- Ontario Medical Students Weekend (OMSW)
- OMSA's Medical Student Education Research Grant (MSERG)

**Note:**
Many of you have wondered about the Toronto Notes logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius’ healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

Thomas O’Brien, MD
Class of 2009, M.D. Program, University of Toronto
Dear Readers,

As the Editors-in-Chief of Toronto Notes 2018, we are proud to present the 34th Edition!

Toronto Notes began humbly in 1985 from a set of student notes circulated among medical students at the University of Toronto. Over time, Toronto Notes has grown into one of the premier study resources for generations of medical trainees in Canada and abroad. This rich history solidified our commitment to publish a comprehensive study resource for medical students engaged in clinical rotations and studying for both the Canadian MCCQE Part 1 and USMLE Step 2.

For the past 33 years we have remained committed to our original vision. The 2018 edition of Toronto Notes contains significant improvements and new editions including:

1. A brand new Medical Genetics chapter with evidence based medicine highlights.
2. Updated versions of the Clinical Handbook and STAT Notes that are more concise, with new figures and additions.
3. An updated website featuring a colour atlas, ECG and heart sound tutorials, essentials of medical imaging, and over 50 OSCE practice questions and scenarios.
4. A significantly improved interactive eBook with many new high-quality colour images.
5. An updated Toronto Notes Quiz App, which is available for free on iTunes and Google Play. This app contains hundreds of questions allowing users to test themselves on the content contained within Toronto Notes.

Toronto Notes 2018 is produced by Toronto Notes for Medical Students Inc., which is a non-for-profit organization supporting various charity organizations and medical student initiatives in the city of Toronto and across the globe. This year, sponsored organizations included Community Affairs, the Ontario Medical Student Weekend (OMSW), the University of Toronto Class Councils, Save A Child's Heart, Earth Tones, Medical Student Research Day (MRSD) The Medical Student Education Research Grant (MSERG), Daffydid, the Conference of the Australian Medical School Association, among others. We would like to thank you for supporting these initiatives through your purchase of Toronto Notes 2018.

We would like to highlight the exceptional work of our team, composed of over 150 medical students, medical illustrators, and faculty members at the University of Toronto Faculty of Medicine. Without the tireless effort expended by these individuals, the production of Toronto Notes 2018 would not have been possible. In particular, we would like to highlight the work of the executive team, all of whom made personal sacrifices in balancing their clinical and academic duties with the responsibilities asked of them: our production managers, Ilya Mukovozov and Kirill Zaslavsky, our associate editors, Graham Mazereeuw, Samik Doshi, Mark Shafarenko, Sangwoo Leem, Tara Tofighi, Sheliza Halani, and our EBM editors, Alexander Sapa, Keeth Krishnan, Shubham Shan, Jin Kyu Kim, Sukhmani Sodhi, Arnav Agarwal. We also want to highlight the work of Rajkumari Chatterjee from University of Toronto Bookstore, who has contributed to the production of Toronto Notes for the past ten years, and has been instrumental in the annual launch of the Toronto Notes Ebook. Lastly, we would like to thank our partners at Type & Graphics Inc., particularly Enrica Aguilera, for their assistance during the production of Toronto Notes 2018.

We would like to continue to encourage feedback – this year's edition saw many improvements thanks to suggestions from our readers. We hope that Toronto Notes 2018 enhances your medical knowledge and allows you to perform better on both your clinical rotations and licensing exams. On behalf of the Toronto Notes 2018 team, we wish you success in your studies and academic endeavours.

Sincerely,

Tina Binesh Marvasti, MSc, MD/PhD Candidate and Sydney McQueen, MSc, MD/PhD Candidate
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We would like to acknowledge the exceptional work of all previous Toronto Notes (formerly MCCQE Notes) Editors-in-Chief and their editorial teams. The 34th edition of this text was made possible with their contributions.

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# Table of Contents

1. **Common Unit Conversions**
2. **Commonly Measured Laboratory Values**
3. Ethical, Legal, and Organizational Medicine .................................................. ELOM
4. Anesthesia and Perioperative Medicine .......................................................... A
5. Cardiology and Cardiac Surgery ........................................................................ C
6. Clinical Pharmacology ....................................................................................... CP
7. Dermatology ....................................................................................................... D
8. Emergency Medicine .......................................................................................... ER
9. Endocrinology ..................................................................................................... E
10. Family Medicine ................................................................................................. FM
11. Gastroenterology ................................................................................................. G
12. General Surgery and Thoracic Surgery ............................................................. GS
13. Geriatric Medicine ............................................................................................. GM
14. Gynecology .......................................................................................................... GY
15. Hematology ......................................................................................................... H
16. Infectious Diseases ............................................................................................. ID
17. Medical Genetics ................................................................................................. MG
18. Medical Imaging .................................................................................................. MI
19. Nephrology .......................................................................................................... NP
20. Neurology ............................................................................................................ N
21. Neurosurgery ....................................................................................................... NS
22. Obstetrics ............................................................................................................ OB
23. Ophthalmology .................................................................................................... OP
24. Orthopedics ......................................................................................................... OR
25. Otolaryngology .................................................................................................... OT
26. Pediatrics ............................................................................................................. P
27. Plastic Surgery ..................................................................................................... PL
28. Population Health and Epidemiology ................................................................. PH
29. Psychiatry ............................................................................................................ PS
30. Respiratory .......................................................................................................... R
31. Rheumatology ...................................................................................................... RH
32. Urology ................................................................................................................ U
33. Vascular Surgery ................................................................................................. VS
34. Index
How to Use This Book

This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of Toronto Notes allows easy identification of important information. These items are indicated by icons interspersed throughout the text:

<table>
<thead>
<tr>
<th>Icon</th>
<th>Icon Name</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Key Objectives Icon" /></td>
<td>Key Objectives</td>
<td>This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics.</td>
</tr>
<tr>
<td><img src="image2" alt="Clinical Pearl Icon" /></td>
<td>Clinical Pearl</td>
<td>This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text.</td>
</tr>
<tr>
<td><img src="image3" alt="Memory Aid Icon" /></td>
<td>Memory Aid</td>
<td>This icon is found in sidebars of the text. It identifies helpful mnemonic devices and other memory aids.</td>
</tr>
<tr>
<td><img src="image4" alt="Clinical Flag Icon" /></td>
<td>Clinical Flag</td>
<td>This icon is found in sidebars of the text. It indicates information or findings that require urgent management or specialist referral.</td>
</tr>
<tr>
<td><img src="image5" alt="Cross-Reference Icon" /></td>
<td>Cross-Reference</td>
<td>This icon is found in sidebars of the text. It indicates a cross-reference for information that is discussed in a separate chapter.</td>
</tr>
<tr>
<td><img src="image6" alt="Evidence Based Medicine Icon" /></td>
<td>Evidence Based Medicine</td>
<td>This icon is found in sidebars of the text. It identifies key research studies for evidence-based clinical decision making related to topics discussed in the accompanying text.</td>
</tr>
<tr>
<td><img src="image7" alt="Colour Photo Atlas Icon" /></td>
<td>Colour Photo Atlas</td>
<td>This icon is found next to headings in the text. It indicates topics that correspond with images found in the Colour Photo Atlas available online (<a href="http://www.torontonotes.ca">www.torontonotes.ca</a>).</td>
</tr>
<tr>
<td><img src="image8" alt="Radiology Atlas Icon" /></td>
<td>Radiology Atlas</td>
<td>This icon is found next to headings in the text. It indicates topics that correspond to images found in the Radiology Atlas available online (<a href="http://www.torontonotes.ca">www.torontonotes.ca</a>).</td>
</tr>
<tr>
<td><img src="image9" alt="Online Resources Icon" /></td>
<td>Online Resources</td>
<td>This icon is found next to headings in the text. It indicates topics that correspond with electronic resources such as Functional Neuroanatomy or ECGs Made Simple, available online (<a href="http://www.torontonotes.ca">www.torontonotes.ca</a>).</td>
</tr>
</tbody>
</table>

Chapter Divisions

To aid in studying and finding relevant material quickly, each chapter is organized in the following general framework:

**Basic Anatomy/Physiology Review**
- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

**Common Differential Diagnoses**
- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

**Diagnoses**
- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

**Common Medications**
- a quick reference section for review of medications commonly prescribed
# Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor
To convert from the SI unit to the conventional unit, **divide** by conversion factor

<table>
<thead>
<tr>
<th>Conventional Unit</th>
<th>Conversion Factor</th>
<th>SI Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH pg/mL</td>
<td>0.22</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>10</td>
<td>g/L</td>
</tr>
<tr>
<td>Bilirubin mg/dL</td>
<td>17.1</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Calcium mg/dL</td>
<td>0.25</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Cortisol µg/dL</td>
<td>27.59</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>88.4</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Creatinine clearance mL/min</td>
<td>0.0167</td>
<td>mL/s</td>
</tr>
<tr>
<td>Ethanol mg/dL</td>
<td>0.217</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Ferritin ng/mL</td>
<td>2.247</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>0.0555</td>
<td>mmol/L</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>0.01</td>
<td>proportion of 1.0</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td>10</td>
<td>g/L</td>
</tr>
<tr>
<td>HDL cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Iron, total µg/dL</td>
<td>0.179</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Lactate (lactic acid) mg/dL</td>
<td>0.111</td>
<td>mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Leukocytes x 10³ cells/mm³</td>
<td>1</td>
<td>x 10⁹ cells/L</td>
</tr>
<tr>
<td>Magnesium mg/dL</td>
<td>0.411</td>
<td>mmol/L</td>
</tr>
<tr>
<td>MCV µm³</td>
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<td>fl</td>
</tr>
<tr>
<td>Platelets x 10³ cells/mm³</td>
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<td>x 10⁹ cells/L</td>
</tr>
<tr>
<td>Reticulocytes % of RBCs</td>
<td>0.01</td>
<td>proportion of 1.0</td>
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<tr>
<td>Salicylate mg/L</td>
<td>0.00724</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Testosterone ng/dL</td>
<td>0.0347</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄) ng/dL</td>
<td>12.87</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Total Iron Binding Capacity µg/dL</td>
<td>0.179</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃) pg/dL</td>
<td>0.0154</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Triglycerides mg/dL</td>
<td>0.0113</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Urea nitrogen mg/dL</td>
<td>0.357</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Uric acid mg/dL</td>
<td>59.48</td>
<td>µmol/L</td>
</tr>
</tbody>
</table>

Celsius → Fahrenheit $F = (C \times 1.8) + 32$
Fahrenheit → Celsius $C = (F - 32) \times 0.5555$
Kilograms → Pounds $1 \text{ kg} = 2.2 \text{ lbs}$
Pounds → Ounces $1 \text{ lb} = 16 \text{ oz}$
Ounces → Grams $1 \text{ oz} = 28.3 \text{ g}$
Inches → Centimetres $1 \text{ in} = 2.54 \text{ cm}$
# Commonly Measured Laboratory Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial Blood Gases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>PCO₂</td>
<td>35-45 mmHg</td>
<td>4.7-6.0 kPa</td>
</tr>
<tr>
<td>PO₂</td>
<td>80-105 mmHg</td>
<td>10.6-14 kPa</td>
</tr>
<tr>
<td><strong>Serum Electrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22-28 mEq/L</td>
<td>22-28 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.4-10.2 mg/dL</td>
<td>2.1-2.5 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95-106 mEq/L</td>
<td>95-106 mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.3-2.1 mEq/L</td>
<td>0.65-1.05 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.7-4.5 mg/dL</td>
<td>0.87-1.45 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.0 mEq/L</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>136-145 mEq/L</td>
<td>136-145 mmol/L</td>
</tr>
<tr>
<td><strong>Serum Nonelectrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5-5.0 g/dL</td>
<td>35-50 g/L</td>
</tr>
<tr>
<td>ALP</td>
<td>35-100 U/L</td>
<td>35-100 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Amylase</td>
<td>25-125 U/L</td>
<td>25-125 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Bilirubin (direct)</td>
<td>&lt;0.3 mg/dL</td>
<td>&lt;0.5 µmol/L</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>0.1-1.0 mg/dL</td>
<td>2.17 µmol/L</td>
</tr>
<tr>
<td>BUN</td>
<td>7-18 mg/dL</td>
<td>2.5-7.1 mmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/dL</td>
<td>&lt;5.2 mmol/L</td>
</tr>
<tr>
<td>Creatinine (female)</td>
<td>10-70 U/L</td>
<td>10-70 U/L</td>
</tr>
<tr>
<td>Creatinine (male)</td>
<td>25-90 U/L</td>
<td>25-90 U/L</td>
</tr>
<tr>
<td>Creatine Kinase – MB fraction</td>
<td>0-12 U/L</td>
<td>0-12 U/L</td>
</tr>
<tr>
<td>Ferritin (female)</td>
<td>12-150 ng/mL</td>
<td>12-150 µg/L</td>
</tr>
<tr>
<td>Ferritin (male)</td>
<td>15-200 ng/mL</td>
<td>15-200 µg/L</td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>70-110 mg/dL</td>
<td>3.8-6.1 mmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;6%</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>LDH</td>
<td>100-250 U/L</td>
<td>100-250 U/L</td>
</tr>
<tr>
<td>Osmolality</td>
<td>275-300 mOsm/kg</td>
<td>275-300 mOsm/kg</td>
</tr>
<tr>
<td><strong>Serum Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH (0800h)</td>
<td>&lt;60 pg/mL</td>
<td>&lt;13.2 pmol/L</td>
</tr>
<tr>
<td>Cortisol (0800h)</td>
<td>5-23 µg/dL</td>
<td>138-635 nmol/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>&lt;20 ng/mL</td>
<td>&lt;20 ng/mL</td>
</tr>
<tr>
<td>Testosterone (male, free)</td>
<td>9-30 ng/dL</td>
<td>0.31-1 pmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄)</td>
<td>5-12 ng/dL</td>
<td>64-155 nmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃)</td>
<td>115-190 ng/dL</td>
<td>1.8-2.9 nmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.5-5 µU/mL</td>
<td>0.5-5 µU/mL</td>
</tr>
<tr>
<td><strong>Hematologic Values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (female)</td>
<td>0-20 mm/h</td>
<td>0-20 mm/h</td>
</tr>
<tr>
<td>ESR (male)</td>
<td>0-15 mm/h</td>
<td>0-15 mm/h</td>
</tr>
<tr>
<td>Hemoglobin (female)</td>
<td>12.3-15.7 g/dL</td>
<td>123-157 g/L</td>
</tr>
<tr>
<td>Hemoglobin (male)</td>
<td>13.5-17.5 g/dL</td>
<td>140-174 g/L</td>
</tr>
<tr>
<td>Hematocrit (female)</td>
<td>36-46%</td>
<td>36-46%</td>
</tr>
<tr>
<td>Hematocrit (male)</td>
<td>41-53%</td>
<td>41-53%</td>
</tr>
<tr>
<td>INR</td>
<td>1.0-1.1</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>4.5-11 x 10⁹ cells/mm³</td>
<td>4.5-11 x 10⁹ cells/L</td>
</tr>
<tr>
<td>MCV</td>
<td>88-100 µm³</td>
<td>88-100 fL</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-400 x 10⁹/mm³</td>
<td>150-400 x 10⁹/L</td>
</tr>
<tr>
<td>PTT</td>
<td>25-35 s</td>
<td>25-35 s</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>0.5-1.5% of RBC</td>
<td>20-84 x 10⁹/L</td>
</tr>
</tbody>
</table>
Further information on these topics can be found in the Objectives of the Considerations of the Legal, Ethical and Organizational Aspects of the Practice of Medicine (CLEO) – which can be downloaded free of charge from the Medical Council of Canada website at http://mcc.ca/wp-content/uploads/CLEO.pdf

Canadian law applicable to medical practice varies between jurisdictions and changes over time. Criminal law is nationwide, but non-criminal (civil) law varies between provinces. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.
The legal foundation of the Canadian health system is based on:

- two constitutional documents:
  1. Constitution Act (1867): deals primarily with the jurisdictional power between federal and provincial governments
  2. The Canadian Charter of Rights and Freedoms (1982): does not guarantee a right to health care but, given government’s decision to finance health care, they are constitutionally obliged to do so consistently with the rights and freedoms outlined in the Charter (including the right to equality, physicians’ mobility rights, etc.)
- two statutes:
  1. Canada Health Act (1984) outlines the national terms and conditions that provincial health systems must meet in order to receive federal transfer payments
  2. Canada Health and Social Transfer Act (1996): federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces’ discretion
History of the Canadian Health Care System

1867 **British North America Act** (now **Constitution Act**) establishes Canada as a confederacy
- “establishment, maintenance, and management of hospitals” under provincial jurisdiction

1965 **Royal Commission on Health Services** (Hall Commission) recommends federal leadership
and financial support with provincial government operation

1984 **Canada Health Act** passed by federal government
- replaces **Medical Care Act** (1966) and **Hospital Insurance and Diagnostic Services Act** (1957)
- provides federal funds to provinces with universal hospital insurance
- maintains federal government contribution at 50% on average, with poorer provinces receiving
  more funds
- medical insurance must be “comprehensive, portable, universal, and publicly administered”
- bans extra-billing by new fifth criterion: accessibility

1996 **Canada Health and Social Transfer Act** passed by federal government
- federal government gives provinces a single grant for health care, social programs, and
  post-secondary education; division of resources at provinces’ discretion

2001 **Kirby and Romanow Commissions** appointed

  **Kirby Commission** (final report, October 2002)
  - examines history of health care system in Canada, pressures and constraints of current health
  care system, role of federal government, and health care systems in foreign jurisdictions

  **Romanow Commission** (final report, November 2002)
  - dialogue with Canadians on the future of Canada’s public health care system

2004 **First Ministers’ Meeting on the Future of Health Care** produces a 10 year plan
- priorities include reductions in waiting times, development of a national pharmacare plan, and
  primary care reform

2005 **Chaudié v Quebec**, Supreme Court of Canada decision
- rules that Quebec’s banning of private insurance is unconstitutional under the **Quebec Charter
  of Rights**, given that patients do not have access to those services under the public system in a
timely way

2011 First progress report by the Health Council reviews progress (2004 First Ministers’ 10 year plan)
- significant reductions in wait times for specific areas (such as cancer, joint replacement and
  sight restoration), but may have inadvertently caused increases in wait times of other services
- despite large investments into EMRs, Canada continues to have very low uptake, ranking last in the
  **Commonwealth Fund International Health Policy** survey, with only 37% use among
  primary care physicians
- little progress in creating a national strategy for equitable access to pharmaceuticals; however,
  there has been some success in increasing pharmacists’ scope of practice, reducing generic
  drug costs, and implementing drug information systems
- increases in funding to provinces at 6% per annum until the 2016-2017 fiscal year; from then
  onwards, increases tied to nominal GDP at a minimum of 3% per annum

2012 Second progress report by the Health Council reviews progress towards 2004 First Ministers’ 10
year plan
- funding is sufficient; however, more innovation is needed including incentivizing through
  models of remuneration
- 46 recommendations made to address the lack of progress

2014 Expiry of current **10 Year Health Care Funding Agreement** between federal and provincial
governments

2015 Negotiations underway for a new Health Accord with a $3 billion investment over four years to
homecare and mental health services by the elected Liberal government

2017 New 10 year Canada Health Accord reached with a $11.5 billion federal investment over 10 years
to homecare and mental health services and a 3% annual rise in the Canada Health Transfer
(down from 6% in the previous agreement) by the elected Liberal government
Health Care Expenditure and Delivery in Canada

- The projected total health care expenditure in 2016 is expected to reach $228 billion, 11% of the GDP, approximately $6,299 CDN per person.

Sources of Health Care Funding
- 70% of total health expenditure in 2016 came from public-sector funding with 65% coming from the provincial and territorial governments and another 5% from other parts of the public sector: federal direct government, municipal, and social security funds. 30% is from private sources including out of pocket (15%), private insurance (12%) and other (3%).
- Public sector covers services offered on either a fee for service, capitation, or alternate payment plan in physicians’ offices and in hospitals.
- Public sector does not cover services provided by privately practicing health professionals (e.g., dentists, chiropractors, optometrists, massage therapists, osteopaths, physiotherapists, podiatrists, psychologists, private duty nurses, and naturopaths), prescription drugs, OTC drugs, personal health supplies, and use of residential care facilities.

![Figure 1. Total health expenditure by use of funds, Canada, 2015](https://secure.cihi.ca/free_products/nhex_trends_narrative_report_2015_en.pdf)

Delivery of Health Care
- Hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities.
- Other countries, such as the United States (a mix of public and private funding, as well as private for-profit and private not-for-profit delivery) and the United Kingdom (primarily public funding and delivery) have different systems of delivery.

Physician Licensure and Certification

Table 2. Key Physician Certification and Licensing Bodies in Canada

<table>
<thead>
<tr>
<th>Certification Body</th>
<th>Description</th>
</tr>
</thead>
</table>
| MCC                | Certifies physicians with the LMCC  
LMCC acquired by passing the MCC Qualifying Examination Parts I and II |
| RCPSC              | Certifies specialists who complete an accredited residency program and pass the appropriate exam  
Voluntary membership of the RCPSC is designated FRCP or FRCS |
| CFPC               | Certifies family physicians who complete an accredited residency program and pass the Certification Examination in Family Medicine |
| Licensing Body     | 13 provincial medical regulatory (licensing) authorities  
All postgraduate residents and all practicing physicians must hold an educational or practice license from the licensing body in the province in which they study or practice |
| CPSO               | Membership to the provincial licensing authority is mandatory  
Licensing authority functions include:  
Provide non-transferable licensure to physicians  
Maintaining ethical, legal, and competency standards and developing policies to guide doctors  
Investigating complaints against doctors  
Disciplining doctors guilty of professional misconduct or incompetence  
At times of license revocation and renewal, physicians must disclose if they have a condition (such as HIV positivity, drug addiction, or other illnesses that may impact their ability to practice safely) |
• physician certification is governed nationally, while the medical profession in Canada self-regulates under the authority of provincial legislation
• self-regulation is based on the premise that the licensing authority must act first and foremost in the interest of the public
• the RCPSC and CFPC are responsible for monitoring ongoing CME and professional development
• certification by the LMCC plus either the RCPSC or CFPC is a minimum requirement for licensure by most provincial licensing authorities

## Role of Professional Associations

<table>
<thead>
<tr>
<th>Association</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMA</td>
<td>Provides leadership to doctors and advocates for access to high quality care in Canada</td>
</tr>
<tr>
<td></td>
<td>Represents physician and population concerns at the national level</td>
</tr>
<tr>
<td></td>
<td>Membership is voluntary</td>
</tr>
<tr>
<td>OMA and Other PTMAs</td>
<td>Negotiates fee and benefit schedules with provincial governments</td>
</tr>
<tr>
<td></td>
<td>Represents the economic and professional interests of doctors</td>
</tr>
<tr>
<td></td>
<td>Membership is voluntary</td>
</tr>
<tr>
<td>CMPA</td>
<td>Physician-run organization that protects the integrity of member physicians</td>
</tr>
<tr>
<td></td>
<td>Provides legal defence against allegations of malpractice or negligence</td>
</tr>
<tr>
<td></td>
<td>Provides risk management and educational programs</td>
</tr>
<tr>
<td></td>
<td>Membership is voluntary</td>
</tr>
<tr>
<td>RDoC and PHO</td>
<td>Upholds economic and professional interests of residents across Canada</td>
</tr>
<tr>
<td></td>
<td>Facilitates discussion amongst PHOs regarding policy and advocacy items</td>
</tr>
<tr>
<td>CMFS and FMÉQ</td>
<td>Medical students are represented at their universities by student bodies, which collectively form the CFMS or FMÉQ</td>
</tr>
<tr>
<td></td>
<td>FMÉQ membership includes that of francophone medical schools</td>
</tr>
</tbody>
</table>

### Ethical and Legal Issues in Canadian Medicine

#### Introduction to the Principles of Ethics

- ethics addresses:
  1. principles and values that help define what is morally right and wrong
  2. rights, duties, and obligations of individuals and groups
- the practice of medicine assumes there is one code of professional ethics for all doctors and that they will be held accountable by that code and its implications
- the doctor-patient relationship is formed on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
- a fiduciary duty is a legal duty to act solely in another party's interest; one may not profit from the relationship with principals unless he/she has the principal's express consent

<table>
<thead>
<tr>
<th>Principle</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomy</td>
<td>Recognizes an individual’s right and ability to decide for himself/herself according to his/her beliefs and values Not applicable in situations where informed consent and choice are not possible or may not be appropriate</td>
</tr>
<tr>
<td>Beneficence</td>
<td>Patient-based ‘best interests’ standard that combines doing good, avoiding harm, taking into account the patient’s values, beliefs, and preferences, so far as these are known Autonomy should be integrated with the physician’s conception of a patient’s medically-defined best interests Aim is to minimize harmful outcomes and maximize beneficial ones Paramount in situations where consent/choice is not possible or may not be appropriate</td>
</tr>
<tr>
<td>Non-Maleficence</td>
<td>Obligation to avoid causing harm; primum non nocere (“First, do no harm”) Limit condition of the Beneficence principle</td>
</tr>
<tr>
<td>Justice</td>
<td>Fair distribution of benefits and harms within a community, regardless of geography or privilege Concept of fairness: Is the patient receiving what he/she deserves – his/her fair share? Is he/she treated the same as equally situated patients? How does one set of treatment decisions impact others? Basic human rights, such as freedom from persecution and the right to have one’s interests considered and respected</td>
</tr>
</tbody>
</table>

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**Autonomy vs. Competence**

**Autonomy**: the right that patients have to make decisions according to their beliefs and preferences

**Competence**: the ability or capacity to make a specific decision for oneself
CMA Code of Ethics
- the CMA developed a Code of Ethics that acts as a common ethical framework for Canadian physicians
- the Code of Ethics is:
  - prepared by physicians for physicians and applies to physicians, residents, and medical students
  - based on the fundamental ethical principles of medicine
  - sources include the Hippocratic Oath, developments in human rights, recent bioethical discussion
  - CMA policy statements address specific ethical issues not mentioned by the code (e.g. abortion, transplantation, and euthanasia)

Confidentiality

Overview of Confidentiality
- a full and open exchange of information between patient and physician is central to a therapeutic relationship
- privacy is the right of patients (which they may forgo) while confidentiality is the duty of doctors (which they must respect barring patient consent or the requirements of the law)
- if inappropriately breached by a doctor, he/she can be sanctioned by the hospital, court, or regulatory authority
- based on the ethical principle of patient autonomy, patients have the right to the following:
  - control of their own information
  - the expectation that information concerning them will receive proper protection from unauthorized access by others (see Privacy of Medical Records, ELOM7)
  - confidentiality may be ethically and legally breached in certain circumstances (e.g. the threat of harm to others)
  - unlike the solicitor-client privilege, there is no ‘physician-patient privilege’ by which a physician, even a psychiatrist, can promise the patient absolute confidentiality
  - physicians should seek advice from their local health authority or the CMPA before disclosing HIV status of a patient to someone else
  - many jurisdictions make mandatory not only the reporting of serious communicable diseases (e.g. HIV), but also the reporting of those who harbour the agent of the communicable disease
  - physicians failing to abide by such regulations could be subject to professional or civil actions
- legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting cases in the common law

Statutory Reporting Obligations
- legislation has defined specific instances where public interest overrides the patient’s right to confidentiality; varies by province, but may include:
  1. suspected child abuse or neglect – report to local child welfare authorities (e.g. Children’s Aid Society)
  2. fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see Geriatric Medicine, GM11)
  3. communicable diseases – report to local public health authority (see Population Health and Epidemiology; PH24)
  4. improper conduct of other physicians or health professionals – report to College or regulatory body
  5. vital statistics must be reported; reporting varies by province (e.g. in Ontario, births are required to be reported within 30 days to Office of Registrar General or local municipality; death certificates must be completed by a MD then forwarded to municipal authorities)
  6. reporting to coroners (see Physician Responsibilities Regarding Death, ELOM14)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

Duty to Protect/Warn
- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detention of violent patients for clinical assessment), informing the police, or warning the potential victim(s) if a patient expresses an intent to harm first established by a Supreme Court of California decision in 1976 (Tarasoff v. Regents of the University of California; supported by Canadian courts
- obliged by the CMAB Code of Ethics and recognized by some provincial/territorial regulatory authorities
- concerns of breaching confidentiality should not prevent the MD from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
- applies in a situation where:
  1. there is a clear risk to identifiable person(s);
  2. there is a risk of serious bodily harm or death; and
  3. the danger is imminent (i.e. more likely to occur than not)

Disclosure for Legal Proceedings
- disclosure of health records can be compelled by a court order, warrant, or subpoena
Privacy of Medical Records
• privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the Canadian Charter of Rights and Freedoms, and the physician's fiduciary duty
• the federal government created the PIPEDA in 2000 which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, private labs)
• PIPEDA has been superseded by provincial legislation in many provinces, such as the Ontario Personal Health Information Protection Act, which applies more specifically to health information

Duties of Physicians with Regard to the Privacy of Health Information
• inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
• obtain the patient's expressed consent to disclose information to third parties
  ■ under Ontario privacy legislation, the patient's expressed consent need not be obtained to share information between health care team members involved in the "circle of care." However, the patient may withdraw consent for this sharing of information and may put parts of the chart in a "lock box."
  ■ provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
  ■ provide secure storage of information and implement measures to limit access to patient records
  ■ ensure proper destruction of information that is no longer necessary
  ■ regarding taking pictures or videos of patients, findings, or procedures, in addition to patient consent and privacy laws, trespassing laws apply in some provinces
• CPSO published policy is designed to help Ontario physicians understand legal and professional obligations set out under the Regulated Health Professions Act, 1991, the Medicine Act, 1991, and the Personal Health Information Protection Act, 2004. This includes regulations regarding express or implied consent, incapacity, lock boxes, disclosure under exceptional circumstances, mandatory reporting, ministry audits, subpoenas, court orders, and police, as well as electronic records and voice messaging communications: http://www.cpso.on.ca/Policies-Publications/Policy/Confidentiality-of-Personal-Health-Information
• it is the physician's responsibility to ensure appropriate security provisions with respect to electronic records and communications

Consent and Capacity

Ethical Principles Underlying Consent and Capacity
• consent is the autonomous authorization of a medical intervention by a patient
• usually the principle of respect for patient autonomy overrides the principle of beneficence
• where a patient cannot make an autonomous decision (i.e. incapable), it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
• there is a duty to discover, if possible, what the patient would have wanted when capable
• central to determining best interests is understanding the patient's values, beliefs, and cultural or religious background
• more recently expressed wishes take priority over remote ones
• patient wishes may be verbal or written
• patients found incapable to make a specific decision should still be involved in that decision as much as possible
• agreement or disagreement with medical advice does not determine findings of capacity/incapacity
• however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed

Four Basic Requirements of Valid Consent
1. Voluntary
• consent must be given free of coercion or pressure (e.g. from parents or other family members who might exert undue influence)
• the physician must not deliberately mislead the patient about the proposed treatment
2. Capable
• the patient must be able to understand and appreciate the nature and effect of the proposed treatment
3. Specific
• the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (e.g. the patient must be informed if students will be involved in providing the treatment)
4. Informed
• sufficient information and time must be provided to allow the patient to make choices in accordance with his/her wishes, including:
  ■ the nature of the treatment or investigation proposed and its expected effects
  ■ all significant risks and special or unusual risks
  ■ alternative treatments or investigations and their anticipated effects and significant risks
  ■ the consequences of declining treatment
  ■ risks that are common sense need not be disclosed (i.e. bruising after venipuncture)
  ■ answers to any questions the patient may have
- the reasonable person test – the physician must provide all information that would be needed “by a reasonable person in the patient’s position” to be able to make a decision
- disclose common adverse events (>1/200 chance of occurrence) and serious risks (e.g. death), even if remote
- it is the physician’s responsibility to make reasonable attempts to ensure that the patient understands the information
- physicians should not withhold information about a legitimate therapeutic option based on personal conscience (e.g. not discussing the option of emergency contraception)

Figure 2. Ontario consent flowchart
Adapted by Hébert P from Sunnybrook Health Sciences Centre Consent Guidelines

**Obtaining Legal Consent**
- consent of the patient must be obtained before any medical intervention is provided; consent can be verbal or written, although written is usually preferred
- a signed consent form is only evidence of consent – it does not replace the process for obtaining valid consent
- most important component is what the patient understands and appreciates, not what the signed consent form states
- implied (e.g. a patient holding out their arm for an immunization) or expressed
- consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm
- HCCA of Ontario (1996) covers consent to treatment, admission to a facility, and personal assistance services (e.g. home care)

**Exceptions to Consent**
1. Emergencies
   - treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their SDM
   - emergency treatment should not violate a prior expressed wish of the patient (e.g. a signed Jehovah’s Witness card)
   - if patient is incapable, MD must document reasons for incapacity and why situation is emergent
   - patients have a right to challenge a finding of incapacity as it removes their decision-making ability
   - if a SDM is not available, MD can treat without consent until the SDM is available or the situation is no longer emergent

Criteria For Administration of Treatment for an Incapable Patient in Emergency Situations
- Patient is experiencing extreme suffering
- Patient is at risk of sustaining serious bodily harm if treatment is not administered promptly

Patients may also ask to waive the right to choice (e.g. “You know what’s best for me, doctor”) or delegate their right to choose to someone else (e.g. a family member)

The Supreme Court of Canada expects physicians to disclose the risks that a “reasonable” person would want to know. In practice, this means disclosing minor risks that are common as well as serious risks that happen infrequently, especially those risks that are particularly relevant to a particular patient (e.g. hearing loss for a musician)

Major Exceptions to Consent
- Emergencies
- Public and Mental Health Legislation
- Communicable diseases
2. Legislation
- Mental Health legislation allows for:
  - the detention of patients without their consent
  - psychiatric outpatients may be required to adhere to a care plan in accordance with Community Treatment Orders (see Psychiatry, PS51)
- Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases

3. Special Situations
- public health emergencies (e.g. an epidemic or communicable disease treatment)
- warrant for information by police

Consequences of Failure to Obtain Valid Consent
- treatment without consent is battery (an offense in tort), even if the treatment is life-saving (excluding situations outlined in exceptions section above)
- treatment of a patient on the basis of poorly informed consent may constitute negligence, also an offense in tort
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)

Overview of Capacity
- capacity is the ability to:
  - understand information relevant to a treatment decision
  - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
  - capacity is specific for each decision (e.g. a person may be capable to consent to having a chest x-ray, but not for a bronchoscopy)
  - capacity can change over time (e.g. temporary incapacity secondary to delirium)
  - most Canadian jurisdictions distinguish capacity to make healthcare decisions from capacity to make financial decisions; a patient may be deemed capable of one, but not the other
  - a person is presumed capable unless there is good evidence to the contrary
  - capable patients are entitled to make their own decisions
  - capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny

Assessment of Capacity
- capacity assessments must be conducted by a physician and, if appropriate, in consultation with other healthcare professionals (e.g. another physician, a mental health nurse)
- clinical capacity assessment may include:
  - specific capacity assessment (i.e. capacity specific to the decision at hand):
    1. effective disclosure of information and evaluation of patient's reason for decision
    2. understanding of:
       - his/her condition
       - the nature of the proposed treatment
       - alternatives to the treatment
       - the consequences of accepting and rejecting the treatment
       - the risks and benefits of the various options
  - for the appreciation needed for decision making capacity, a person must
    - acknowledge the condition that affects him/herself
    - be able to assess how the various options would affect him or her
    - be able to reach a decision and adhere to it, and make a choice, not based primarily upon delusional belief
  - general impressions
  - input from psychiatrists, neurologists, etc.
  - employ "Aid to Capacity Evaluation"
  - a decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board), or the courts
  - judicial review is open to patients if found incapable

Treatment of the Incapable Patient in a Non-Emergent Situation
- obtain informed consent from SDM
- an incapable patient can only be detained against his/her will to receive treatment if he/she meets criteria for certification under the Mental Health Act (see Psychiatry, PS50); in such a situation:
  - document assessment in chart
  - notify patient of assessment using appropriate Mental Health Form(s) (Form 42 in Ontario)
  - notify Rights Advisor
Substitute Decision-Makers
- SDMs must follow the following principles when giving informed consent:
  - act in accordance with wishes previously expressed by the patient while capable
  - if wishes unknown, act in the patient’s best interest, asking the following into account:
    1. Values and beliefs held by the patient while capable
    2. Whether well-being is likely to improve with vs. without treatment
    3. Whether the expected benefit outweighs the risk of harm
    4. Whether a less intrusive treatment would be as beneficial as the one proposed
- the final decision of the SDM may and should be challenged by the MD if the MD believes the SDM is not abiding by the above principles

Instructional Advance Directives
- allow patients to exert control over his/her care once they are no longer capable
- the patient sets out his/her decisions about future health care, including who he/she would allow to make treatment decisions on his/her behalf and what types of interventions he/she would want
- takes effect once the patient is incapable with respect to treatment decisions
- in Ontario, a person can appoint a power of attorney for personal care to carry out his/her advance directives
- patients should be encouraged to review these documents with their family and physicians and to reevaluate them often to ensure they are current with their wishes

POWERS OF ATTORNEY
- all Guardians and Attorneys have fiduciary duties for the dependent person

Definitions
- Power of Attorney for Personal Care
  - a legal document in which one person gives another the authority to make personal care decisions (health care, nutrition, shelter, clothing, hygiene, and safety) on their behalf if they become mentally incapable.
- Guardian of the Person
  - someone who is appointed by the Court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care.
- Continuing Power of Attorney for Property
  - legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions.
- Guardian of Property
  - someone who is appointed by the Public Guardian and Trustee or the Courts to look after an incapable person’s property or finances.
- Public Guardian and Trustee
  - acts as a SDM of last resort on behalf of mentally incapable people who do not have another individual to act on their behalf.
- Pediatric Aspects of Capacity Covered
  - no age of consent in all provinces and territories except Quebec; consent depends on patient’s decision-making capacity.
  - Quebec has a specific age of consent, but common law and case law deem underage legal minors capable, allowing these individuals to make their own choices.
  - infants and children are assumed to lack mature decision-making capacity for consent but they should still be involved (i.e., be provided with information appropriate to their comprehension level).
  - adolescents are usually treated as adults
  - preferably, assessment should still be obtained from patient, even if not capable of giving consent.
  - in the event that the physician believes the SDM is not acting in the child’s best interests, an appeal must be made to the local child welfare authorities.
  - under normal circumstances, parents have right of access to the child’s medical record.

Negligence

Ethical Basis
- the doctor-patient relationship is formed on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
- negligence or malpractice is a form of failure on the part of the physician in fulfilling his/her fiduciary duty in providing appropriate care and leading to harm of the patient (and/or abuse of patient's trust)

Legal Basis
- physicians are legally liable to their patients for causing harm (tort) through a failure to meet the standard of care applicable under the circumstances
- standard of care is defined as one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, specialization, and standing.
- liability arises from physician’s common law duty of care to his/her patients in the doctor/patient relationship (or, in Quebec, from the Civil Code provisions regarding general civil liability)
- action(s) in negligence (or civil liability) against a physician must be launched by a patient within a specific prescribed period required by the respective province in which the actions occurred.

Most provinces have legislated hierarchies for SDMs, the hierarchy in Ontario is:
- Legally appointed guardian
- Appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see Powers of Attorney)
- Representative appointed by the Consent and Capacity Board.
- Spouse or partner
- Child (age 16 or older) or parent (unless the parent has only a right of access)
- Parent with only a right of access
- Sibling
- Other relative(s)
- Public guardian and trustee.

There is no age of consent in Ontario. Capacity is assessed on an individual basis.

Other Types of Capacity Not Covered by the HCCA
- Testamentary (ability to make a will)
- Fitness (ability to stand trial)
- Financial (ability to manage property – Form 21 of the Mental Health Act)
- Personal (ability to care for oneself on a daily basis)

Errors of care are compatible with non-negligent care if they are ones that a reasonably cautious and skilled MD could make (i.e., mistakes can be made due to ‘honest error’).

Four Basic Elements for Action Against a Physician to Succeed in Negligence
1. A duty of care owed to the patient (i.e., doctor/patient relationship must be established)
2. A breach of the standard of care
3. Some harm or injury to the patient
4. The harm or injury must have been caused by the breach of the duty of care.
Truth-Telling

Ethical Basis
- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed decisions about health care and their lives

Legal Basis
- required for valid patient consent (see Consent and Capacity, ELOM7)
  - goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision (“standard of disclosure”)
  - withholding information can be a breach of fiduciary duty and duty of care
  - obtaining consent on the basis of misleading information can be seen as negligent

Evidence about Truth Telling
- most patients want to know what is wrong with them
- although many patients want to protect family members from bad news, themselves would want to be informed in the same situation
- truth-telling improves adherence and health outcomes
- informed patients are more satisfied with their care
- negative consequences of truth-telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability

Challenges in Truth-Telling

Medical Error
- medical error may be defined as ‘preventable adverse events (AEs)’ caused by the patient’s medical care and not the patient’s underlying illness; some errors may be identified before they harm the patient, so not all error is truly ‘adverse’
- many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient’s family and reported to the appropriate health authorities
- physicians should disclose to patients the occurrence of AEs or errors caused by medical management, but should not suggest that they resulted from negligence because:
  - negligence is a legal determination
  - error is not equal to negligence (see Negligence, ELOM6)
- disclosure allows the injured patient to seek appropriate corrective treatment promptly
- physicians should avoid simple attributions as to cause and sole responsibility of others or oneself
- physicians should offer apologies or empathic expressions of regret (e.g. “I wish things had turned out differently”) as these can increase trust and are not admissions of guilt or liability
- Apology Acts across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence

Breaking Bad News
- ‘bad news’ may be any information that reveals conditions or illnesses threatening the patient’s sense of well-being
- poorly done disclosure may be as harmful as non-disclosure
  - caution patients in advance of serious tests and disclose possible bad findings
  - give time for patient to reflect prior to receiving such news
  - give warnings of impending bad news by reviewing prior discussions
  - provide time for the patient and questions
  - adequate supports and strategies should always be provided following disclosure of difficult news
- SPIKES protocol was developed to facilitate “breaking bad news”
  - SETTLE and LISTENING SKILL
  - Patient PERCEPTIONS of condition and seriousness
  - INVITATION from patient to receive information
  - KNOWLEDGE - provide medical facts
  - Explore EMOTIONS and EMPATHIZE
  - STRATEGY and SUMMARY

Arguments Against Truth-Telling
- may go against certain cultural norms and expectations
- may lead to patient harm and increased anxiety
- 10-20% of patients prefer not to be informed
- medical uncertainty may result in the disclosure of uncertain or inaccurate information

Exceptions to Truth-Telling
- a patient may waive his/her right to know the truth about their situation (i.e. decline information that would normally be disclosed) when:
  - the patient clearly declines to be informed
  - a strong cultural component exists that should be respected and acknowledged
  - the patient may wish others to be informed and make the medical decisions for him/her
the more weighty the consequences for the patient from non-disclosure, the more carefully one must consider the right to ignorance
- ‘emergencies’: an urgent need to treat may legitimately delay full disclosure; the presumption is that most people would want such treatment and the appropriate SDM cannot be found
- ‘therapeutic privilege’
  • withholding of information by the clinician in the belief that disclosure of the information would itself lead to severe anxiety, psychological distress or physical harm to the patient
  • clinicians should avoid invoking therapeutic privilege due to its paternalistic overtones and is a defence of non-disclosure that is rarely accepted anymore
  • it is often not the truth that is unpalatable; it is how it is conveyed that can harm the patient

Managing Controversial and Ethical Issues in Practice
MCC-CLEO Objectives 1998
- discuss in a non-judgmental manner
- ensure patients have full access to relevant and necessary information
- identify if certain options lie outside of your moral boundaries and refer to another physician if appropriate
- consult with appropriate ethics committees or boards
- protect freedom of moral choice for students or trainees

Reproductive Technologies

Overview of the Maternal-Fetal Relationship
- in general, maternal and fetal interests align
- in some situations, a conflict between maternal autonomy and the best interests of the fetus may arise

Ethical Issues and Arguments
- principle of reproductive freedom: women have the right to make their own reproductive choices
- coercion of a woman to accept efforts to promote fetal well-being is an unacceptable infringement of her personal autonomy

Legal Issues and Arguments
- the law upholds a woman’s right to life, liberty, and security of person, and does not recognize fetal rights; key aspects of the mother’s rights include:
  • if a woman is competent and refuses medical advice, her decision must be respected even if the fetus will suffer
  • the fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman

Royal Commission on New Reproductive Technologies (1993) recommendations:
1. medical treatment must never be imposed upon a competent pregnant woman against her wishes
2. no law should be used to confine a pregnant woman in the interest of her fetus
3. the conduct of a pregnant woman in relation to her fetus should not be criminalized
4. child welfare should never be used to control a woman’s behaviour during pregnancy
5. civil liability should never be imposed upon a woman for harm done to her fetus during pregnancy

Examples involving the use of established guidelines
- a woman is permitted to refuse HIV testing during pregnancy, even if vertical transmission to fetus results
- a woman is permitted to refuse Caesarean section in labour that is not progressing, despite evidence of fetal distress

Advanced Reproductive Therapies
- includes non-coital insemination, hormonal ovarian stimulation, and IVF
- topics with ethical concerns:
  • donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical history)
  • preimplantation genetic testing for diagnosis before pregnancy
  • use of new techniques without patients appreciating their experimental nature
  • embryo status – the Supreme Court of Canada maintains that fetuses are “unique” but not persons under law; this view would likely apply to embryos as well
- access to ART
- private vs. public funding of ART
- social factors limiting access to ART (e.g. same-sex couples)
- the ‘commercialization’ of reproduction

Ethical Appropriate Actions
- Educate patients and address contributors to infertility (e.g. stress, alcohol, medications, etc.)
- Investigate and treat underlying health problems causing infertility
- Wait at least 1 yr before initiating treatment with ART (exceptions – advanced age or specific indicators of infertility)
- Educate and prepare patients for potential negative outcomes of ART
**Fetal Tissue**
- Pluripotent stem cells can currently be derived from human embryonic and fetal tissue.
- Potential uses of stem cells in research:
  - Studying human development and factors that direct cell specialization.
  - Evaluating drugs for efficacy and safety in human models.
  - Cell therapy: Using stem cells grown in vitro to repair or replace degenerated/destroyed/malignant tissues (e.g., Parkinson's disease).
  - Genetic treatment aimed at altering somatic cells (e.g., myocardial or immunological cells) is acceptable and ongoing.

**Induced Abortion**
- CMA definition of induced abortion: the active termination of a pregnancy before fetal viability (fetus >500 g or >20 wk GA).
- CMA policy on induced abortion:
  1. Induced abortion should not be used as an alternative to contraception.
  2. Counselling on contraception must be readily available.
  3. Full and immediate counselling services must be provided in the event of unwanted pregnancy.
  4. There should be no delay in the provision of abortion services.
  5. No patient should be compelled to have a pregnancy terminated.
  6. Physicians should not be compelled to participate in abortion – if morally opposed, the physician should inform the patient so she may consult another physician.
  7. No discrimination should be directed towards either physicians who do not perform or assist at induced abortions or physicians who do.
  8. Induced abortion should be uniformly available to all women in Canada and health care insurance should cover all the costs (note: the upper limit of GA for which coverage is provided varies between provinces).
  9. Elective termination of pregnancy after fetal viability may be indicated under exceptional circumstances.

**Ethical and Legal Concerns and Arguments**
- No law currently regulates abortion in Canada.
- It is a woman's medical decision to be made in consultation with whom she wishes; there is no mandatory role for spouse/family.
- 2nd and even 3rd trimester abortions are not illegal in Canada, but are usually only carried out when there are serious risks to the woman's health, or if the fetus has died in utero or has major malformations (e.g., anencephaly).

**Prenatal/Antenatal Genetic Testing**
- Uses:
  1. To confirm a clinical diagnosis.
  2. To detect genetic predisposition to a disease.
  3. Allows preventative steps to be taken and helps patient prepare for the future.
  4. Gives parents the option to terminate a pregnancy or begin early treatment.
- Ethical dilemmas arise because of the sensitive nature of genetic information; important considerations of genetic testing include:
  - The individual and familial implications.
  - Its pertinence to future disease.
  - Its ability to identify disorders for which there are no effective treatments or preventive steps.
  - Its ability to identify the sex of the fetus.
  - Ethical issues and arguments regarding the use of prenatal/antenatal genetic testing include:
    - Obtaining informed consent is difficult due to the complexity of genetic information.
    - Doctor's duty to maintain confidentiality vs. duty to warn family members.
    - Risk of social discrimination (e.g., insurance) and psychological harm.

**Legal Aspects**
- No current specific legislation exists.
- Testing requires informed consent.
- No standard of care exists for clinical genetics but physicians are legally obligated to inform patients that prenatal testing exists and is available.
- A physician can breach confidentiality terms in order to warn family members about a condition if harm can possibly be prevented via treatment or prevention (e.g., familial adenomatous polyposis).

**Genetic Testing: Ethically Appropriate Actions**
- Thorough discussion and realistic planning with patient before testing is done.
- Genetic counseling for delivery of complex information.
End-of-Life Care

Overview of Palliative and End-of-Life Care
- focus of care is comfort and respect for person near death and maximizing quality of life for patient, family, and loved ones
- appropriate for any patient at any stage of a serious or life-limiting illness
- may occur in a hospital, hospice, in the community, or at home
- often involves an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care

Euthanasia and Medical-Assistance in Dying
- euthanasia: a deliberate act undertaken by one person with the intention of ending the life of another person to relieve that person’s suffering, where the act is the cause of death
- medical-assistance in dying: the administering or prescribing for self-administration, by a medical practitioner or nurse practitioner, of a substance, at the request of a person, that causes their death

Common Ethical Arguments/Opinions
- patient has the right to make autonomous choices about the time and manner of their own death
- belief that there is no ethical difference between the acts of euthanasia/assisted suicide and forgoing life sustaining treatments
- belief that these acts benefit terminally ill patients by relieving suffering
- patient autonomy has limits
- death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death

Legal Aspect
- in Canada, euthanasia is no longer a punishable offence under the Criminal Code of Canada
- in the Carter v. Canada decision of February 2015, physician-assisted suicide ruled to be not criminal, with the decision taking effect in 2016, now postponed to June 2016
- until June 2016, applicants for assistance in dying (MAID - ‘Medical Aid in Dying’) must obtain court sanction (as an exemption to the Criminal Code)
- Bill C-14 (June 17, 2016) legalized MAID by amending the Criminal Code to create exemptions
- refusal of care by the patient that may lead to death as well as requests for a hastened death, ought to be carefully explored by the physician to rule out any ‘reversible’ factors (e.g. poor palliation, depression, poverty, ill-education, isolation) that may be hindering authentic choice

Acceptable Use of Palliative and End-of-Life Care
- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from euthanasia and assisted suicide as it is seen as allowing the underlying disease to take its ‘natural course’ but this distinction may be more theoretical than real
- consent for withdrawal of life-support must be sought from SDMs, as ruled in Cuthbertson v. Rasouli in 2013 as palliative care would be instituted and consent for that would require SDM consent

Bill C-14 Criteria for MAID
- patient is eligible for health services funding by government of Canada
- at least 18 yr of age, and has capacity for clear and freely given consent
- grievous and irremediable medical condition: in an advanced state of irreversible decline in capability
- suffering intolerable to the patient, no relieved under conditions they consider acceptable
- natural death is reasonably foreseeable

Acceptable Use of Palliative and End-of-Life Care
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- consent for withdrawal of life-support must be sought from SDMs, as ruled in Cuthbertson v. Rasouli in 2013 as palliative care would be instituted and consent for that would require SDM consent

Physician Responsibilities Regarding Death
- physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence
- Coronor’s Act, 1990 (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
  - due to violence, negligence, misconduct, misadventure, or malpractice
  - during pregnancy or is attributable to pregnancy

Mental Health Outcomes of Family Members of Patients Who Request Physician Aid in Dying

Conclusion
- Results: 95 family members were surveyed, including 59 of those whose loved ones received a lethal prescription and 36 whose loved ones died by lethal ingestion. Among those whose family member requested aid in dying, whether or not the patient accessed a lethal prescription had no influence on subsequent depression, grief, or mental health services use; however, family members of patients who received a lethal prescription were more likely to believe that their loved one’s choices were honored and less likely to have regrets about how the loved one died. Comparing family members of those who requested aid in dying to those who did not reveal no differences in primary mental health outcomes of depression, grief, or mental health services use. Family members of patients who requested aid in dying felt more prepared and accepting of the death than comparison family members.
- Conclusion: Pursuit of aid in dying does not have negative effects on surviving family members and may be associated with greater preparation and acceptance of death.

Notify Coroner if Death Occurs due to:

- Violence, negligence, misconduct
- Pregnancy
- Sudden or unexpected causes
- Disease not treated
- Cause other than disease
- Suspicious circumstances
Physician Competence and Professional Conduct

CanMEDS Competencies (Ethical/Policy Statement)
- a framework of professional competencies established by the MCC as objectives for the MCC Qualifying Exam
- further information on MCC objectives can be found at www.mcc.ca

Legal Considerations
- physicians’ conduct and competence are legally regulated to protect patients and society via mandatory membership to provincial governing bodies (e.g., the CPSO)
- physicians are legally required to maintain a license with the appropriate authority, and are thus legally bound to outlined policies on matters of conduct within his/her medical practice
- the ultimate constraint on MD behaviour with regards to unprofessionalism is ‘conduct unbecoming a physician’, such as inappropriate behaviour with colleagues, conflicts of interest, untruthfulness, unethical billing practices, and sexual impropriety with patients

Common Policies on Physician Conduct
- physicians must ensure that patients have access to continuous on-call coverage and are never abandoned
- sexual conduct with patients, even when consented to by the patient, is a serious matter that can lead to accusations of battery by the patient and provincial governing body. Important notes on this topic include:
- inappropriate sexual conduct includes intercourse, undue touching, references to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
- in specified situations, physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact
- physicians are permanently prohibited from personal relationships with patients whom they saw for psychotherapy
- in Ontario, physicians must report any colleagues of whom they have information regarding sexual impropriety (as per CPSO Code of Ethics)
- physicians must maintain adequate records for each patient, which include:
- demonstration that care has been continuous and comprehensive
- minimal standards for record-keeping, including readability, diagnosis, differential diagnosis, appropriate tests and referrals, and a coherent patient record, including drugs, a Cumulative Patient profile, all aspects of charting that are required for safe patient care (full standards available at www.cpso.on.ca). Another physician should be able to take over the safe care of the patient based on the record
- records stored for 10 years in most jurisdictions
- although the medical record is the property of the physician or an institution, the patient or the patient’s delegate must be allowed full access to information in the medical record in a reasonable period of time, and can charge a reasonable fee, upon (usually written) request
- in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain adequate hospital records
Table 5. Ethical Principles for Research Involving Human Subjects

- Patient’s participation in research should not put him/her at a known or probable disadvantage with respect to medical care (i.e. cannot deny participants in research ‘known effective care’, such as randomizing some depressed patients to a placebo arm with no treatment)
- Participant’s voluntary and informed choice is usually required, except in special circumstances (i.e. chart reviews without patient contact, or emergency situations for which there is no accepted or helpful standard of care and the proposed intervention is not likely to cause more harm than such patients already face)
- Access to the treatment that is considered standard (i.e. placebo controlled trials are generally acceptable where patients all receive still receive the standard of care, or, if not, are informed about the placebo arm and what that entails)
- Must employ a scientifically valid design to answer the research question (ensured via peer review, expert opinion)
- Must demonstrate sufficient value to justify any risk posed to participants
- Must be conducted honestly (i.e. carried out as stated in the approved protocol)
- Findings must be reported promptly and accurately without exaggeration, to allow practicing clinicians to draw reasonable conclusions
- Patients must not be enticed into risky research by the lure of money and investigators must not trade the interests of patients for disproportionate recompense by a sponsor; both participants and investigators are due fair recompense for their time and efforts
- Any significant interventional trial ought to have a data safety monitoring board that is independent of the sponsor and can ensure safety of the ongoing trial

Resource Allocation

- **definition:** the distribution of goods and services to programs and people
- **physicians** have the duty to inform patients about therapeutic options even if they are not available
- **physicians** must make health care resources available to patients in a manner which is fair and equitable, without bias or discrimination
- need and benefit are morally relevant criteria for resource allocation
- gender, sexual orientation, religion, level of education, or age alone are morally irrelevant criteria
- ethical dilemmas that arise when deciding how best to allocate resources
- fair chances vs. best outcome: favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
- priorities problem: how much priority should the sickest patients receive?
- aggregation problem: modest benefits to many vs. significant benefits to few
- democracy problem: when to rely on a fair democratic process to arrive at a decision

Guiding Principles for Research Ethics

- Respect for persons: informed consent
- Beneficence: harm vs. benefit
- Justice: avoid exploitation/unjustified exclusion

Informed Consent for Research

- Purpose of study
- Sum of funding
- Name and probability of harm and benefits
- Nature of physician’s participation including compensation
- Proposals for research must be submitted to a research ethics board

Randomization is allowed even if there is an efficacious standard if, for example, there are drawbacks to it (such as it doesn’t work for all, has side effects, and is not wanted by all patients). In such cases, there must be a good safety net established to make sure subjects in the placebo arm do not deteriorate (i.e. there must be a safety monitoring plan for such studies)

CMA and CPSO Guidelines for Ethically Appropriate Physician-Industry Relations

- The primary goal should be the advancement of the health of Canadians
- Relationships should be guided by the CMA Code of Ethics
- The physician’s primary obligation is to the patient
- Physicians should avoid any self-interest in their prescribing and referral practices
- Physicians should always maintain professional autonomy, independence, and commitment to the scientific method

Professional Considerations

**Elderly Patient**
- Identify their resuscitation options (CPR or DNR), if applicable
- Check for documentation of advance directives and POA where applicable
- Identify the primary decision-maker (patients, guardian, wards-of-state, emancipated)
- Regarding capacity assessment see Pediatric Aspects of Capacity Covered, ELOM10
- Be wary of custody issues if applicable

**Terminal Ill or Palliative Patient**
- Consider the SPIKES approach to breaking bad news
- What are his/her goals of care (i.e. disease vs. symptom management)?
- Identify advance directives, POA, or SDM, if applicable (see ELOM10)
- Check for documentation of resuscitation options (CPR or DNR) and likelihood of success

**Incapable Patient**
- If not already present, perform a formal capacity assessment
- Identify if the patient has a SDM or who has their POA
- Check the patient’s chart for any Mental Health Forms (e.g. Form 1) or any forms they may have on their person (e.g. Form 42)
Guidelines for Appropriately Allocating Resources

- the physician’s primary obligation is to:
  - protect and promote the welfare and best interests of his/her patients
  - choose interventions known to be beneficial on the basis of evidence of effectiveness
  - seek the tests or treatments that will accomplish the diagnostic or therapeutic goal for the least cost
  - advocate for one’s patients, but avoid manipulating the system to gain unfair advantage for them
  - resolve conflicting claims for scarce resources justly, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures
  - inform patients of the impact of cost constraints on care, but in a sensitive way
  - seek resolution of unacceptable shortages at the level of hospital management or government

Conscientious Objection

Patients Refusing Treatment

- in accordance with the principle of autonomy, it is generally acceptable for competent patients to refuse medical interventions for themselves or others, although exceptions may occur
- if parents or SDMs make decisions that are clearly not in the “best interests” of an incapable child, physicians may have ethical grounds for administering treatment, depending on the acuity of the clinical situation
  - in high-acuity scenarios (e.g. refusing blood transfusion based on religious grounds for a child in hemorrhagic shock), physicians have a stronger obligation to act in the child’s best interests
  - in lower acuity scenarios (e.g. refusing childhood immunization in a developed nation) there is a stronger obligation to respect the autonomy of the decision-makers
  - pursuing traditional First Nations healing (in conjunction or in the place of standard biomedical therapy) is legally considered a constitutionally protected right, which can be made by a SDM, as ruled in *Hamilton Health Sciences v. DH* in 2014

Physicians Refusing to Provide Treatment

- physicians may refuse to provide treatment or discontinue relationships with patients, but must ensure these patients can access services elsewhere (e.g. a pediatrician who refuses to treat an unvaccinated child should refer the family to another practice)

Aboriginal Legal and Health Policy

- Aboriginal peoples collectively refers to original inhabitants of Canada and their descendants: First Nations, Inuit, and Métis peoples defined in the Canadian Constitution Act, 1982
  - First Nations people encompasses most of geographic Canada and constitutes many distinct communities and languages.
  - Inuit peoples refers to original inhabitants of arctic regions including Labrador, northern Quebec, Nunavut, and Northwest Territories.
  - Métis are historic people of mixed First Nations and European heritage
  - *Canadian Indian Act*, 1976, defined who is considered a “status Indian” and thus eligible for programs and services by federal and provincial agencies. Non-Status First Nations, are Aboriginals who are not a “Registered Indian” with the federal government
  - the *Daniels Decision*, 2013 Federal Court of Canada, deemed Métis and non status be considered “Indians” under Canadian Constitution Act
- Aboriginal Health Policy in Canada is made up of a complicated “patchwork” of policies, legislation and agreements between federal, provincial, municipal, and Aboriginal governments which is in a constant state of flux; reviewed by the National Collaborating Centre for Aboriginal Health (NCCAH): http://www.nccah-ccnsa.ca/en/publications.aspx?sortcode=2.8.10&publication=28
  - while some Aboriginal health services are adequate, gaps and ambiguities created by complicated policy and jurisdictions have created barriers to health equity
  - for majority of Métis, off-reserve, and non-status Indians, health services are financed through the National Health Insurance plan administered at the provincial and territorial level
  - for on-reserve First Nations and Inuit, the federal government finances and administers health services through the First Nations and Inuit Health Branch (FNIIH)
  - the *Indian Health Policy*, 1979, and *Health Transfer Policy*, 1989, transferred control to individual communities to negotiate with the FNIIH varying levels of health care responsibility to the community or council level
  - treaties and Self Government Agreements define areas of jurisdiction for federal, provincial/territorial, and Aboriginal governments
  - in general, multiple levels of authority and responsibility are involved with the general tendency towards delegating responsibility to local levels
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Law

Research Ethics
Anesthesia and Perioperative Medicine

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Acronyms .................................................. 2

Overview of Anesthesia ............................ 2
Types of Anesthesia

Pre-Operative Assessment ....................... 2
History and Physical
Pre-Operative Investigations
American Society of Anesthesiology Classification

Pre-Operative Optimization ................... 4
Medications
Hypertension
Coronary Artery Disease
Respiratory Diseases
Aspiration
Fasting Guidelines
Hematological Disorders
Endocrine Disorders
Obesity and Obstructive Sleep Apnea

Monitoring .............................................. 6

Airway Management ............................... 7
Airway Anatomy
Methods of Supporting Airways
Tracheal Intubation
Difficult Airway
Oxygen Therapy
Ventilation

Intraoperative Management .................... 12
Temperature
Heart Rate
Blood Pressure
Fluid Balance and Resuscitation
IV Fluids
Blood Products

Induction ............................................... 15
Routine Induction vs. Rapid Sequence Induction
Induction Agents
Muscle Relaxants and Reversing Agents
Analgesia

Maintenance .......................................... 20

Extubation ........................................... 20
Complications of Extubation

Regional Anesthesia .............................. 20
Epidural and Spinal Anesthesia
Peripheral Nerve Blocks

Local Anesthesia .................................... 22
Local Anesthetic Agents
Systemic Toxicity
Local Infiltration and Hematoma Blocks
Topical Anesthetics

Post-Operative Care ............................... 23
Common Post-Operative Anesthetic Complications

Pain Management ................................. 24
Acute Pain
Neuropathic Pain
Chronic Pain

Obstetrical Anesthesia ......................... 26

Pediatric Anesthesia .............................. 27

Uncommon Complications .................... 28
Malignant Hyperthermia
Abnormal Pseudocholinesterase

Appendices ......................................... 29
Difficult Tracheal Intubation in Unconscious Patient
Difficult Tracheal Intubation
Advanced Cardiac Life Support Guidelines

References ........................................... 33
# Overview of Anesthesia

anesthesia: lack of sensation/perception

## Approach to Anesthesia

<table>
<thead>
<tr>
<th>Pre-operative</th>
<th>Pre-operative/Peri-operative</th>
<th>Post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. pre-operative assessment</td>
<td>3. plan anesthetic</td>
<td>4. post-operative care</td>
</tr>
<tr>
<td>2. patient optimization</td>
<td>various types of anesthesia</td>
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<td></td>
<td>pre-medication</td>
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<td>airway management</td>
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<td>emergence</td>
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<td>extubation</td>
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</tbody>
</table>

### Types of Anesthesia

- **general**
  - general anesthesia (GA)
  - total IV anesthesia (TIVA)

- **regional**
  - spinal, epidural
  - peripheral nerve block
  - IV regional

Note that different types of anesthesia can be combined (general + regional)

## Pre-Operative Assessment

### Purpose

- identify concerns for medical and surgical management of patient
- a low for questions to help allay any fears or concerns patient and/or family may have
- arrange further investigations, consultations and treatments for patients not yet optimized
- plan and consent for anesthetic techniques

### History and Physical

#### History

- age, gender
- indication for surgery
- surgical/anesthetic Hx: previous anesthetics, any complications, previous intubations, medications, drug allergies, post-operative N/V
- FHx: abnormal anesthetic reactions, malignant hyperthermia, pseudocholinesterase deficiency (see Uncommon Complications, A28)
Pre-Operative Assessment

PMHx
- CNS: seizures, TIA/strokes, raised ICP, spinal disease, aneurysm
- CVS: angina/CAD, MI, CHF, HTN, valvular disease, dysrhythmias, peripheral vascular disease (PVD), conditions requiring endocarditis prophylaxis, exercise tolerance, CCS/NYHA class (Cardiology and Cardiac Surgery: C35 sidebar for NYHA Classification)
- respiratory: smoking, asthma, COPD, recent upper respiratory tract infection, sleep apnea
- GI: GERD, liver disease, NPO status
- renal: insufficiency, dialysis, chronic kidney disease
- hematologic: anemia, coagulopathies, blood dyscrasias
- MSK: conditions associated with difficult intubations – arthritides (e.g. rheumatoid arthritis), cervical tumours, cervical infections/abscesses, trauma to cervical spine, previous cervical spine surgery, Trisomy 21, scleroderma, conditions affecting neuromuscular junction (e.g. myasthenia gravis)
- endocrine: DM, thyroid disorders, adrenal disorders
- other: morbid obesity, pregnancy, ethanol/other drug use

Physical Exam
- weight, height, BP, pulse, respiratory rate, oxygen saturation
- focused physical exam of the CNS, CVS, and respiratory systems
- general assessment of nutrition, hydration, and mental status
- airway assessment is done to determine intubation difficulty (no single test is specific or sensitive) and ventilation difficulty
  - cervical spine stability and neck movement – upper cervical spine extension, lower cervical spine flexion ("sniffing position")
  - Mallampati classification
  - "3-2-1 rule”
    - thyromental distance (distance of lower mandible in midline from the mentum to the thyroid notch); <3 finger breadths (<6 cm) is associated with difficult intubation
    - mouth opening (<2 finger breadths is associated with difficult intubation)
    - anterior jaw subluxation (<1 finger breadth is associated with difficult intubation)
- tongue size
- dentition, dental appliances/prosthetic caps, existing chipped/loose teeth – pose aspiration risk if dislodged and must inform patients of rare possibility of damage
- nasal passage patency (if planning nasotracheal intubation)
- assess potential for difficult ventilation
- examination of anatomical sites relevant to lines and blocks
  - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
  - sites for IV, central venous pressure (CVP), and pulmonary artery (PA) catheters

Figure 1. Mallampati classification of oral opening
Pre-Operative Investigations

- routine pre-operative investigations are only necessary if there are comorbidities or certain indications

Table 1. Suggested Indications for Specific Investigations in the Pre-Operative Period

<table>
<thead>
<tr>
<th>Test</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Major surgery requiring group and screen or cross and match; chronic cardiovascular, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression; patient &gt; 1 yr of age</td>
</tr>
<tr>
<td>Sickle Cell Screen</td>
<td>Patients from geographic areas with high prevalence of sickle cell disease and/or genetically predisposed patients (hemoglobin electrophoresis if screen is positive)</td>
</tr>
<tr>
<td>INR, aPTT</td>
<td>Anticoagulant therapy, bleeding diathesis, liver disease</td>
</tr>
<tr>
<td>Electrolytes and Creatinine</td>
<td>Hypertension, renal disease, DM, pituitary or adrenal disease; vascular disease, digoxin, diuretic, or other drug therapies affecting electrolytes</td>
</tr>
<tr>
<td>Fasting Glucose Level</td>
<td>DM (repeat on day of surgery)</td>
</tr>
<tr>
<td>Pregnancy (β-hCG)</td>
<td>Women of reproductive age</td>
</tr>
<tr>
<td>ECG</td>
<td>Heart disease, DM, other risk factors for cardiac disease; subarachnoid or intracranial hemorrhage, cerebrovascular accident, head trauma</td>
</tr>
<tr>
<td>Chest Radiograph</td>
<td>Patients with new or worsening respiratory symptoms/signs</td>
</tr>
</tbody>
</table>

Guidelines to the Practice of Anesthesia Revised Edition 2013. Supplement to the Canadian Journal of Anesthesia

American Society of Anesthesiology Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- ASA 1: a healthy, fit patient
  - e.g. controlled Type 2 DM, controlled essential HTN, obesity, smoker
- ASA 2: a patient with mild systemic disease
  - e.g. stable CAD, COPD, DM, obesity
- ASA 4: a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure
- ASA 5: a moribund patient not expected to survive 24 hr without surgery
  - e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- ASA 6: declared brain dead, a patient whose organs are being removed for donation purposes
  - for emergency operations, add the letter E after classification (e.g. ASA 3E)

Pre-Operative Optimization

- in general, prior to elective surgery:
  - any fluid and/or electrolyte imbalance should be corrected
  - extent of existing comorbidities should be understood and these conditions should be optimized prior to surgery
  - medications may need adjustment

Medications

- pay particular attention to cardiac and respiratory medications, opioids and drugs with many side effects and interactions
- pre-operative medications to consider
  - prophylaxis
    - risk of GE reflux: sodium citrate and/or ranitidine and/or metoclopramide 30 min-1 h prior to surgery
    - risk of infective endocarditis, GI/GU interventions: antibiotics
    - risk of adrenal suppression: steroid coverage
    - anxiety: consider benzodiazepines
    - COPD, asthma: bronchodilators
    - CAD risk factors: nitroglycerin and β-blockers
- pre-operative medications to stop
  - oral antihyperglycemics: stop on morning of surgery
  - ACEI and angiotension receptor blockers: stop the day before the surgery
• warfarin (consider bridging with heparin), anti-platelet agents (e.g. clopidogrel), Xa inhibitor, direct thrombin inhibitors
• discuss perioperative use of ASA, NSAIDs with surgeon (+ patient’s cardiologist/internist)
• in patients undergoing non-cardiac surgery, starting or continuing low-dose aspirin in the perioperative period does not appear to protect against post-operative MI or death, but increases the risk of major bleeding
  – note: this does not apply to patients with bare metal stents or drug-eluting coronary stents
• pre-operative medications to adjust
  • insulin (consider insulin/dextrose infusion or holding dose), prednisone, bronchodilators

### Hypertension

• BP <180/110 is not an independent risk factor for perioperative cardiovascular complications
• target SBP <180 mmHg, DBP <110 mmHg
• assess for end-organ damage and treat accordingly

### Coronary Artery Disease

• ACC/AHA Guidelines (2014) recommend that at least 60 days should elapse after a MI before a non-cardiac surgery in the absence of a coronary intervention
  • this period carries an increased risk of re-infarction/death
  • if operative procedure is essential and cannot be delayed then invasive intra- and post-operative ICU monitoring is required to reduce the above risk
  • mortality with perioperative MI is 20-50%
• perioperative β-blockers
  • may decrease cardiac events and mortality (controversial, as recent data suggests stroke risk)
  • continue β-blocker if patient is routinely taking it prior to surgery
  • consider initiation of β-blocker in:
    • patients with CAD or indication for β-blocker
    • intermediate or high risk surgery, especially vascular surgery

### Respiratory Diseases

• smoking
  • adverse effects: altered mucus secretion and clearance, decreased small airway calibre, altered oxygen carrying capacity, increased airway reactivity and altered immune response
  • abstain at least 8 wk pre-operatively if possible
  • if unable, abstaining even 24 h pre-operatively has been shown to increase oxygen availability to tissues
• asthma
  • pre-operative management depends on degree of baseline asthma control
  • increased risk of bronchospasm from intubation
  • administration of short course (up to 1 wk) pre-operative corticosteroids and inhaled β2-agonists decreases the risk of bronchospasm and does not increase the risk of infection or delay wound healing
  • avoid non-selective β-blockers due to risk of bronchospasm
  • cardioselective β-blockers (metoprolol, atenolol) do not increase risk of bronchospasm in the short-term
  • delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
  • delay elective surgery by a minimum of 6 wk if patient develops URTI
• COPD
  • anesthesia, surgery (especially abdominal surgery, in particular upper abdominal surgery) and pain predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation, and respiratory failure
  • pre-operative ABG is needed for all COPD stage II and III patients to assess baseline respiratory acidosis and plan post-operative management of hypercapnea
  • cancel/delay elective surgery for acute exacerbation

### Aspiration

• increased risk of aspiration with:
  • decreased LOC
  • trauma
  • meals within 8 h
  • suspected sphincter incompetence (GERD, hiatus hernia, nasogastric tube)
  • increased abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
  • laryngeal mask vs. endotracheal tube (ETT)
• management
  • reduce gastric volume and acidity
  • delay inhibiting airway reflexes with muscular relaxants
  • employ rapid sequence induction (see Rapid Sequence Induction, A15)
Fasting Guidelines

Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists’ Society)

- 8 h after a meal that includes meat, fried or fatty foods
- 6 h after a light meal (such as toast or crackers) or after ingestion of infant formula or non-human milk
- 4 h after ingestion of breast milk
- 2 h after clear fluids (water, black coffee, tea, carbonated beverages, juice without pulp)

Hematological Disorders

- history of congenital or acquired conditions (sickle cell anemia, factor VIII deficiency, ITP, liver disease)
- evaluate hemoglobin, hematocrit and coagulation profiles when indicated (see Table 1)
- anemia
  - pre-operative treatments to increase hemoglobin (P.O. or I.V. iron supplementation, erythropoietin or pre-admission blood collection in certain populations)
- coagulopathies
  - discontinue or modify anticoagulation therapies (warfarin, clopidogrel, ASA, apixaban, dabigatran) in advance of elective surgeries
  - administration of reversal agents if necessary: vitamin K, FFP, prothrombin complex concentrate, recombinant activated factor VII

Endocrine Disorders

- diabetes mellitus
  - clarify type 1 vs. type 2
  - clarify treatment – oral anti-hyperglycemics and/or insulin
  - assess glucose control with history and HbA1c; well controlled diabetics have more stable glucose levels intraoperatively
  - end organ damage: be aware of damage to cardiovascular, renal, and nervous systems, including autonomic neuropathy
  - formulate intraoperative glucose management plan based on type (1 vs. 2), glucose control, and extent of end organ damage
- hyperthyroidism and hypothyroidism
  - can experience sudden release of thyroid hormone (thyroid storm) if not treated or well-controlled pre operatively
  - treatment: β-blockers and pre-operative prophylaxis. Hypothyroidism - may result in myxedema coma, weakness
  - adrenocortical insufficiency (Addison’s, exogenous steroid use)
  - consider intraoperative steroid supplementation

Obesity and Obstructive Sleep Apnea

- assess for co-morbid conditions in obese patient (independent risk factor for CVD, DM, OSA, cholelithiasis, HTN)
- previously undiagnosed conditions may require additional testing to characterize severity
- both obesity and OSA increase risk of difficult ventilation, intubation and post-operative respiratory complications
  - risk may be magnified with both diseases present

Monitoring

Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

- an anesthetist present: “the only indispensable monitor”
- a completed pre-anesthetic checklist: including ASA class, NPO policy, Hx and investigations
- a perioperative anesthetic record: HR and BP every 5 min, O₂ saturation, End Tidal CO₂, dose and route of drugs and fluids
- continuous monitoring: see Routine Monitors for All Cases

Routine Monitors for All Cases

- pulse oximeter, BP monitor, electrocardiography and capnography are required for general anesthesia and sedation (Ramsey Sedation Scale 4-6), agent-specific anesthetic gas monitor when inhalational anesthetic agents are used
- the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometer
Elements to Monitor

• anesthetic depth
  ■ inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing or sweating
  ■ excessive: hypotension, bradycardia
• oxygenation: pulse oximetry, fraction of inspired O2 (FiO2)
• ventilation: verify correct position of ETT, chest excursions, breath sounds, ETCO₂ analysis, end tidal inhaled anesthesia analysis
• circulation: pulse, rhythm, BP, telemetry, oximetry, CVP, pulmonary capillary wedge pressure
• temperature
• hourly urine output

Airway Management

Airway Anatomy

• resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
• pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
• glottic opening (triangular space formed between the true vocal cords) is the narrowest segment of the laryngeal opening in adults
• the glottic opening is the space through which one visualizes proper placement of the ETT
• the trachea begins at the level of the thyroid cartilage, C6, and bifurcates into the right and left main bronchi at T4-T5 (approximately the sternal angle)

Methods of Supporting Airways

1. non-definitive airway (patent airway)
   ■ jaw thrust/chin lift
   ■ oropharyngeal and nasopharyngeal airway
   ■ bag mask ventilation
   ■ LMA
2. definitive airway (patent and protected airway)
   ■ ETT
   ■ surgical airway (cricothyrotomy or tracheostomy)
### Table 2. Methods of Supporting the Airway

<table>
<thead>
<tr>
<th>Method</th>
<th>Bag and Mask</th>
<th>Laryngeal Mask Airway (LMA)</th>
<th>Endotracheal Tube (ETT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages/Indications</strong></td>
<td>Basic</td>
<td>Easy to insert</td>
<td>Indications for intubation (5 Ps)</td>
</tr>
<tr>
<td></td>
<td>Non-invasive</td>
<td>Less airway trauma/irritation</td>
<td>Patent airway</td>
</tr>
<tr>
<td></td>
<td>Readily available</td>
<td>than ETT</td>
<td>Protects against aspiration</td>
</tr>
<tr>
<td><strong>Disadvantages/Contraindications</strong></td>
<td>Risk of aspiration if decreased LOC</td>
<td>Risk of gastric aspiration</td>
<td>Insertion can be difficult</td>
</tr>
<tr>
<td></td>
<td>Cannot ensure airway patency</td>
<td>PPV &lt; 20 cmH2O needed</td>
<td>Muscle relaxant usually needed</td>
</tr>
<tr>
<td></td>
<td>Inability to deliver precise tidal volume</td>
<td>Oropharyngeal/retropharyngeal pathology or foreign body</td>
<td>Most invasive – see Complications During Laryngoscopy and Intubation, A9</td>
</tr>
<tr>
<td></td>
<td>Operator fatigue</td>
<td>Does not protect against laryngospasm or gastric aspiration</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Facilitate airway patency with jaw thrust and chin lift</td>
<td>Sizing by body weight (approx)</td>
<td>Auscultate to avoid endobronchial intubation</td>
</tr>
<tr>
<td></td>
<td>Can use oropharyngeal/nasoharyngeal airway</td>
<td>40-50 kg: 3</td>
<td>Sizing (approx):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-70 kg: 4</td>
<td>Male: 8.0-9.0 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-100 kg: 5</td>
<td>Female: 7.0-8.0 mm</td>
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<td></td>
<td></td>
<td></td>
<td>Pediatric Uncuffed (&gt; age 2)</td>
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<td></td>
<td>(age/4) + 4 mm</td>
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</tbody>
</table>

### Tracheal Intubation

#### Preparing for Intubation
- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare, and assess for potential difficulties (see Pre-Operative Assessment, A2)
- ensure equipment is available and working (test ETT cuff, check laryngoscope light and suction, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% O2 for 3-5 min or for 4-8 vital capacity breaths
- may need to suction mouth and pharynx first

#### Proper Positioning for Intubation
- align the three axes (mouth, pharynx, and larynx) to allow visualization from oral cavity to glottis
  - ’sniffing position’: flexion of lower C-spine (C5 C6), bow head forward, and extension of upper C-spine at atlanto-occipital joint (C1), nose in the air
  - contraindicated in known/suspected C-spine fracture/instability
  - laryngoscope tip placed in the epiglottic vallecula in order to visualize cord

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**Tube Insertion**

- Laryngoscopy and ETT insertion can incite a significant sympathetic response via stimulation of cranial nerves 9 and 10 due to a "foreign body reflex" in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP, and coughing.
- A malpositioned ETT is a potential hazard for the intubated patient.

  - If too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax.
  - If too shallow, may lead to accidental extubation, vocal cord trauma, or laryngeal paralysis as a result of pressure injury by the ETT cuff.
- The tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina and the proximal end of the cuff should be placed at least 2 cm below the vocal cords.
- Approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women.

**Confirmation of Tracheal Placement of ETT**

- Direct
  - Visualization of ETT passing through cords.
  - Bronchoscopic visualization of ETT in trachea.
- Indirect
  - ETCO₂ in exhaled gas measured by capnography – a mandatory method for confirming the ETT is in the airway.
  - Auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium.
  - Bilateral chest movement, condensation of water vapour in ETT visible during exhalation and no abdominal distention.
  - Refilling of reservoir bag during exhalation.
  - CXR (rarely done): Only confirms position of the tip of ETT and not that ETT is in the trachea.
- Esophageal intubation suspected when:
  - ETCO₂ zero or near zero on capnograph.
  - Abnormal sounds during assisted ventilation.
  - Impairment of chest excursion.
  - Hypoxia/cyanosis.
  - Presence of gastric contents in ETT.
  - Breath sounds heard when auscultating over epigastrium/LUQ.
  - Distention of stomach/epigastrium with ventilation.

**Complications During Laryngoscopy and Intubation**

- Dental damage.
- Laceration (lips, gums, tongue, pharynx, vallecula, esophagus).
- Laryngeal trauma.
- Esophageal or endobronchial intubation.
- Accidental extubation.
- Insufficient cuff inflation or cuff laceration: results in leaking and aspiration.
- Laryngospasm (see Extubation, A20, for definition).
- Bronchospasm.

**Difficult Airway**

- Difficulties with bag-mask ventilation, supraglottic airway, laryngoscopy, passage of ETT through the cords, infraglottic airway or surgical airway.
- Pre-operative assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures.
- If difficult airway expected, consider:
  - Awake intubation.
  - Intubating with bronchoscope, trachlight (lighted stylet), fibre optic laryngoscope, glidescope, etc.
- If intubation unsuccessful after induction:
  1. Call for help.
  2. Ventilating with 100% O₂ via bag and mask.
  3. Consider returning to spontaneous ventilation and/or waking patient.
- If bag and mask ventilation inadequate:
  1. Call for help.
  2. Attempt ventilation with oral airway.
  3. Consider/attempts LMA.
  4. Emergency invasive airway access (e.g. rigid bronchoscope, cricothyrotomy, or tracheostomy).

---

**Difficult Airway**

- **Predicting Difficult Intubation in Apparently Normal Patients**

  - **Meta-analysis.**
  - **Purpose:** To assess widely available bedside tests and widely used laryngoscopic techniques in the prediction of difficult intubations.
  - **Patients:** 35 studies encompassing 50,760 patients.
  - **Definitions:** Difficult intubation was defined usually as Cormack–Lehane grade of 3 or greater, but some authors reported the requirement of a special technique, multiple unsuccessful attempts, or a combination of these as the accepted standard for difficult intubation.
  - **Results:** The overall incidence of difficult intubation was 5.8% (95% CI 4.5–7.5%) for the overall patient population, 6.2% (95% CI 4.6–8.3%) for normal patients excluding obstetric and obese patients, 3.1% (95% CI 1.7–5.5%) for obstetric patients, and 15.8% (95% CI 14.3–17.5%) for obese patients.
  - **Mallampati score:** SN: 49% SP: 86% PLR: 3.7 NLR: 0.5, thyromental distance: SN: 20% SP: 94% PLR: 3.4 NLR: 0.8, sternomental distance: SN: 62% SP: 82% PLR: 7.7 NLR: 0.5, mouth opening: SN: 22% SP: 97% PLR: 4.0 NLR: 0.3, Wilson risk-sum: SN: 48% SP: 99% PLR: 9.8 NLR: 0.6; combination: SN: 98% SP: 87% PLR: 9 NLR: 0.6.
  - **Conclusions:** A combination of the Mallampati score and thyromental distance is the most accurate at predicting difficult intubation. The PLR (9.9) is supportive of the test as a good predictor of difficult intubation.

  - **PLR:** positive likelihood ratio; **NLR:** negative likelihood ratio; **SN:** sensitivity; **SP:** specificity.
Oxygen Therapy

- in general, the goal of oxygen therapy is to maintain arterial oxygen saturation ($\text{SaO}_2$) $>90\%$
- small decrease in saturation below $\text{SaO}_2$ of 90% corresponds to a large drop in arterial partial pressure of oxygen ($\text{PaO}_2$)
- in intubated patients, oxygen is delivered via the ETT
- in patients not intubated, there are many oxygen delivery systems available; the choice depends on oxygen requirements (FiO2) and the degree to which precise control of delivery is needed
- cyanosis can be detected at $\text{SaO}_2 <85\%$, frank cyanosis at $\text{SaO}_2 = 67\%$

Low Flow Systems

- provide $\text{O}_2$ at flows between 0-10 L/min
- acceptable if tidal volume 300-700 mL, respiratory rate (RR) $<25$, consistent ventilation pattern
- dilution of oxygen with room air results in a decrease in FiO2
- an increase in minute ventilation (tidal volume x RR) results in a decrease in FiO2
  - e.g. nasal cannula (prongs)
    - well tolerated if flow rates $<5-6$ L/min; drying of nasal mucosa at higher flows
    - nasopharynx acts as an anatomic reservoir that collects $\text{O}_2$
    - delivered oxygen concentration (FiO2) can be estimated by adding 4% for every additional litre of $\text{O}_2$ delivered
    - provides FiO2 of 24-44% at $\text{O}_2$ flow rates of 1-6 L/min

Reservoir Systems

- use a volume reservoir to accumulate oxygen during exhalation thus increasing the amount of oxygen available for the next breath
- simple face mask
  - covers patient’s nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore O2 tubing at a rate of at least 6 L/min to ensure that exhaled CO2 is flushed through the exhalation ports and not rebreathed
  - provides FiO2 of 55% at $\text{O}_2$ flow rates of 10 L/min
- non-rebreather mask
  - a reservoir bag and a series of one-way valves prevent expired gases from re-entering the bag
  - during the exhalation phase, the bag accumulates with oxygen
  - provides FiO2 of 80% at $\text{O}_2$ flow rates of 10-15 L/min

High Flow Systems

- generate flows of up to 50-60 L/min
- meet/exceed patient’s inspiratory flow requirement
- deliver consistent and predictable concentration of $\text{O}_2$
- Venturi mask
  - delivers specific FiO2 by varying the size of air entrapment
  - oxygen concentration determined by mask’s port and NOT the wall flow rate
  - enables control of gas humidity
  - FiO2 ranges from 24-50%

Ventilation

- ventilation is maintained with PPV in patients given muscle relaxants
- assisted or controlled ventilation can also be used to assist spontaneous respirations in patients not given muscle relaxants as an artificial means of supporting ventilation and oxygenation

Mechanical Ventilation

- indications for mechanical ventilation
  - apnea
  - hypoventilation/acute respiratory acidosis
  - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
  - required hyperventilation (to lower ICP)
  - deliver positive end expiratory pressure (PEEP)
  - increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation
  - airway complications
    - tracheal stenosis, laryngeal edema
  - alveolar complications
    - ventilator-induced lung injury (barotrauma, volutrauma atelectrauma), ventilator-associated pneumonia (nosocomial pneumonia), inflammation, auto PEEP, patient-ventilator asynchrony
  - cardiovascular complications
    - reduced venous return (secondary to increased intrathoracic pressure), reduced cardiac output, hypotension

Positive End Expiratory Pressure (PEEP)

- Positive pressure applied at the end of ventilation that helps to keep alveoli open, decreasing V/Q mismatch
- Used with all invasive modes of ventilation

Tracheostomy

- Tracheostomy should be considered in patients who require ventilator support for extended periods of time
- Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities
- neuromuscular complications
- muscle atrophy
- increased intracranial pressure
- metabolic
  - decreased CO₂ due to hyperventilation
- alkalemia with over correction of chronic hypercarbia

### Ventilator Strategies
- mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation
- hypoxemic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

### Modes of Ventilation
- assist-control ventilation (ACV) or volume control (VC)
  - every breath is delivered with a pre-set tidal volume and rate or minute ventilation
  - extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath
- pressure control ventilation (PCV)
  - a minimum frequency is set and patient may trigger additional breaths above the ventilator
  - all breaths delivered at a preset constant inspiratory pressure
- synchronous intermittent mandatory ventilation (SIMV)
  - ventilator provides controlled breaths (either at a set volume or pressure depending on whether in VC or PCV, respectively)
  - patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths
- pressure support ventilation (PSV)
  - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
  - useful for weaning off ventilator
- high-frequency oscillatory ventilation (HFOV)
  - high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes
  - used commonly in neonatal and pediatric respiratory failure
  - occasionally used in adults when conventional mechanical ventilation is failing
- non-invasive positive pressure ventilation (NPPV)
  - achieved without intubation by using a nasal or face mask
  - BiPAP: increased pressure (like PSV) on inspiration and lower constant pressure on expiration (i.e. PEEP)
  - CPAP: delivers constant pressure on both inspiration and expiration

### Table 3. Causes of Abnormal End Tidal CO₂ Levels

<table>
<thead>
<tr>
<th>Hypocapnea (Decreased CO₂)</th>
<th>Hypercapnea (Increased CO₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Hypothermia (decreased metabolic rate)</td>
<td>Hyperthermia and other hypermetabolic states</td>
</tr>
<tr>
<td>Decreased pulmonary blood flow (decreased cardiac output)</td>
<td>Improved pulmonary blood flow after resuscitation or hypotension</td>
</tr>
<tr>
<td><strong>Technical issues</strong></td>
<td><strong>Technical issues</strong></td>
</tr>
<tr>
<td>Incorrect placement of sampling catheter</td>
<td>Water in capnography device</td>
</tr>
<tr>
<td>Inadequate sampling volume</td>
<td>Anesthetic breathing circuit error</td>
</tr>
<tr>
<td>V/Q mismatch</td>
<td>Inadequate fresh gas flow</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Rebreathing</td>
</tr>
<tr>
<td>Incipient pulmonary edema</td>
<td>Exhausted soda lime</td>
</tr>
<tr>
<td>Air embolism</td>
<td>Faulty circuit absorber valves</td>
</tr>
<tr>
<td></td>
<td>Low bicarbonate</td>
</tr>
</tbody>
</table>

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### Toronto Notes 2018

- Monitoring Ventilatory Therapy
  - Pulse oximetry, end-tidal CO₂ concentration
  - Regular arterial blood gases
  - Assess tolerance regularly

- Patients who develop a pneumothorax while on mechanical ventilation require a chest tube

- Causes of Intraoperative Hypoxemia
  - Inadequate oxygen supply e.g. breathing system disconnection, obs ructed or malpositioned ETT, leaks in the anesthetic machine, loss of oxygen supply
  - Hypoventilation
  - Ventilation-perfusion inequalities e.g. atelectasis, pneumonia, pulmonary edema, pneumothorax
  - Reduction in oxygen carrying capacity e.g. anemia, carbon monoxide poisoning, methemoglobinemia, hemoglobinopathy
  - Leftward shift of the hemoglobin-oxygen saturation curve e.g. hypothermia, decreased 2,3-BPG, alkalosis, hypocarbia, carbon monoxide poisoning

- Right-to-left cardiac shunt

---

### A Comparison of Four Methods of Weaning Patients from Mechanical Ventilation

**NEJM** 1995;332:345-350

**Study:** Prospective, randomized, multicentre trial.

**Participants:** 130 of 546 patients who received mechanical ventilation and were considered ready for weaning but had respiratory distress during a 2 h trial of spontaneous breathing.

**Intervention:** One of four weaning techniques following standardized protocol.

**Outcome:** Median duration of weaning.

**Results:** The median duration of weaning for intermittent mandatory ventilation, pressure-support ventilation, intermittent (multiple) trials of spontaneous breathing, and once-daily trial of spontaneous breathing was 5 d, 4 d, and 3 d, respectively. The rate of successful weaning was higher with once-daily trial of spontaneous breathing than with intermittent mandatory ventilation (rate ratio 2.83; 95% CI 1.36-5.89; p<0.006) or pressure-support ventilation (ratio 2.05; 95% CI 1.04-4.04; p<0.04). There was no significant difference in the rate of success between once-daily trials and multiple trials of spontaneous breathing.

**Conclusions:** Once-daily or multiple trials of spontaneous breathing led to extubation more quickly than intermittent mandatory or pressure-support ventilation.

---
Intraoperative Management

Temperature

Causes of Hypothermia (<36.0°C)
Intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
- OR environment (cold room, IV fluids, instruments)
- open wound
- prevent with forced air warming blanket and warmed IV fluids

Causes of Hyperthermia (>37.5-38.3°C)
- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- malignant hyperthermia (see Uncommon Complications, A28)
- over-zealous warming efforts

Heart Rate

Cardiac Arrest
- pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-shockable rhythms
  - shockable: ventricular fibrillation (VF) and ventricular tachycardia (VT)
  - non-shockable: asystole and pulseless electrical activity (PEA)
- for VF/VT, key to survival is good early CPR and defibrillation
- for asystole/PEA, key to survival is good early CPR and exclusion of all reversible causes
- reversible causes of PEA arrest (5 Hs and 5 Ts)
  - 5 Hs: hypothermia, hypovolemia, hypoxia, hydrogen ions (acidosis), hyp/hyperkalemia
  - 5 Ts: tamponade (cardiac), thrombosis (pulmonary), thrombosis (coronary), tension pneumothorax, toxins (overdose/poisoning)
- when a patient sustains a cardiac arrest during anesthesia, it is important to remember that there are other causes on top the Hs and Ts to consider (i.e. local anesthetic systemic toxicity (LAST), excessive anesthetic dosing and others)
- for management of cardiac arrest, see ACLS Guidelines (Figure 16), A31

Intraoperative Tachycardia
- tachycardia = HR >150 bpm; divided into narrow complex supraventricular tachycardias (SVT) or wide complex tachycardias
- SVT: sinus tachycardia, atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
- wide complex tachycardia: VT, SVT with aberrant conduction
- causes of sinus tachycardia
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis
  - drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium) and withdrawal
  - Addisonian crisis, hypoglycemia, transfusion reaction, malignant hyperthermia
- for management of tachycardia, see ACLS Guidelines (Figure 17), A32

Intraoperative Bradycardia
- bradycardia = HR <50 bpm; most concerning are 2nd degree (Mobitz type II) and 3rd degree heart block, which can both degenerate into asystole
- causes of sinus bradycardia
  - increased parasympathetic tone vs. decreased sympathetic tone
  - must rule out hypoxemia
  - arrhythmias (see Cardiology and Cardiac Surgery, C16)
  - baroreceptor reflex due to increased ICP or increased BP
  - vagal reflex (oculocardiac reflex, carotid sinus reflex, airway manipulation)
  - drugs (e.g. Sch, opioids, edrophonium, neostigmine, halothane, digoxin, β-blockers)
  - high spinal/epidural anesthesia
- for management of bradycardia, see ACLS Guidelines (Figure 18), A32

Impact of Hypothermia (<36°C)
- increased risk of wound infections due to impaired immune function
- increases the period of hospitalization by delaying healing
- reduces platelet function and impairs activation of coagulation cascade increasing blood loss and transfusion requirements
- triples the incidence of VT and morbidity cardiac events
- decreases the metabolism of anesthetic agents prolonging post-operative recovery
Blood Pressure

Causes of Intraoperative Hypotension/Shock

- shock condition characterized by inability of cardiovascular system to maintain adequate end-organ perfusion and delivery of oxygen to tissues
  a) hypovolemic/hemorrhagic shock
     - most common form of shock, due to decrease in intravascular volume
  b) obstructive shock
     - obstruction of blood into or out of the heart
     - increased JVP, distended neck veins, increased systemic vascular resistance, insufficient cardiac output (CO)
     - e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism (and other emboli – i.e. fat, air)
  c) cardiogenic shock
     - increased JVP, distended neck veins, increased systemic vascular resistance, decreased CO
     - e.g. myocardial dysfunction, dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction
  d) septic shock
     - see Infectious Diseases, ID21
  e) spinal/neurogenic shock
     - decreased sympathetic tone
     - hypotension without tachycardia or peripheral vasoconstriction (warm skin)
  f) anaphylactic shock
     - see Emergency Medicine, ER28
  g) drugs
     - vasodilators, high spinal anesthetic interfering with sympathetic outflow
  h) other
     - transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome
     - see Hematology, H52 and Endocrinology, E33

Causes of Intraoperative Hypertension

- inadequate anesthesia causing pain and anxiety
- pre-existing HTN, coarctation, or preeclampsia
- hypoxemia/hypercarbia
- hypervolemia
- increased intracranial pressure
- full bladder
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine) and withdrawal
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome (see Psychiatry, PS46), thyroid storm, pheochromocytoma (see Endocrinology, E25)

Fluid Balance and Resuscitation

- total requirement = maintenance + deficit + ongoing loss
- in surgical settings this formula must take into account multiple factors including pre-operative fasting/decreased fluid intake, increased losses during or before surgery, fluid shifting during surgery, fluids given with blood products and medications

What is the Maintenance?

- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (beware of renal failure)
  - 4:2:1 rule to calculate maintenance requirements (applies to crystalloids only)
    - 4 mL/kg/h first 10 kg
    - 2 mL/kg/h second 10 kg
    - 1 mL/kg/h for remaining weight >20 kg
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation, and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres, and CHF
- maintenance electrolytes
  - Na\(^+\): 3 mEq/kg/d
  - K\(^+\): 1 mEq/kg/d
- 50 kg patient maintenance requirements
  - fluid = 40 + 20 + 30 = 90 mL/h = 2160 mL/d = 2.16 L/d
  - Na\(^+\) = 150 mEq/d (therefore 150 mEq / 2.16 L/d = 69 mEq/L)
  - K\(^+\) = 50 mEq/d (therefore 50 mEq / 2.16 L/d = 23 mEq/L)
- above patients requirements roughly met with 2/3 D5W, 1/3 NS
  - 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per litre
What is the Deficit?
- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total Na⁺ content determines ECF volume, [Na⁺] determines ICF volume
- hypovolemia due to volume contraction
  - extra-renal Na⁺ loss
    - GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - skin/respiratory: insensible losses (fever), sweating, burns
    - vascular: hemorrhage
    - renal Na⁺ and H₂O loss
    - diuretics
    - osmotic diuresis
    - hypoaldosteronism
    - salt-wasting nephropathies
    - renal H₂O loss
    - diabetes insipidus (central or nephrogenic)
  - hypovolemia with normal or expanded ECF volume
  - decreased CO
  - redistribution
    - hypovolemic: cirrhosis, nephrotic syndrome
    - capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
  - replace water and electrolytes as determined by patient's needs
- with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

Table 4. Signs and Symptoms of Dehydration

<table>
<thead>
<tr>
<th>Percentage of Body Water Loss</th>
<th>Severity</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>Mild</td>
<td>Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating</td>
</tr>
<tr>
<td>6%</td>
<td>Moderate</td>
<td>Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemoconcentration, apathy</td>
</tr>
<tr>
<td>9%</td>
<td>Severe</td>
<td>Profound oliguria or anuria and compromised CNS function with or without altered sensorium</td>
</tr>
</tbody>
</table>

What are the Ongoing Losses?
- losses from Foley catheter, NG, surgical drains
- third-spacing (other than ECF, ICF)
  - pleura, GI, retroperitoneal, peritoneal
  - evaporation via exposed viscera, burns
- blood loss
- ongoing loss due to surgical exposure and evaporative losses

IV Fluids
- replacement fluids include crystalloid and colloid solutions
- IV fluids improve perfusion but NOT O₂ carrying capacity of blood

Initial Distribution of IV Fluids
- H₂O follows ions/molecules to their respective compartments

Crystalloid Infusion
- salt containing solutions that distribute only within ECF
- maintain euvolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement)
- if large volumes are to be given, use balanced fluids such as Ringer’s lactate or Plasmalyte®, as too much normal saline (NS) may lead to hyperchloremic metabolic acidosis

Colloid Infusion (see Blood Products, Hematology, H52)
- includes protein colloids (albumin and gelatin solutions) and non-protein colloids (dextran and starches e.g. hydroxethyl starch [HES])
- distributes within intravascular volume
- 1:1 ratio (infusion:blood loss) only in terms of replacing intravascular volume
- the use of HES solutions is controversial because of recent RCTs and meta-analyses highlighting their renal (especially in septic patients) and coagulopathic side effects, as well as a lack of specific indications for their use
- colloids are being used based on mechanistic and experimental evidence but there is a paucity of definitive studies investigating their safety and efficacy; routine use of colloids should be avoided
### Table 5. IV Fluid Solutions

<table>
<thead>
<tr>
<th></th>
<th>ECF</th>
<th>Ringer’s Lactate</th>
<th>0.9% NS</th>
<th>0 45% NS in D5W</th>
<th>D5W</th>
<th>2/3 D5W + 1/3 NS</th>
<th>Plasmalyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEq/L</td>
<td>Na+</td>
<td>142</td>
<td>130</td>
<td>154</td>
<td>77</td>
<td>-</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>K+</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Ca2+</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mg2+</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Cl–</td>
<td>103</td>
<td>109</td>
<td>154</td>
<td>77</td>
<td>-</td>
<td>51</td>
</tr>
<tr>
<td>mOsm/L</td>
<td></td>
<td>280-310</td>
<td>273</td>
<td>308</td>
<td>154</td>
<td>252</td>
<td>269</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td>7.4</td>
<td>6.5</td>
<td>5.0</td>
<td>4.5</td>
<td>4.0</td>
<td>4.3</td>
</tr>
</tbody>
</table>

*Converted from lactate

### Table 6. Colloid HES Solutions

<table>
<thead>
<tr>
<th></th>
<th>Concentration</th>
<th>Plasma Volume Expansion</th>
<th>Duration (h)</th>
<th>Maximum Daily Dose (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluven®</td>
<td>6%</td>
<td>1:1</td>
<td>4-6</td>
<td>33-50</td>
</tr>
<tr>
<td>Pentaspan®</td>
<td>10%</td>
<td>1:1.2-1.5</td>
<td>18-24</td>
<td>28</td>
</tr>
</tbody>
</table>

### Blood Products

- see Hematology, H52

### Induction

#### Routine Induction vs. Rapid Sequence Induction

- Routine induction is the standard in general anesthesia, however a RSI is indicated in patients at risk of regurgitation/aspiration (see Aspiration, A5)
- RSI uses pre-determined doses of induction drugs given in rapid succession to minimize the time patient is at risk for aspiration (i.e. from the time when they are asleep without an ETT until the time when the ETT is in and the cuff inflated)

#### Table 7. Comparison of Routine Induction vs. RSI

<table>
<thead>
<tr>
<th>Steps</th>
<th>Routine Induction</th>
<th>RSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equipment Preparation</td>
<td>Check equipment, drugs, suction, monitor; prepare an alternative laryngoscope blade and a second ETT tube one size smaller, suction on</td>
<td></td>
</tr>
<tr>
<td>2. Pre-Oxygenation/ Denitrogenation</td>
<td>100% O₂ for 3 min or 4-8 vital capacity breaths</td>
<td></td>
</tr>
<tr>
<td>3. Pre-Treatment Agents</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy</td>
<td></td>
</tr>
<tr>
<td>4. Induction Agents</td>
<td>Use IV or inhalation induction agent of choice</td>
<td></td>
</tr>
<tr>
<td>5. Muscle Relaxants</td>
<td>Muscle relaxant of choice given after the onset of the induction agent</td>
<td></td>
</tr>
<tr>
<td>6. Ventilation</td>
<td>Bag-mask ventilation</td>
<td></td>
</tr>
<tr>
<td>7. Cricoid Pressure</td>
<td>Posterior pressure on thyroid cartilage to improve view of vocal cords as indicated</td>
<td></td>
</tr>
<tr>
<td>8. Intubation</td>
<td>Intubate, inflate cuff, confirm ETT position</td>
<td></td>
</tr>
<tr>
<td>9. Secure Machines</td>
<td>Secure ETT, and begin manual/machine ventilation</td>
<td></td>
</tr>
</tbody>
</table>

#### Calculating Acceptable Blood Losses (ABL)

- Blood volume
  - term infant 80 mL/kg
  - adult male 70 mL/kg
  - adult female 60 mL/kg
- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion, (e.g. 70 g/L for a person with Hb(i) = 150 g/L)
- Hb(i) = 70 g/L
- Calculate
  \[ ABL = \frac{Hb(i) - Hb(f)}{EBV} \]
  \[ = \frac{150 - 70}{4900} \]
  \[ = 2613 mL \]
- Therefore in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost

#### Transfusion Infection Risks

<table>
<thead>
<tr>
<th>Virus</th>
<th>Risk per 1 unit pRBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 21 million</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1 in 13 million</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1 in 7.5 million</td>
</tr>
<tr>
<td>HTLV</td>
<td>1 in 1-1.3 million</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>1 in 40,000 from platelets and 1 in 250,000 from RBC</td>
</tr>
<tr>
<td>Bacterial Sepsis</td>
<td></td>
</tr>
<tr>
<td>West Nile virus</td>
<td>No cases since 2003</td>
</tr>
</tbody>
</table>

Induction Agents

- induction in general anesthesia may be achieved with intravenous agents, volatile inhalation agents, or both

Intravenous Agents
- see Table 8
- IV induction agents are non-opioid drugs used to provide hypnosis, amnesia and blunt reflexes
- these are initially used to draw the patient into the maintenance phase of general anesthesia rapidly, smoothly and with minimal adverse effects
- examples include propofol, sodium thiopental (not available in North America), or ketamine
- a continuous propofol infusion may also be used for the maintenance phase of GA

Table 8. Intravenous Induction Agents

<table>
<thead>
<tr>
<th>Propofol (Diprivan*)</th>
<th>Thiopental (sodium thiopental, sodium thiompentone)*</th>
<th>Ketamine (Ketalar®, Ketaject*)</th>
<th>Benzodiazepines (midazolam [Versed®], diazepam [Valium®], lorazepam [Ativan®])</th>
<th>Etomidate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Alkylphenol – hypnotic</td>
<td>Ultra-short acting thiobarbiturate – hypnotic</td>
<td>Phencyclidine (PCP) derivative – dissociative</td>
<td>Benzodiazepines – anxiolytic</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Inhibitory at GABA synapse</td>
<td>Inhibitory at GABA synapse</td>
<td>May act on NMDA (antagonistically), opiate, and other receptors</td>
<td>Imidazole derivative - hypnotic</td>
</tr>
<tr>
<td></td>
<td>Decreased cerebral metabolism and blood flow, decreased CPP, decreased CO, decreased BP, and decreased SV</td>
<td>Decreased cerebral metabolism and blood flow, decreased CPP, decreased CO, decreased BP, and decreased SV</td>
<td>Increased HR, increased BP, increased SV, increased coronary flow, increased myocardial O2 uptake CNS and respiratory depression, bronchial smooth muscle relaxation</td>
<td>Decreases concentration of GABA required to activate receptor CNS depression Minimal cardiac or respiratory depression</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Induction Maintenance</td>
<td>Induction Control of convulsive states, obstetric patients</td>
<td>Major trauma, hypovolemia, obstetric bleeding, severe asthma because sympathomimetic</td>
<td>Used for sedation, amnesia, and anxiolysis</td>
</tr>
<tr>
<td></td>
<td>Total intravenous anesthesia (TIVA)</td>
<td></td>
<td></td>
<td>Induction Poor cardiac function, severe valve lesions, uncontrolled hypertension</td>
</tr>
<tr>
<td><strong>Caution</strong></td>
<td>Patients who cannot tolerate sudden decreased BP (e.g fixed cardiac output or shock)</td>
<td>Allergy to barbiturates Uncontrolled hypotension, shock, cardiac failure Postoperative bleeding, severe asthama, liver disease, status asthmaticus, myxedema</td>
<td>Ketamine allergy TCA medication (interaction causes HTN and dysrhythmias) History of psychosis Patients who cannot tolerate HTN (e.g. CHF, increased ICP, aneurysm)</td>
<td>Marked respiratory depression HTN-history of psychosis Poor cardiac function, severe valve lesions, uncontrolled hypertension</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>IV induction: 2.5-3.0 mg/kg (less with opioids) Unconscious &lt; 1 min Lasts 4-6 min t1/2 = 55 min Decreased post-operative sedation, recovery time, N/V</td>
<td>IV induction: 3-5 mg/kg Unconscious about 30 s Lasts 5 min Accumulation with repeat dosing – not for maintenance t1/2 = 5-10 h Post-operative sedation lasts hours</td>
<td>IV induction 1-2 mg/kg Dissociation in 15 s, analgesia amnesia, and unconsciousness in 45-60 s Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 h t1/2 = ~ 3 h</td>
<td>Onset less than 5 min if given IV Duration of action long but variable/somewhat unpredictable IV induction 0.3 mg/kg Onset 30-60 seconds Lasts 4-8 minutes</td>
</tr>
<tr>
<td><strong>Special Considerations</strong></td>
<td>0-30% decreased BP due to vasodilatation Reduce burning at IV site by mixing with lidocaine Combining with rocuronium causes precipitates to form</td>
<td>High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions) Pretreat with glycopyrrolate to decrease salivation</td>
<td>Antagonist: flumazenil (Anexate®) competitive inhibitor, 0.2 mg IV over 1 s, repeat with 0.1 mg/mn (max of 2 mg), t1/2 of 60 min Midazolam also has amnestic (antegrade) effect and decreased risk of thrombophlebitis</td>
<td>Adrenal suppression after first dose, cannot repeat dose or use as infusion Myoclonic movements during induction</td>
</tr>
</tbody>
</table>

*As of 2011, Thiopental has been discontinued from production for North America

Volatile Inhalational Agents
- examples include sevoflurane, desflurane, isoflurane, enflurane, halothane, and nitrous oxide
- see Table 9
Table 9. Volatile Inhalational Agents

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane</th>
<th>Desflurane</th>
<th>Isoflurane</th>
<th>Enflurane</th>
<th>Halothane</th>
<th>Nitrous oxide (N2O)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC (% gas in O2)</td>
<td>2.0</td>
<td>6.0</td>
<td>1.2</td>
<td>1.7</td>
<td>0.8</td>
<td>104</td>
</tr>
<tr>
<td>CNS</td>
<td>Increased ICP</td>
<td>Increased ICP</td>
<td>Decreased cerebral metabolic rate</td>
<td>Increased ICP</td>
<td>Increased ICP and cerebral blood flow</td>
<td>—</td>
</tr>
<tr>
<td>Resp</td>
<td>Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory CO2 reflexes, bronchodilation</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CVS</td>
<td>Less decrease of contractility, stable HR</td>
<td>Tachycardia with rapid increase in concentration</td>
<td>Decreased BP and CO, increased HR, theoretical chance of coronary steal**</td>
<td>Stable HR, decreased contractility</td>
<td>Decreased BP, CO, HR, and conduction</td>
<td>Sensitizes myocardium to epinephrine-induced arrhythmias</td>
</tr>
<tr>
<td>MSK</td>
<td>Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Properties and Adverse Effects of N2O

Due to its high MAC, nitrous oxide is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only.

Second Gas Effect

Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen and ET cuff will markedly enlarge if N2O is administered. Diffusion hypoxia: during anesthesia, the washout of N2O from body stores into alveoli can dilute the alveolar O2, creating a hypoxic mixture if the original O2 is low.

**Coronary steal: isoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion (e.g. stents, atherosclerosis).

MAC (Minimum Alveolar Concentration)

- The alveolar concentration of a volatile anesthetic at one atmosphere (atm) of pressure that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision).
- Potency of inhalational agents is compared using MAC.
- 1.2-1.3 times MAC will often ablate response to stimuli in the general population.
- MAC values are roughly additive when mixing N2O with another volatile agent; however, this only applies to movement, not other effects such as BP changes (e.g. 0.5 MAC of a potent agent + 0.5 MAC of N2O = 1 MAC of potent agent).
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation, generally 1.3 MAC.
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli, generally 1.5 MAC.
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command, generally 0.3-0.4 of the usual MAC.

**Muscle Relaxants and Reversing Agents**

![Figure 8: Review of anatomy and physiology of the neuromuscular junction (NMJ)](image)}
Muscle Relaxants

- Two types of muscle relaxants: succinylcholine (SCh)
  1. Depolarizing muscle relaxants: succinylcholine (SCh)
  2. Non-depolarizing muscle relaxants: rocuronium, mivacurium, vecuronium, cistronicum, pancuronium
- Block nicotinic cholinergic receptors in NMJ
- Provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- Never use muscle relaxants without adequate preparation and equipment to maintain airway and ventilation

Muscle relaxation produces the following desired effects:
  1. Facilitates intubation
  2. Assists with mechanical ventilation
  3. Prevents muscle stretch reflex and decreases muscle tone
  4. Allows access to the surgical field (intracavitary surgery)

Nerve stimulator (i.e. train of four) is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade

See Tables 10 and 11, for more details including mechanism of action

Table 10. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubating Dose (mg/kg)</td>
<td>1-1.5</td>
</tr>
<tr>
<td>Onset</td>
<td>30-60 s – rapid (fastest of all muscle relaxants)</td>
</tr>
<tr>
<td>Duration</td>
<td>3-5 min – short (no reversing agent for SCh)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>SCh is hydrolyzed by plasma cholinesterase (pseudocholinesterase), found only in plasma and not at the NMJ</td>
</tr>
<tr>
<td>Indications</td>
<td>Assist intubation</td>
</tr>
<tr>
<td></td>
<td>Increased risk of aspiration (need rapid paralysis and airway control (e.g. full stomach), hiatus hernia, obesity, pregnancy, trauma)</td>
</tr>
<tr>
<td></td>
<td>Short procedures</td>
</tr>
<tr>
<td></td>
<td>Electroconvulsive therapy (ECT)</td>
</tr>
<tr>
<td></td>
<td>Laryngospasm</td>
</tr>
<tr>
<td>Side Effects</td>
<td>1. SCh also stimulates muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors; may cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children)</td>
</tr>
<tr>
<td></td>
<td>2. Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors</td>
</tr>
<tr>
<td></td>
<td>Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells</td>
</tr>
<tr>
<td></td>
<td>Patients at risk</td>
</tr>
<tr>
<td></td>
<td>3rd degree burns 24 h-6 mo after injury</td>
</tr>
<tr>
<td></td>
<td>Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy)</td>
</tr>
<tr>
<td></td>
<td>Severe intra-abdominal infections</td>
</tr>
<tr>
<td></td>
<td>Severe closed head injury</td>
</tr>
<tr>
<td></td>
<td>Upper motor neuron lesions</td>
</tr>
<tr>
<td></td>
<td>3. Can trigger MH (see Malignant Hyperthermia, A28)</td>
</tr>
<tr>
<td></td>
<td>4. Increased ICP/intracerebral pressure/intragastrik pressure (no increased risk of aspiration if competent lower esophageal sphincter)</td>
</tr>
<tr>
<td></td>
<td>5. Fasciculations, post-operative myalgia – may be minimized if small dose of non-depolarizing agent given before SCh administration</td>
</tr>
</tbody>
</table>

Contraindications

Absolute
- Known hypersensitivity or allergy, positive history of malignant hyperthermia, myotonia (m. congenita, m. dystrophica, paramyotonia congenital), high risk for hyperkalemic response

Relative
- Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury

Plasma Cholinesterase

Plasma cholinesterase is produced by the liver and metabolizes SCh, ester local anesthetics, and mivacurium. A prolonged duration of blockade by SCh occurs with:
(a) Decreased quantity of plasma cholinesterase, e.g. liver disease, pregnancy, malignancy, malnutrition, collagen vascular disease, hypothyroidism
(b) Abnormal quality of plasma cholinesterase, e.g. normal levels but impaired activity of enzymes, genetically inherited
Table 11. Non-Depolarizing Muscle Relaxants (Competitive)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Competitive blockade of postsynaptic ACh receptors preventing depolarization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification</td>
<td>Intubating Dose (mg/kg)</td>
</tr>
<tr>
<td>Mivacuronium</td>
<td>0.2</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6-1.0</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.2</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Side Effects

- **Histamine Release**: Yes, No, No, No, No
- **Other**: —, —, —, —, Tachycardia
- **Cons derations**: Increased duration of action in renal or liver failure, Quick onset of rocuronium allows its use in rapid sequence induction, Cisatracurium is good for patients with renal or hepatic insufficiency, Pancuronium if increased HR and BP desired

Reversing Agents

- sugammadex is a selective relaxant binding agent
- neostigmine, pyridostigmine, edrophonium are acetylcholinesterase inhibitors
- administer reversal agents when there has been some recovery of blockade (i.e. muscle twitch)
- can only reverse the effect of non-depolarizing muscle relaxants
- anticholinergic agents (e.g. atropine, glycopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation, increased peristalsis and bronchoconstriction)

Table 12. Reversal Agents for Non-Depolarizing Relaxants

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pyridostigmine</th>
<th>Neostigmine</th>
<th>Edrophonium</th>
<th>Sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Fast</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>(acetylcholinesterase inhibitors) Inhibits enzymatic degradation of ACh, increases ACh at nicotinic and muscarinic receptors, displaces non-depolarizing muscle relaxants</td>
<td>Muscarinic effects of reversing agents include unwanted bradycardia, salivation, and increased bowel peristalsis*</td>
<td>Encapsulates and inactivates rocuronium and vecuronium → ↓ amount of agent available to bind to receptors in NMJ</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>0.1-0.4 mg/kg</td>
<td>0.04-0.08 mg/kg</td>
<td>0.5-1 mg/kg</td>
<td>2-16 mg/kg</td>
</tr>
<tr>
<td>Recommended Anticholinergic</td>
<td>Glycopyrrolate</td>
<td>Glycopyrrolate</td>
<td>Atropine</td>
<td>NA</td>
</tr>
<tr>
<td>Dose of Anticholinergic (per mg)</td>
<td>0.05 mg</td>
<td>0.2 mg</td>
<td>0.014 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Atropine and glycopyrrolate are anticholinergic agents administered during the administration of reversal agents to minimize muscarinic effects

Analgesia

- options include opioids (e.g. morphine, fentanyl, hydromorphone), NSAIDS, acetaminophen, ketamine, gabapentin, local, and regional anesthetic (see Table 15, A25)
Maintenance

- general anesthesia is maintained using volatile inhalation agents and/or IV agents (i.e. propofol infusion)
- analgesia (usually IV opioids) and muscle relaxants are also given as needed

Extubation

- criteria: patient must no longer have intubation requirements
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- general guidelines
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - allow ventilation (spontaneous or controlled) with 100% O₂ for 3-5 min
  - suction secretions from pharynx, deflate cuff, remove ETT on inspiration (vocal cords abducted)
  - ensure patient is breathing adequately after extubation
  - ensure face mask for O₂ delivery available
  - proper positioning of patient during transfer to recovery room (supine, head elevated)

Complications of Extubation

- early extubation: aspiration, laryngospasm
- late extubation: transient vocal cord incompetence, edema (glottic, subglottic), pharyngitis, tracheitis

Laryngospasm

- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (by oropharyngeal secretions, blood, extubation)
- causes partial or total airway obstruction
- more likely to occur in semi-conscious patients
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: apply sustained positive pressure with bag-mask ventilation with 100% oxygen, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose succinylcholine (approximately 0.25 mg/kg) and reintubation if hypoxia develops

Regional Anesthesia

- local anesthetic agent (LA) applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) for the purpose of reducing or preventing impulse transmission
- no CNS depression (unless overdose of local anesthetic); patient remains conscious
- regional anesthetic techniques categorized as follows:
  - epidural and spinal anesthesia (neuraxial anesthesia)
  - peripheral nerve blocks
  - IV regional anesthesia (e.g. Bier block)

Patient Preparation

- sedation may be indicated before block
- monitoring should be as extensive as for general anesthesia

Epidural and Spinal Anesthesia

- most useful for surgeries performed below level of umbilicus

Anatomy of Spinal/Epidural Area

- spinal cord extends to L2, dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated (outside to inside)
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

Benefits of Regional Anesthesia

- Reduced perioperative pulmonary complications
- Reduced perioperative analgesia requirements
- Decreased PONV
- Reduced perioperative blood loss
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE
- Shorter recovery and improved rehabilitation
- Pain blockade with preserved motor function

Landmarking Epidural/Spinal Anesthesia

- Spinal processes should be maximally flexed
- L₄ spinous processes found between iliac crests
- T₇ landmark at the tip of the scapula

Classic Presentation of Dural Puncture Headache

- Onset 6 h-3 d after dural puncture
- Postural component (worse when sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia
Table 13. Epidural vs. Spinal Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deposition Site</strong></td>
<td>LA injected in epidural space (space between ligamentum flavum and dura) Initial blockade is at the spinal roots followed by some degree of spinal cord anesthesia as LA diffuses into the subarachnoid space through the dura</td>
<td>LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Significant blockade requires 10-15 min; slower onset of side effects</td>
<td>Rapid blockade (onset in 2-5 min)</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>Effectiveness of blockade can be variable</td>
<td>Very effective blockade</td>
</tr>
<tr>
<td><strong>Difficulty</strong></td>
<td>Technically more difficult; greater failure rate</td>
<td>Easier to perform due to visual confirmation of CSF flow</td>
</tr>
<tr>
<td><strong>Patient Positioning</strong></td>
<td>Position of patient not as important; specific gravity not an issue</td>
<td>Hyperbaric LA solution – position of patient important</td>
</tr>
<tr>
<td><strong>Specific Gravity/ Spread</strong></td>
<td>Epidural injections spread throughout the potential space; specific gravity of solution does not affect spread</td>
<td>LA solution may be made hyperbaric (of greater specific gravity than the cerebrospinal fluid by mixing with 10% dextrose, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space)</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>Larger volume/dose of LA (usually &gt; toxic IV dose)</td>
<td>Smaller dose of LA required (usually &lt; toxic IV dose)</td>
</tr>
<tr>
<td><strong>Continuous Infusion</strong></td>
<td>Use of catheter allows for continuous infusion or repeat injections</td>
<td>None</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Failure of technique, Hypotension, Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), e.g. “high spinal” Epidural or subarachnoid hematoma Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications) Systemic toxicity of LA (accidental intravenous) Catheter complications (shearing, kinking, vascular or subarachnoid placement) Infection Dural puncture</td>
<td>Failure of technique, Hypotension, Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), e.g. “high spinal” Epidural or subarachnoid hematoma Post-spinal headache (CSF leak) Transient paresthesias Spinal cord trauma, infection</td>
</tr>
<tr>
<td><strong>Combined Spinal- Epidural</strong></td>
<td>Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter</td>
<td></td>
</tr>
</tbody>
</table>

Contraindications to Spinal/Epidural Anesthesia

- **absolute contraindications**
  - lack of resuscitative drugs/equipment
  - patient refusal
  - allergy to local anesthetic
  - infection at puncture site or underlying tissues
  - coagulopathies/bleeding diathesis
  - raised ICP
  - sepsis/bacteremia
  - severe hypovolemia
  - cardiac lesion with fixed output states (severe mitral/aortic stenosis)
  - lack of IV access
- **relative contraindications**
  - pre-existing neurological disease (demyelinating lesions)
  - previous spinal surgery, severe spinal deformity
  - prolonged surgery
  - major blood loss or maneuvers that can compromise reaction
Peripheral Nerve Blocks

- deposition of LA around the target nerve or plexus
- ultrasound guidance and peripheral nerve stimulation (needle will stimulate target nerve/plexus) may be used to guide needle to target nerve while avoiding neural trauma or intraneural injection
- most major nerves or nerve plexi can be targeted (brachial plexus block, femoral nerve block, sciatic nerve block, etc.)
- performed with standard monitors
- approximately 2-4 per 10,000 risk of late neurologic injury
- resuscitation equipment must be available

Contraindications to Peripheral Nerve Blockade

- absolute contraindications
  - allergy to LA
  - patient refusal
- relative contraindications
  - certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
  - local infection at block site
  - bleeding disorder

Local Anesthesia

Local Anesthetic Agents

- see Table 14, for list of LA agents

Definition and Mode of Action

- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptor on the cytosolic side of the Na+ channel, inhibiting Na+ flux and thus blocking impulse conduction
- different types of nerve fibres undergo blockade at different rates

Absorption, Distribution, Metabolism

- LA readily crosses the blood-brain barrier (BBB) once absorbed into the bloodstream
- ester-type LA (procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- amide-type LA (lidocaine, bupivacaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

Selection of LA

- choice of LA depends on:
  - onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA, and the faster the onset of action)
  - duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  - potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  - unique needs (e.g. sensory blockade with relative preservation of motor function by bupivacaine at low doses)
  - potential for toxicity

Table 14. Local Anesthetic Agents

<table>
<thead>
<tr>
<th>Local Anesthetic Agents</th>
<th>Maximum Dose</th>
<th>Maximum Dose with Epinephrine</th>
<th>Potency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloroprocaine</td>
<td>11 mg/kg</td>
<td>14 mg/kg</td>
<td>Low</td>
<td>15-30 min</td>
</tr>
<tr>
<td>lidocaine</td>
<td>5 mg/kg</td>
<td>7 mg/kg</td>
<td>Medium</td>
<td>1-2 h</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>2.5 mg/kg</td>
<td>3 mg/kg</td>
<td>High</td>
<td>3-8 h</td>
</tr>
<tr>
<td>ropivacaine</td>
<td>2.5 mg/kg</td>
<td>3 mg/kg</td>
<td>High</td>
<td>2-8 h</td>
</tr>
</tbody>
</table>
Systemic Toxicity

- see Table 16, A25 for maximum doses, potency, and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption

CNS Effects
- CNS effects first appear to be excitatory due to initial block of inhibitory fibres, then subsequent block of excitatory fibres
- effects in order of appearance
  - numbness of tongue, perioral tingling, metallic taste
  - disorientation, drowsiness
  - tinnitus
  - visual disturbances
  - muscle twitching, tremors
  - unconsciousness
  - convulsions, seizures
  - generalized CNS depression, coma, respiratory arrest

CVS Effects
- vasodilation, hypotension
- decreased myocardial contractility
- dose-dependent delay in cardiac impulse transmission
  - prolonged PR, QRS intervals
  - sinus bradycardia
- CVS collapse

Treatment of Systemic Toxicity
- early recognition of signs, get help
- 100% O2, manage ABCs
- diazepam
- manage arrhythmias (see ACLS Guidelines, A32)
- Intralipid® 20% to bind local anesthetic in circulation

Local Infiltration and Hematoma Blocks

Local Infiltration
- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerves
- suitable for small incisions, suturing, excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100,000-1:200,000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

Fracture Hematoma Block
- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

Topical Anesthetics
- various preparations of local anesthetics available for topical use, may be a mixture of agents (EMLA cream is a combination of 2.5% lidocaine and prilocaine)
- must be able to penetrate the skin or mucous membrane

Post-Operative Care
- pain management should be continuous from OR to post-anesthetic care unit (PACU) to hospital ward and home

Common Post-Operative Anesthetic Complications

Uncontrolled/Poorly Controlled Pain

Nausea and Vomiting
- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), metoclopramide (Maxeran®; not with bowel obstruction)
  - prochlorperazine (Stemetil®), ondansetron (Zofran®) granisetron (Kytril®)
Confusion and Agitation
- ABCs first: confusion or agitation can be caused by airway obstruction, hypercapnea, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers, language barriers
- metabolic disturbance (hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (stroke, raised intracranial pressure)
- drug effect (ketamine, anticholinergics, serotonin)
- elderly patients are more susceptible to post-operative delirium

Respiratory Complications
- susceptible to aspiration of gastric contents due to PONV and unreliable airway reflexes
- airway obstruction (secondary to reduced muscle tone from residual anesthetic, soft tissue trauma and edema, or pooled secretions) may lead to inadequate ventilation, hypoxemia, and hypercapnia
- airway obstruction can often be relieved with head tilt, jaw elevation, and anterior displacement of the mandible. If the obstruction is not reversible, a nasal or oral airway may be used

Hypotension
- must be identified and treated quickly to prevent inadequate perfusion and ischemic damage
- reduced cardiac output (hypovolemia, most common cause) and/or peripheral vasodilation (residual anesthetic agent)
- first step in treatment is usually the administration of fluids ± inotropic agents

Hypertension
- pain, hypercapnia, hypoxemia, increased intravascular fluid volume, and sympathomimetic drugs can cause hypertension
- sodium nitroprusside or β-blocking drugs (e.g. esmolol and metoprolol) can be used to treat hypertension

Pain Management

Definitions
- pain: perception of nociception, which occurs in the brain
- nociception: detection, transduction, and transmission of noxious stimuli

Pain Classifications
- temporal: acute vs. chronic
- mechanism: nociceptive vs. neuropathic

Acute Pain
- pain of short duration (<6 wk) usually associated with surgery, trauma, or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

Figure 11. Acute pain mechanism

Figure 12. WHO analgesia ladder
Pharmacological Management of Acute Pain

- ask the patient to rate the pain out of 10, or use visual analog scale, to determine severity
- pharmacological treatment guided by WHO analgesia ladder
- patient controlled analgesia (PCA)
  - involves the use of computerized pumps that can deliver a constant infusion and bolus breakthrough doses of parenterally-administered opioid analgesics
  - limited by lockout intervals
  - most commonly used agents: morphine and hydromorphone
- see Table 17, A26 for suggested infusion rate, PCA dose and lockout intervals

### Table 15. Commonly Used Analgesics

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples</strong></td>
<td>Tylenol®</td>
<td>Aspirin®, ibuprofen, naproxen, ketorolac (IV)</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>First-line for mild acute pain</td>
<td>Mild-moderate pain</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Unclear, hypothesized cyclooxygenase-2 (COX-2) inhibition</td>
<td>Non-selective COX-1 and 2 inhibition reducing proinflammatory prostaglandin synthesis</td>
</tr>
<tr>
<td><strong>Dosing/Administration</strong></td>
<td>Limited by analgesic ceiling beyond which there is no additional analgesia</td>
<td>Limited by analgesic ceiling beyond which there is no additional analgesia</td>
</tr>
<tr>
<td><strong>Side Effects/Toxicity</strong></td>
<td>Considered relatively safe Liver toxicity in elevated doses</td>
<td>Gastric ulceration/bleeding Decreased renal perfusion Photosensitivity Premature closure of the ductus arteriosus in pregnancy</td>
</tr>
</tbody>
</table>

### Table 16. Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Dose to 10 mg Morphine IV</th>
<th>Moderate Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>200 mg PO</td>
<td>15-30 mg PO</td>
<td>Late (30-60 min)</td>
<td>Moderate (4-6 h)</td>
<td>Primarily post-operative use, not for IV use</td>
</tr>
<tr>
<td>Meperidine (Demerol®)</td>
<td>75 mg IV</td>
<td>2-3 mg/kg IV</td>
<td>Moderate (10 min)</td>
<td>Moderate (2-4 h)</td>
<td>Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg IV</td>
<td>0.2-0.3 mg/kg IV</td>
<td>Moderate (5-10 min)</td>
<td>Moderate (4-5 h)</td>
<td>Histamine release leading to decrease in BP</td>
</tr>
<tr>
<td>Oxycodone Cont. elled Release (Oxyneo®)</td>
<td>15 mg PO</td>
<td>10-20 mg PO (no IV)</td>
<td>Late (30-45 min)</td>
<td>Long (8-12 h)</td>
<td>Do not split, crush, or chew tablet</td>
</tr>
<tr>
<td>Oxycodone Regular Tablet (Oxy IR®)</td>
<td>15 mg PO (no IV)</td>
<td>5-15 mg PO</td>
<td>Moderate (15 min)</td>
<td>Moderate (3-6 h)</td>
<td>Percocet® = oxycodone 5 mg + acetaminophen 325 mg</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid®)</td>
<td>2 mg IV</td>
<td>40-60 µg/kg IV</td>
<td>Moderate (15 min)</td>
<td>Moderate (4-5 h)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100 µg IV</td>
<td>2-3 µg/kg IV</td>
<td>Rapid (&lt; 5 min)</td>
<td>Short (0.5-1 h)</td>
<td>Transient muscle rigidity in very high doses</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>100 µg IV</td>
<td>0.5-1.5 µg/kg IV</td>
<td>Rapid (1-3 min)</td>
<td>Ultra short (&lt; 10 min)</td>
<td>Only use during induction and maintenance of anesthesia</td>
</tr>
</tbody>
</table>

In general, parenteral route is 2-3x more potent than oral
Table 17. Opioid PCA Doses

<table>
<thead>
<tr>
<th>Agent</th>
<th>PCA Dose</th>
<th>PCA Lockout Interval</th>
<th>PCA 4 h Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphin</td>
<td>1 mg</td>
<td>5 min</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.2 mg</td>
<td>5 min</td>
<td>6 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25-50 µg</td>
<td>5 min</td>
<td>400 µg</td>
</tr>
</tbody>
</table>

Opioid Antagonists (naloxone, naltrexone)
- indication: opioid overdose (manifests primarily at CNS, e.g. respiratory depression)
- mechanism of action: competitively inhibit opioid receptors, predominantly µ receptors
  - naloxone is short-acting (t1/2 = 1 h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
  - naltrexone is longer-acting (t1/2 = 10 h); less likely to see return of opioid effects
- side effects: relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, hypertension, re-emergence of pain, pulmonary edema, seizures (essentially opioid withdrawal)

Neuropathic Pain

- see Neurology, N41

Chronic Pain

- chronic pain: greater than 3 mo, or recurrent pain that occurs at least 3 times throughout three month period
- pain of duration or intensity that persists beyond normal tissue healing and adversely affects functioning
- may have nociceptive and neuropathic components; dysregulation of analgesic pathways implicated
  - in the perioperative period, consider continuing regular long-acting analgesics and augmenting with regional techniques, adjuvants, additional opioid analgesia and non-pharmacological techniques

Obstetrical Anesthesia

Anesthesia Considerations in Pregnancy

- airway
  - possible difficult airway as tissues becomes edematous and friable especially in labour
- respiratory
  - decreased FRC and increased O2 consumption cause more rapid desaturation during apnea
- cardiovascular system
  - increased blood volume > increased RBC mass results in mild anaemia
  - decreased SVR proportionately greater than increased CO results in decreased BP
  - prone to decreased BP due to aortocaval compression – therefore for surgery, a pregnant patient is positioned in left uterine displacement using a wedge under her right flank
- central nervous system
  - decreased MAC due to hormonal effects
  - increased block height due to engorged epidural veins
- gastrointestinal system
  - delayed gastric emptying
  - increased volume and acidity of gastric fluid
  - decreased LES tone
  - increased abdominal pressure
  - combined, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity

Options for Analgesia during Labour

- psychoprophylaxis – Lamaze method
  - patterns of breathing and focused attention on fixed object
- systemic medication
  - easy to administer, but risk of maternal or neonatal respiratory depression
  - opioids most commonly used if delivery is not expected within 4 h
- inhalational analgesia
  - easy to administer makes uterine contractions more tolerable, but does not relieve pain completely
  - 50% nitrous oxide
- neuraxial anesthesia
  - provides excellent analgesia with minimal depressant effects
  - hypotension is the most common complication
  - maternal BP monitored q2-5min for 15-20 min after initiation and regularly thereafter
  - epidural usually given as it preferentially blocks sensation, leaving motor function intact

Epidural vs. Non-Epidural or No Analgesia in Labour

Cochrane Database Syst Rev 2011;(12):CD000331

Purpose: To assess all modalities of epidural analgesia (including combined-spinal-epidural) versus non-epidural analgesia and no analgesia during labour in terms of maternal and neonatal outcomes.

Methods: Systematic review of randomized controlled trials comparing all modalities of epidural analgesia to any form of pain relief not involving regional blockade, or no pain relief. The Cochrane Pregnancy and Childbirth Group’s Trials Register was searched up to end March 2011. Primary analysis was by intention to treat.

Results: 38 studies involving 9658 women were included; 33 studies compared epidural analgesia with opiates. Epidural analgesia was associated with better pain relief (risk ratio (RR) 0.05, 95%, CI 0.02 to 0.17), reduced risk of admission (RR 0.017, 0.01 to 0.04), and reduced risk of naloxone administration (RR 0.015, 0.10 to 0.23), but was also associated with increased risk of assisted vaginal birth (RR 1.42, 1.28 to 1.57), maternal hypotension (RR 1.19, 1.03 to 1.39) and caesarean section for fetal distress (RR 1.43, 1.03 to 1.97). No significant differences were found in terms of overall risk of caesarean section (RR 1.0, 0.97 to 1.03), long-term backache (RR 0.98, 0.88 to 1.07), Apgar score less than seven at five minutes (RR 0.80, 0.68 to 1.00), and maternal satisfaction with pain relief (RR 1.31, 0.94 to 1.85).

Conclusions: While epidural analgesia appears effective for pain control during labour, it places women at an increased risk of an instrumental delivery, and is not associated with significant differences in C-section risk, maternal pain relief satisfaction long-term back ache or Apgar scores.

Nociceptive Pathways in Labour and Delivery

Labour

- Cervical dilation and effacement stimulates visceral nerve fibres entering the spinal cord at T10-L1

Delivery

- Distension of lower vagina and perineum causes somatic nociceptive impulses via the pudendal nerve entering the spinal cord at S2-S4
Options for Caesarean Section
- neuraxial: spinal or epidural
- general: used if contraindications or time precludes regional blockade

Pediatric Anesthesia

Respiratory System
- in comparison to adults, anatomical differences in infants include:
  - large head, short trachea/neck, large tongue, adenoids, and tonsils
  - narrow nasal passages (obligate nasal breathers until 5 mo)
  - narrowest part of airway at the level of the cricoid vs. glottis in adults
  - epiglottis is longer, U shaped and angled at 45°; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include:
  - faster RR, immature respiratory centres which are depressed by hypoxia/hypercapnea (airway closure occurs in the neonate at the end of expiration)
  - less oxygen reserve during apnea – decreased total lung volume, vital and functional reserve capacity together with higher metabolic needs
  - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm, and higher resistance to airflow

Cardiovascular System
- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume lost
- children have a high HR and low BP
- CO is dependent on HR, not stroke volume because of low heart wall compliance; therefore, bradycardia severe compromise in CO

Temperature Regulation
- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant’s head, humidification of inspired gases, and warming of infused solutions

Central Nervous System
- MAC of halothane is increased compared to the adult (0.75% adult, 1.2% infant, 0.87% neonate)
- NMJ is immature for the first 4 wk of life and thus there is an increased sensitivity to non-depolarizing relaxants
- parasympathetics mature at birth, sympathetic at 4-6 mo thus autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

Glucose Maintenance
- infants <1 yr can become seriously hypoglycemic during pre-operative fasting and post-operatively if feeding is not recommenced as soon as possible
- after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

Pharmacology
- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB
- muscle relaxants
  - non-depolarizing
    - immature NMJ, variable response
  - depolarizing
    - must pre-treat with atropine or may experience profound bradycardia and/or sinus node arrest due to PNS > SNS (also dries oral secretions)
    - more susceptible to arrhythmias, hyperkalemia, rhabdomyolysis, myoglobinemia, masseter spasm and malignant hyperthermia

To increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume.
Neonate: 30-40 breaths/min
Age 1-13: (24 – [age/2]) breaths/min

ETT Sizing in Pediatrics
Diameter (mm) of tracheal tube in children
after 1 year = (age/4) + 4
Length (cm) of tracheal tube = (age/2) + 12
Uncommon Complications

Malignant Hyperthermia

- hypermetabolic disorder of skeletal muscle
- due to an uncontrolled increase in intracellular Ca\(^{2+}\) (because of an anomaly of the ryanodine receptor which regulates Ca\(^{2+}\) channel in the sarcoplasmic reticulum of skeletal muscle)
- autosomal dominant inheritance
- incidence of 1-5 in 100,000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH include:
  - all inhalational agents except nitrous oxide
  - depolarizing muscle relaxants: SCh

Clinical Picture

- onset: immediate or hours after contact with trigger agent
- increased oxygen consumption
- increased ETCO\(_2\) on capnograph
- tachycardia/dysrhythmia
- tachypnea/cyanosis
- diaphoresis
- hypertension
- increased temperature (late sign)
- muscular symptoms
  - trismus (masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  - tender, swollen muscles due to rhabdomyolysis
  - trunk or total body rigidity

Complications

- coma
- DIC
- rhabdomyolysis
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema
- can be fatal if untreated

Prevention

- suspect MH in patients with a family history of problems/death with anesthetic
- avoid all trigger medications, use vapour free equipment, use regional anesthesia if possible
- central body temp and ETCO\(_2\) monitoring

Malignant Hyperthermia Management
(Based on Malignant Hyperthermia Association of the U.S. [MHAUS] Guidelines, 2008)

1. notify surgeon, discontinue volatile agents and succinylcholine, hyperventilate with 100% oxygen at flows of 10 L/min or more, halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
   - repeat until there is control of signs of MH; up to 30 mg/kg as necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis
4. cool patients with core temperature >39°C
   - lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
   - stop cooling if temperature is <38°C to prevent drift to <36°C
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
   - use standard drug therapy except Ca\(^{2+}\) channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene
6. hyperkalemia
   - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
   - bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia and check glucose levels hourly
7. follow ETCO\(_2\), electrolytes, blood gases, creatine kinase (CK), core temperature, urine output/colour with Foley catheter, coagulation studies
   - if CK and/or potassium rises persistently or urine output falls to <0.5 mL/kg/h, induce diuresis to >1 mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids, and propofol
9. transfer to ICU bed

Signs of Malignant Hyperthermia

- Unexplained rise in ETCO\(_2\)
- Increase in minute ventilation
- Tachycardia
- Rigidity
- Hyperthermia (late sign)

Basic Principles of MH Management

“Some Hot Dude Better Get Iced Fluids Fast”
Stop all triggering agents, give 100% O\(_2\)

Hyperventilate
Dantrolene 2.5 mg/kg every 5 min
Bicarbonate
Glucose and insulin
IV fluids; cool patient to 38°C
Fluid output; consider furosemide
Tachycardia: be prepared to treat VT
Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- individuals with abnormal pseudocholinesterase will have prolonged muscular blockade
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors rebound neuromuscular blockade once drug effect is terminated)

Appendices

Difficult Tracheal Intubation in Unconscious Patient

Figure 14. Difficult tracheal intubation encountered in the unconscious patient

Difficult Tracheal Intubation

Figure 15. Anticipated difficult tracheal intubation

IV = intravenous; RSI = rapid sequence induction/intubation; SGD = supraglottic device

### Advanced Cardiac Life Support Guidelines

**Figure 16. Adult cardiac arrest algorithm**

### Adult Tachycardia (With Pulse)

1. **Assess appropriateness for clinical condition**
   - Heart rate typically ≥150/min if tachyarrhythmia

2. **Identify and treat underlying cause**
   - Maintain patent airway; assist breathing as necessary
   - Oxygen (if hypoxemic)
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry

3. **Persistent tachyarrhythmia causing:**
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. **Synchronized cardioversion**
   - Consider sedation
   - If regular narrow complex, consider adenosine
   - IV access and 12-lead ECG if available
   - Consider adenosine only if regular and monomorphic
   - Consider antiarrhythmic infusion
   - Consider expert consultation

5. **Wide QRS? ≥0.12 second**
   - Yes
     - IV access and 12-lead ECG if available
     - Consider adenosine only if regular and monomorphic
     - Consider antiarrhythmic infusion
     - Consider expert consultation
   - No

6. **Doses/Details**
   - **Synchronized Cardoversion**
     - Initial recommended doses:
       - Narrow regular: 50-100 J
       - Narrow irregular: 120-200 J biphasic or 200 J monophasic
       - Wd de regular: 100 J
       - Wide irregular: defibrillation dose (NOT synchronized)

   - **Adenosine IV Dose:**
     - First dose: 6 mg rapid IV push; follow with NS flush
     - Second dose: 12 mg if required

   - **Antiarrhythmic Infusions for Stable Wide-QRS Tachycardia**
     - Procainamide IV Dose:
       - 20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases >50%, or maximum dose 17 mg/kg given
       - Maintenance infusion: 1-4 mg/min Avoid if prolonged QT or CHF

   - **Amiodarone IV Dose:**
     - First dose: 150 mg over 10 min
     - Repeat as needed if VT recurs
     - Follow by maintenance infusion of 1 mg/min for first 6 h

   - **Sotalol IV Dose:**
     - 100 mg (1.5 mg/kg) over 5 min
     - Avoid if prolonged QT

### Adult Bradycardia (With Pulse)

1. **Assess appropriateness for clinical condition**
   - Heart rate typically <50/min if bradyarrhythmia

2. **Identify and treat underlying cause**
   - Maintain patent airway; assist breathing as necessary
   - Oxygen (if hypoxemic)
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
   - IV access
   - 12-Lead ECG if available; do not delay therapy

3. **Persistent bradyarrhythmia causing:**
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. **Monitor and observe**
   - Yes
   - No

5. **Atropine**
   - If atropine ineffective:
     - Transcutaneous pacing OR
     - Dopamine infusion OR
     - Epinephrine infusion

6. **Consider:**
   - Expert consultation
   - Transvenous pacing

---

**Figure 17. Adult tachycardia algorithm**

**Figure 18. Adult bradycardia algorithm**
# Cardiology and Cardiac Surgery

Manpreet Basuita, Yehia Fanous, and Jason Gencher, chapter editors
Samik Doshi and Graham Mazereeuw, associate editors
Keeth Krishnan and Alexander Sapa, EBM editors
Dr. Chi-Ming Chow, Dr. Michael McDonald, and Dr. Anna Woo, staff editors

## Acronyms
- **ECG**: Electrocardiogram
- **ECG**: Electromyogram
- **ICD**: Implantable Cardioverter Defibrillator

## Basic Anatomy Review
- Coronary Circulation
- Cardiac Anatomy

## Differential Diagnoses of Common Presentations
- Chest Pain
- Loss of Consciousness
- Local Edema
- Generalized Edema
- Palpitations
- Dyspnea

## Cardiac Diagnostic Tests
- Electrocardiography Basics

## Approach to ECGs
- Classical Approach to ECGs
- Alternative PQRSTU Approach to ECGs
- Cardiac Biomarkers
- Ambulatory ECG
- Echocardiography
- Stress Testing
- Cardiac Catheterization and Angiography
- Coronary Angiography
- Contrast-Enhanced CT Coronary Angiography
- Magnetic Resonance Imaging

## Cardiac Disease
### Arrhythmias
- Mechanisms of Arrhythmias
- Bradyarrhythmias
- Supraventricular Tachyarrhythmias
- Pre-Excitation Syndromes
- Ventricular Tachyarrhythmias
- Sudden Cardiac Arrest
- Electrophysiology Studies
- Electrical Pacing
- Implantable Cardioverter Defibrillators
- Catheter Ablation

### Ischemic Heart Disease
- Chronic Stable Angina
- Acute Coronary Syndromes
- Treatment Algorithm for Chest Pain
- Coronary Revascularization

### Heart Failure
- Congestive Heart Failure
- Sleep-Disordered Breathing

### Cardiac Transplantation
- Ventricular Assist Devices

### Myocardial Disease
- Myocarditis
- Dilated Cardiomyopathy
- Hypertrophic Cardiomyopathy
- Restrictive Cardiomyopathy

## Valvular Heart Disease
- Rheumatic Fever
- Valve Repair and Valve Replacement
- Choice of Valve Prosthesis
- Summary of Valvular Disease

## Pericardial Disease
- Acute Pericarditis
- Pericardial Effusion
- Cardiac Tamponade
- Constrictive Pericarditis

## Common Medications
- Antiarrhythmics

## Landmark Cardiac Trials

## References
### Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>ABI</td>
<td>Ankle-branch index</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AFs</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AR</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic acid (Aspirin®)</td>
</tr>
<tr>
<td>ARDS</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>AT</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AV</td>
<td>Aortic valve</td>
</tr>
<tr>
<td>AVN</td>
<td>Atrioventricular node</td>
</tr>
<tr>
<td>AVRT</td>
<td>Atrioventricular re-entrant tachycardia</td>
</tr>
<tr>
<td>C2</td>
<td>Cardiology and Cardiac Surgery</td>
</tr>
<tr>
<td>CTA</td>
<td>CT angiography</td>
</tr>
<tr>
<td>AAA</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVAD</td>
<td>Left ventricular assist device</td>
</tr>
<tr>
<td>LVH</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>MAT</td>
<td>Multifocal atrial tachycardia</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MRA</td>
<td>MRI angiography</td>
</tr>
<tr>
<td>MS</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non-ST elevation myocardial infarction</td>
</tr>
<tr>
<td>RVAD</td>
<td>Right ventricular assist device</td>
</tr>
<tr>
<td>RVH</td>
<td>Right ventricular hypertrophy</td>
</tr>
<tr>
<td>SA</td>
<td>Sinoatrial node</td>
</tr>
<tr>
<td>SCD</td>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>SEM</td>
<td>Systolic ejection murmur</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>STMI</td>
<td>ST elevation myocardial infarction</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume</td>
</tr>
<tr>
<td>SVC</td>
<td>Superior vena cava</td>
</tr>
<tr>
<td>SVR</td>
<td>Systemic vascular resistance</td>
</tr>
<tr>
<td>TAA</td>
<td>Thoracic aortic aneurysm</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TR</td>
<td>Tricuspid regurgitation</td>
</tr>
<tr>
<td>TTE</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>UA</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>VAD</td>
<td>Ventricular assist device</td>
</tr>
<tr>
<td>VFb</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff-Parkinson-White</td>
</tr>
</tbody>
</table>

### Basic Anatomy Review

#### Coronary Circulation

- Conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the root of the aorta.
  - Right coronary artery (RCA):
    - Acute marginal branches
    - Atrioventricular (AV) nodal artery
    - Posterior interventricular artery (PIV) = posterior descending artery (PDA)
  - Left main coronary artery (LCA):
    - Left anterior descending artery (LAD)
      - Septal branches
      - Diagonal branches
    - Left circumflex artery (LCx)
      - Obtuse marginal branches
  - Dominance of circulation:
    - Right-dominant circulation: PIV and at least one posterolateral branch arise from RCA (80%)
    - Left-dominant circulation: PIV and at least one posterolateral branch arise from LCx (15%)
    - Balanced circulation: dual supply of posteroinfarction LV from RCA and LCx (5%)
  - The sinoatrial (SA) node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCx (40%)
  - Most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through thebesian veins into all four chambers, contributing to the physiologic R-L shunt

![Image: Anatomy of the coronary arteries (right anterior oblique projection)](image-url)

**Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)**
Cardiac Anatomy

- layers of the heart
  - endocardium, myocardium, epicardium, visceral pericardium, pericardial cavity, parietal pericardium

- valves
  - semilunar valves:
    - aortic valve, 3 valve leaflets: separates LV and ascending aorta
    - pulmonic valve, 3 valve leaflets: separates RV and main pulmonary artery (PA)
  - atrioventricular valves: subvalvular apparatus present in the form of chordae tendinae and papillary muscles
    - tricuspid valve, 3 valve leaflets: separates RA and RV
    - mitral/bicuspid valve, 2 valve leaflets: separates LA and LV

- conduction system
  - SA node governs pacemaking control
  - anterior-, middle-, and posterior-internal nodal tracts carry impulses in the right atrium and along Bachmann's bundle in the left atrium
  - atrial impulses converge at the AV node
    - the AV node is the only conducting tract from the atria to the ventricles because of electrical isolation by the annulus fibrosis (except when accessory pathways are present)
  - the bundle of His bifurcates into left and right bundle branches (LBB and RBB)
  - LBB further splits into anterior and posterior fascicles
  - RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium

Legend:
- AV – aortic valve
- LA – left atrium
- LV – left ventricle
- MV – mitral valve

Features of Abnormal JVP Wave Formation
- Atrial fibrillation: absent a wave
- 3rd degree heart block: cannon a waves
- Tricuspid regurgitation: c' wave, elevated JVP
- Cardiac tamponade: x descent only, absent y descent
- Constrictive pericarditis: prominent y descent, Kussmaul's sign
  (paradoxical increase in JVP with inspiration)
• cardiovascular innervation
  • sympathetic nerves
    • innervate the SA node, AV node, ventricular myocardium and vasculature
    • SA node (β1) fibres increase pacemaking activity (chronotropy - HR)
    • cardiac muscle (β1) fibres increase contractility (inotropy - SV)
    • stimulation of β1- and β2-receptors in the skeletal and coronary circulation causes vasodilatation
  • parasympathetic nerves
    • innervate the SA node, AV node, atrial myocardium but few vascular beds
    • basal vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node resulting in slowing of pacemaker activity and conduction (i.e. reduced dromotropy – if only affecting AV node conduction)
    • parasympathetics have very little impact on total peripheral vascular resistance

Differential Diagnoses of Common Presentations

Note: **bold** text indicates most common, *underlined* text indicates life threatening condition

### Chest Pain

- **cardiac**
  - MI/angina, myocarditis, pericarditis/Dressler’s syndrome
- **pulmonary**
  - PE, pneumothorax/hemothorax, tension pneumothorax, pneumonia, empyema, pulmonary neoplasm, bronchiectasis, TB
- **gastrointestinal**
  - esophageal: GERD, esophageal rupture, spasm, esophagitis, ulceration, achalasia, neoplasm, Mallory-Weiss syndrome
  - other structures: PUD, gastritis, pancreatitis, biliary colic
- **mediastinal**
  - lymphoma, thymoma
- **vascular**
  - dissecting aortic aneurysm, aortic rupture
- **surface structures**
  - costochondritis
  - rib fracture
  - skin (bruising, herpes zoster)
  - breast
- **anxiety/psychosomatic**

### Loss of Consciousness

- **hypovolemia**
- **vasovagal**
  - cardiac
    - structural or obstructive causes
      - ACS, AS, HCM, cardiac tamponade, constrictive pericarditis
    - arrhythmias *(see Arrhythmias, C16)*
  - respiratory
    - massive pulmonary embolism, pulmonary hypertension hypoxia, hypercapnia
  - neurologic
    - stroke/TIA (especially vertebrobasilar insufficiency), migraine, seizure
  - metabolic
    - anemia, hypoglycemia
  - drugs
    - antihypertensives, antiarrhythmics, diuretics
  - autonomic dysfunction
    - diabetic neuropathy
  - psychiatric
    - panic attack

### Local Edema

- inflammation/infection
- venous or lymphatic obstruction
  - thrombophlebitis/deep vein thrombosis, venous insufficiency, chronic lymphangitis, lymphatic tumour infiltration, filariasis
**Generalized Edema**

- increased hydrostatic pressure/fluid overload
  - heart failure, pregnancy, drugs (e.g. CCBs), iatrogenic (e.g. IV fluids)
- decreased oncotic pressure/hypoalbuminemia
  - liver cirrhosis, nephrotic syndrome, malnutrition
- increased interstitial oncotic pressure
  - myxedema
- increased capillary permeability
  - severe sepsis
- hormonal
  - hypothyroidism, exogenous steroids, pregnancy, estrogens

**Palpitations**

- cardiac
  - arrhythmias (PAC, PVC, SVT, VT), valvular heart disease, HCM
- endocrine
  - thyrotoxicosis, pheochromocytoma, hypoglycemia
- systemic
  - anemia, fever
- drugs
  - stimulants and anticholinergics
- psychiatric
  - panic attack

**Dyspnea**

- cardiovascular
  - acute MI, CHF/LV failure, aortic/mitral stenosis, aortic/mitral regurgitation, arrhythmia, cardiac tamponade, constrictive pericarditis, left-sided obstructive lesions (e.g. left atrial myxoma), elevated pulmonary venous pressure
- respiratory
  - airway disease
    - asthma, COPD exacerbation, upper airway obstruction (anaphylaxis, foreign body, mucus plugging)
  - parenchymal lung disease
    - ARDS, pneumonia, interstitial lung disease
  - pulmonary vascular disease
    - PE, pulmonary HTN, pulmonary vasculitis
  - pleural disease
    - pneumothorax, pleural effusion
- neuromuscular and chest wall disorders
  - C-spine injury
  - polymyositis, myasthenia gravis, Guillain-Barré syndrome, kyphoscoliosis
- anxiety/psychosomatic
- hematological/metabolic
  - anemia, acidosis, hypercapnia
- drugs and poisons
  - CNS depressants, carbon monoxide poisoning

**Cardiac Diagnostic Tests**

**Electrocardiography Basics**

**Description**

- a graphical representation (time versus amplitude of electrical vector projection) of the electrical activity of the heart
- on the ECG graph
  - the horizontal axis represents time (at usual paper speed 25 mm/s)
    - 1 mm (1 small square) = 40 msec
    - 5 mm (1 large square) = 200 msec
  - the vertical axis represents voltage (at usual standard gain setting 10 mm/mV)
    - 1 mm (1 small square) = 0.1 mV
    - 10 mm (2 large squares) = 1 mV

Figure 5. ECG lead placement

Figure 6. ECG waveforms and normal values
Approach to ECGs

leads
- standard 12-lead ECG
  - limb leads: I, II, III, aVL, aVR, aVF
  - precordial leads: V1-V6 (V1-V2 septal, V3-V4 anterior, V5-V6 lateral)
  - additional leads
  - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
- lateral = I, aVL, V5, V6; inferior = II, III, aVF; anterior = V1-V4

Indications
- detect myocardial injury, ischemia, and the presence of prior infarction
- palpitations, syncope, antiarrhythmic drug monitoring
- arrhythmia surveillance in patients with documented or potentially abnormal rhythms
- surveillance of non-sustained arrhythmias that can lead to prophylactic intervention

Contraindications
- no absolute contraindications except patient refusal or electrode latex adhesive allergy

Approach to ECGs

Introduction
Below, we are presenting both the Classical Approach and the newer PQRSTU Approach to provide students with different ways to view the ECG. Despite methodological differences, the rigor and final result is the same. These two approaches should help you better understand the concepts of ECG interpretation and equip you with the necessary skills to interpret ECGs in exam scenarios and clinical practice

Classical Approach to ECGs

RATE
- normal = 60-100 bpm (atrial rate: 150-250 bpm = paroxysmal tachycardia, 250-350 bpm = atrial flutter, >350 bpm = AFib)
- regular rhythm
to calculate the rate, divide 300 by number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 sec)
or remember 300-150-100-75-60-50-43 (rate falls in this sequence with the number of large squares between 2 QRS complexes)
- irregular rhythm
rate = 6 x number of R-R intervals in 10 s (the “rhythm strips” are 10 sec recordings)
atrial escape rhythm = 60-80 bpm; junctional escape rhythm = 40-60 bpm; ventricular escape rhythm = 20-40 bpm

RHYTHM
- regular: R-R interval is the same across the tracing
- irregular: R-R interval varies across the tracing
- regularly irregular: repeating pattern of varying R-R intervals e.g. AFlutter
- irregularly irregular: R-R intervals vary erratically e.g. AFib, VFib
- normal sinus rhythm (NSR)
P wave precedes each QRS; QRS follows each P wave
P wave axis is normal (positive in 2 out of the 3 following leads I, II, aVF)
rate between 60-100 bpm

AXIS
- mean axis indicates the direction of the mean vector
- can be determined for any waveform (PQRS T)
the standard ECG reported QRS axis usually refers to the mean axis of the frontal plane – it indicates the mean direction of ventricular depolarization forces
- QRS axis in the frontal plane
  - normal axis: -30º to 90º (i.e. positive QRS in leads I and II)
  - left axis deviation (LAD): axis <-30º
  - right axis deviation (RAD): axis >90º
- QRS axis in the horizontal plane is not routinely calculated
  - transition from negative to positive is usually in lead V3

Differential Diagnosis for Left Axis Deviation (LAD)
- Left anterior hemiblock
- Inferior MI
- WPW
- RV pacing
- Normal variant
- Elevated diaphragm
- Lead misplacement
- Endocardial cushion defect

Differential Diagnosis for Right Axis Deviation (RAD)
- RVH
- Left posterior hemiblock
- Pulmonary embolism
- COPD
- Lateral MI
- WPW
- Dextrocardia
- Septal defects

Figure 7. Axial reference system
Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead results in an upward deflection in that lead. Normal QRS axis is between -30º and +90º
Approach to ECGs

C7  Cardiology and Cardiac Surgery

Toronto Notes 2018

Table 1. Conduction Abnormalities

<table>
<thead>
<tr>
<th>Left Bundle Branch Block (LBBB)</th>
<th>Right Bundle Branch Block (RBBB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete LBBB</strong></td>
<td><strong>Complete RBBB</strong></td>
</tr>
<tr>
<td>QRS duration &gt; 120 msec</td>
<td>QRS duration &gt; 120 msec</td>
</tr>
<tr>
<td>Broad notched R waves in leads V4, V5, and usually I, aVL</td>
<td>Positive QRS in lead V1 (S'R' or occasionally broad R wave)</td>
</tr>
<tr>
<td>Deep broad S waves in leads V1-2</td>
<td>Broad S waves in leads I, V5-6 (&gt; 40 msec)</td>
</tr>
<tr>
<td>Secondary ST-T changes +ve in leads with broad notched R waves, -ve in V1-2 are usually present</td>
<td>Usually secondary T wave inversion in leads V1-2</td>
</tr>
<tr>
<td>LBBB can mask ECG signs of MI</td>
<td>Frontal axis determination using only the first 60 msec</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left Anterior Fascicular Block (LAFB)</th>
<th>Left Posterior Fascicular Block (LPFB)</th>
<th>Bifascicular Block</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Axis Deviation (-30° to -90°)</strong></td>
<td><strong>Right Axis Deviation (110° to 180°)</strong></td>
<td><strong>RBBB Pattern</strong></td>
</tr>
<tr>
<td>Small q and prominent R in leads I and aVL</td>
<td>Small r and prominent S in leads I and aVL</td>
<td>Small q and prominent R</td>
</tr>
<tr>
<td>Small s and prominent R in leads II, III, and aVF</td>
<td>Small q and prominent R in leads II, III, and aVF</td>
<td>The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB</td>
</tr>
<tr>
<td>Additional criteria</td>
<td>Additional criteria</td>
<td>Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks</td>
</tr>
<tr>
<td>LV strain pattern (asymmetric ST depression and T wave inversion in leads I, aVL, V4-V6)</td>
<td>LV strain pattern (asymmetric ST depression and T wave inversion in leads I, aVL, V4-V6)</td>
<td></td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>Left atrial enlargement</td>
<td></td>
</tr>
<tr>
<td>N.B. The more criteria present, the more likely LVH is present. If only one voltage criteria present, it is called minimal voltage criteria for LVH which could be a normal variant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nonspecific Intraventricular Block
- QRS duration > 120 msec
- absence of definitive criteria for LBBB or RBBB

Table 2. Hypertrophy/Chamber Enlargement

<table>
<thead>
<tr>
<th>Left Ventricular Hypertrophy (LVH)</th>
<th>Right Ventricular Hypertrophy (RVH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S in V1 + R in V5 or V6 &gt; 35 mm above age 40, I &gt; 40 mm for age 31-40, &gt; 45 mm for age 21-30</td>
<td>Right axis deviation</td>
</tr>
<tr>
<td>R in aVL &gt; 11 mm</td>
<td>R/S ratio &gt; 1 or qR in lead V1</td>
</tr>
<tr>
<td>R in I + S in III &gt; 25 mm</td>
<td>RV strain pattern: ST segment depression and T wave inversion in leads V1-2</td>
</tr>
<tr>
<td>Additional criteria</td>
<td>Further criteria for RVH</td>
</tr>
<tr>
<td>LV strain pattern (asymmetric ST depression and T wave inversion in leads I, aVL, V4-V6)</td>
<td>LV strain pattern (asymmetric ST depression and T wave inversion in leads I, aVL, V4-V6)</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left Atrial Enlargement (LAE)</th>
<th>Right Atrial Enlargement (RAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic P wave with the negative terminal component of the P wave in lead V1 ± 1 mm wide and ± 1 mm deep</td>
<td>P wave &gt; 2.5 mm in height in leads II, III, or aVF (“P pulmonale”)</td>
</tr>
<tr>
<td>P wave &gt; 100 msec, could be notched in lead II (“P mitrale”)</td>
<td></td>
</tr>
</tbody>
</table>

ISCHEMIA/INFARCTION
- look for the anatomic distribution of the following ECG abnormalities (see Table 3, C8)
- ischemia
  - ST segment depression
  - T wave inversion (most commonly in V1-V6)
- injury/infarct
  - transmural (involving the epicardium)
  - ST elevation in the leads facing the area injured/infarcted
  - subendocardial
  - marked ST depression in the leads facing the affected area
  - may be accompanied by enzyme changes and other signs of MI

Figure 10. Typical ECG changes with infarction
- ST elevation: at least 1 mm in 2 adjacent limb leads or at least 1.2 mm in adjacent precordial leads in STEMI (signifies complete occlusion and transmural ischemic injury) vs. diffuse pattern in early pericarditis vs transient ST elevation in patients with coronary artery spasm (e.g. Prinzmetal angina) which can be slight or prominent (> 10 mm)
Approach to ECGs

• “typical” sequential changes of evolving MI
  1. hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
  2. ST elevation (injury pattern) in the leads facing the infarcted area
     • usually in the first hours post infarct
     • in acute posterior MI, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads, that are not recorded in the standard 12-lead ECG) - get a 15-lead ECG
  3. significant Q waves: >40 msec or 1/3 of the total QRS and present in at least 2 consecutive leads in the same territory (hours to days post-infarct)
     • Q waves of infarction may appear in the very early stages, with or without ST changes
     • non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction
  4. inverted T waves (one day to weeks after infarction)

• completed infarction
  • abnormal Q waves (Q waves may be present in leads III and aVL in normal individuals due to initial septal depolarization)
  • duration >40 msec (>30 msec in aVF for inferior infarction)
  • Q/QRS voltage ratio is >33%
  • present in at least 2 consecutive leads in the same territory
  • abnormal R waves (R/S ratio >1, duration >40 msec) in V1 and occasionally in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)

Table 3. Areas of Infarction/Ischemia (right dominant anatomy)

<table>
<thead>
<tr>
<th>Vessel Usually Involved</th>
<th>Infarct Area (LAD and LC)</th>
<th>Leads (LAD and LC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Anterior Descending (LAD)</td>
<td>Anterosetal</td>
<td>V1, V2</td>
</tr>
<tr>
<td></td>
<td>Anterior</td>
<td>V3, V4</td>
</tr>
<tr>
<td></td>
<td>Anterolateral</td>
<td>aVL, V3-6</td>
</tr>
<tr>
<td></td>
<td>Extensive anterior</td>
<td>aVL, V1-6</td>
</tr>
<tr>
<td>Right Coronary Artery (RCA)</td>
<td>Inferior</td>
<td>II, III, aVF</td>
</tr>
<tr>
<td></td>
<td>Right ventricle</td>
<td>V3R, V4R (right sided chest leads)</td>
</tr>
<tr>
<td></td>
<td>Posterior MI (assoc. with inf. MI)</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
<tr>
<td>Left Circumflex (LCX)</td>
<td>Lateral</td>
<td>aVL, V5-6</td>
</tr>
<tr>
<td></td>
<td>Isolated posterior MI</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
</tbody>
</table>

MISCELLANEOUS ECG CHANGES

Electrolyte Disturbances

• hyperkalemia
  • mild to moderate (K+ 5-7 mmol/L): tall peaked T waves
  • severe (K+ >7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show bizarre patterns, axis shifts left or right, ST shift with tall T waves, eventually becomes a “sine wave” pattern

• hypokalemia
  • ST segment depression, prolonged QT interval, low T waves, prominent U waves (U>T)
  • enhances the toxic effects of digitalis

• hypercalcemia
  • shortened QT interval (more extracellular Ca2+ means shorter plateau in cardiac action potential)

• hypocalcemia
  • prolonged QT interval (less extracellular Ca2+ means longer plateau in cardiac action potential)

Figure 11. Hyperkalemia

Figure 12. Hypokalemia

Hypothermia

• sinus bradycardia
• when severe, prolonged QRS and QT intervals
• AFib with slow ventricular response and other atrial/ventricular dysrhythmias
• Osborne J waves: “hump-like” waves at the junction of the J point and the ST segment

Pericarditis

• early: diffuse ST segment elevation ± PR segment depression, upright T waves
• later: isoelectric ST segment, flat or inverted T waves
• ± tachycardia

Pacemakers

• Demand pacemaker has discharge (narrow vertical spike on ECG strip) prior to widened QRS
• Atrial pacemaker has discharge prior to P wave
• Triggered pacemaker has discharge following the P wave but prior to the widened QRS
• Atrial and ventricular pacing have discharge before the P wave and widened QRS wave
Drug Effects
- digitalis
  - therapeutic levels may be associated with “digitalis effect”
    - ST downsloping or “scooping”
    - T wave depression or inversion
    - QT shortening ± U waves
    - slowing of ventricular rate in AFib
  - toxic levels associated with:
    - arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradycardia in AFib, accelerated junctional rhythms, PVCs, ventricular tachycardia (see Arrhythmias, C16)
    - “regularization” of ventricular rate in AFib due to a junctional rhythm and AV dissociation
- amiodarone, quinidine, phenothiazines, tricyclic antidepressants, antipsychotics, some antihistamines, and some antibiotics (prolonged QT interval, U waves)

Pulmonary Disorders
- cor pulmonale (often secondary to COPD)
  - low voltage, right axis deviation (RAD), poor R wave progression in precordial leads
  - RAE and RVH with strain
  - multifocal atrial tachycardia (MAT)
- massive pulmonary embolism (PE)
  - sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  - RAD, RVH with strain
  - most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III) but rather uncommon

Alternative PQRSTU Approach to ECGs

Note: the information seen in this alternative approach – the PQRSTU Approach – is the same as the information in the Classical Approach; it is just organized in a different way based on the anatomy of the ECG
P WAVE

- the P wave represents atrial contraction; best leads: II, VI
  - lead II: the P wave should be rounded, <120 msec and <2.5 mm in height
  - lead V1: the P wave is biphasic with a negative phase slightly greater than the positive phase
- atrial flutter: sawtooth P wave (Hint: flip the ECG upside-down to see it better if unclear)
- atrial fibrillation: absent P wave, may have fibrillatory wave, irregular rhythm
- right atrial enlargement: tall P wave (>2.5 mm) in II or V1 (P pulmonale)
- left atrial enlargement: negative deflection >1 mm deep or >1 mm wide in V1, wide (>100 msec) notched P wave in II may be present (P mitrale)

P-R INTERVAL

- the P-R interval shows the delay between atrial and ventricular contraction that is mediated by the AV node; the magnitude of the delay is referred to as "dromotropy"
- positive dromotropy increases conduction velocity (e.g. epinephrine stimulation), negative dromotropy decreases velocity (e.g. vagal stimulation)
- P-R interval should be 120-200 msec
- long P-R interval (>200 msec)
  - heart block
    - first degree: fixed, prolonged P-R interval
    - second degree Mobitz I/Wenckebach: steadily prolonging P-R interval to eventual dropped beat
    - second degree Mobitz II/Hay: fixed P-R interval with ratio of beat to dropped beat (e.g. for every 3 beats, there is one dropped beat [3:1])
    - third degree/complete: variable P-R intervals, P-P and R-R intervals individually constant but not in sync
  - atrial flutter
  - sinus bradycardia (normal to have long P-R if heart rate slow)
  - hypokalemia
  - "trifascicular" block - 1st degree AV block with LAHF and complete RBBB
- short P-R interval (<120 msec)
  - pre-excitation syndrome (delta wave: upswooping of the P-R segment into the QRS complex indicating pre-excitation)
  - accessory pathways
  - WPW
- low atrial rhythm

QRS COMPLEX

- the QRS is where ventricular contraction is visualized
- rate: check the R-R interval to see if it matches the P-P interval
- amplitude: check for hypertrophy (see Table 2, C7)
- narrow width (<120 msec) QRS means that the His-Purkinje system is being used
- wide width (>120 msec) QRS means that the His-Purkinje system is being bypassed or is diseased
  - BBB, VT, ventricular hypertrophy, cardiomyopathy, WPW, ectopic ventricular beat, hyperkalemia, drugs (e.g. TCAs, antiarrhythmics)
- Q wave: the first downward deflection of the QRS complex
  - significant Q wave: >40 msec or >33% of total QRS amplitude; indicate myocardial necrosis (new or historical)
- R and S wave abnormalities typically show pathology in terms of BBB or intraventricular abnormalities

ST SEGMENT

- located between QRS complex and the beginning of T wave
- corresponds to the completion of ventricular depolarization
- normally at the same level as "baseline/TP segment"
- ST elevation: please see the infarct section above
- ST depression: ischemia
  - schema which causes ST depression can result in myocardial damage (NSTEMI)
  - lateral ST depression (leads I, aVL, V5, V6) may actually indicate a STEMI in the right heart

T WAVE

- this is the repolarization phase of the ventricles (repolarization of the atria are obscured by the QRS complex)
- typically positive (except in aVR and V1) on ECG but normal isolated negative T waves may be present (especially in V1 and V2)
- pathology when T wave variation occur in consecutive leads
  - inversion: BBB, ischemia, hypertrophy, drugs (e.g. digitalis), pulmonary embolism (lead III as part of SIQ3T3 sign)
  - elevation: infarction (STEMI, Prinzmetal, hyperacute), hyperkalemia (wider, peaked)
  - flattened: hypokalemia, pericarditis, drugs (e.g. digitalis), pericardial effusion
  - variations: T wave alternans; beat-to-beat variations due to PVC overlap (R on T phenomenon which may precipitate VT or VFib)
- appropriate T wave discordance: in BBB, T wave deflection should be opposite to that of the terminal QRS deflection (i.e. T wave negative if ends with R or R'; positive if ends with S)
- inappropriate T wave concordance suggests ischemia or infarction
**Q-T INTERVAL**

- this represents the duration of ventricular depolarization and repolarization and is often difficult to interpret.
- corrected QT (QTc) is often used instead in practice to correct for the repolarization duration: \( QTc = \frac{QT}{\sqrt{RR}} \)
- normal QTc is 360-450 msec for males and 360-460 msec for females
  - increased (>450 msec for males and >460 msec for females): risk of Torsades de Pointes (a lethal tachyarrhythmia)
    - genetic Long QT Syndrome (often a channelopathy)
    - drugs: antibiotics, SSRIs, antipsychotics, antiarrhythmics
    - electrolytes: low Ca\(^{++}\), low Mg\(^{++}\), low K\(^{+}\)
    - others: hypothyroidism, hypothermia, cardiomyopathy
  - decreased (<360 msec): risk of VFib
    - electrolytes: high Ca\(^{++}\)
    - drugs: digoxin
    - others: hyperthyroidism

**U WAVE**

- origin unclear but may be repolarization of Purkinje fibres or delayed/prolonged repolarization of the myocardium
- more visible at slower heart rates
- deflection follows T wave with <25% of the amplitude
- variations from norm could indicate pathologic conditions:
  - prominent (>25% of T wave): electrolyte (low K\(^{+}\)), drugs (digoxin, antiarrhythmics)
  - inverted (from T wave): electrolyte (low K\(^{+}\)), drugs (digoxin, antiarrhythmics)
- others: hyperthyroidism

### Cardiac Biomarkers

- provide diagnostic and prognostic information in acute coronary syndromes and in heart failure

<table>
<thead>
<tr>
<th>Table 4. Cardiac Enzymes</th>
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<tbody>
<tr>
<td>Enzyme</td>
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<tr>
<td>--------</td>
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<tr>
<td>Troponin I, Troponin T</td>
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<tr>
<td>CK-MB</td>
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</tbody>
</table>

- check troponin I at presentation and 8 h later ± creatine kinase-MB (CK-MB; depends on local laboratory protocol)
- new CK-MB elevation can be used to diagnose re-infarction
- other biomarkers of cardiac disease
  - AST and LDH also increased in MI (low specificity)
  - BNP and NT-proBNP: secreted by ventricles in response to increased end-diastolic pressure and volume
  - DDx of elevated BNP: CHF, AFib, PE, COPD exacerbation, pulmonary HTN

### Ambulatory ECG

- description
  - extended ambulatory ECG of 24 or 48 h or 14 or 28 d duration
  - provides a view of only two or three leads of electrocardiographic data over an extended period of time
  - permits evaluation of changing dynamic cardiac electrical phenomena that are often transient and of brief duration
  - **continuous loop**: a small, lightweight, battery operated recorder that records two or three channels of electrocardiographic data
  - **patient activated event markers**
  - minimum of 24-48 h
  - **implantable device**: subcutaneous monitoring device for the detection of cardiac arrhythmias
    - typically implanted in the left pectoral region and stores events when the device is activated automatically according to programmed criteria or manually with magnet application
    - can be used for months to years
- **indications**
  - evaluation of cardiac rhythm abnormalities
  - has also been used for assessing pacemaker and implantable cardioverter defibrillator function, evidence of myocardial ischemia, late potentials, and heart rate variability
- **contraindications**
  - no absolute contraindications
  - patient refusal
  - allergies (sensitivities to latex adhesive)
- **risks**: no absolute risks
Echocardiography

**Transthoracic Echocardiography (TTE)**
- **description:** ultrasound beams are directed across the chest wall to obtain images of the heart
- **indications**
  - evaluation of LVEF, wall motion abnormalities, myocardial ischemia and complications of MI
  - evaluation of chamber size, wall thickness, valve morphology, proximal great vessel morphology, pericardial effusion
  - evaluation of unexplained hypotension, murmurs, syncope, and congenital heart disease

**Transoesophageal Echocardiography (TEE)**
- **description:** invasive procedure used to complement transthoracic echocardiography
  - ultrasound probe inserted into the esophagus to allow for better resolution of the heart and structures
  - better visualization of posterior structures, including left atrium, mitral, and aortic valves, inter-atrial septum
- **indications**
  - should be performed as the initial test in certain life-threatening situations, (e.g. aortic dissection) when other tests contraindicated (e.g. CT angiography in patient with renal failure)
  - intracardiac thrombi, tumours, valvular vegetations (infective endocarditis), aortic dissection, aortic atheromas, prosthetic valve function, shunt, technically inadequate transthoracic study
  - evaluation for left atrial/left atrial appendage thrombus in a patient with atrial fibrillation/atrial flutter to facilitate clinical decision making regarding electrical cardioversion or ablation
- **risks**
  - serious complications are extremely rare (<1 in 5,000)
  - esophageal perforation
  - gastrointestinal bleeding
  - pharyngeal hematoma

**Stress Echocardiography (SE)**
- **description:** echocardiography using either exercise (treadmill or bicycle) or pharmacologic agents (dobutamine) as the stress mechanism
- **indications**
  - useful alternative to other stress imaging modalities
  - when ECG cannot be interpreted appropriately
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - post-ACS when used to decide on potential efficacy of revascularization
  - evaluate the clinical significance of valvular heart disease
  - evaluation of myocardial viability, dyspnea of possible cardiac origin, mitral valve disease, aortic stenosis, mitral regurgitation, pulmonary hypertension, and patients with hypertrophic cardiomyopathy (for LVOT obstruction)
  - dobutamine
    - pharmacologic stress for patients who are physically unable to exercise; same indications as exercise stress echo
    - low dose dobutamine stress echo can be used to assess myocardial viability and for assessing aortic stenosis with LV systolic dysfunction
- **contraindications**
  - contraindications to exercise testing
  - contraindications to dobutamine stress echocardiography: tachyarrhythmias and systemic hypertension
  - AAA has been considered as a relative contraindication to exercise testing or dobutamine stress echocardiography

**Contrast Echocardiography with Agitated Saline Contrast**
- **description:** improves resolution and provides real-time assessment of intracardiac blood flow
  - conventional agent is agitated saline (contains microbubbles of air)
  - allows visualization of right heart and intracardiac shunts, most commonly patent foramen ovale (PFO) and intrapulmonary shunt

**Contrast Echocardiography with Transpulmonary Contrast Agents**
- **description:** newer contrast agents are capable of crossing the pulmonary bed and achieving left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders and enhance evaluation of LV ejection fraction and wall motion abnormalities (in patients with technically inadequate echocardiograms), and intracardiac mass
- **risks**
  - risk of non-fatal MI and death are rare
  - ultrasound contrast agents may cause back pain, headache, urticaria, and anaphylaxis
Stress Testing

**EXERCISE TESTING**
- **description:** cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring
- **indications**
  - patients with intermediate (10-90%) pretest probability of CAD based on age, gender, and symptoms
  - ST depression <1 mm at rest, no left bundle branch block, no digoxin or estrogen use
  - exercise test results stratify patients into risk groups
    1. low risk patients can be treated medically without invasive testing
    2. intermediate risk patients may need additional testing in the form of exercise imaging studies or cardiac catheterization
    3. high risk patients should be referred for cardiac catheterization
- **contraindications**
  - acute myocardial infarction (within 2 days)
  - unstable angina pectoris
  - uncontrolled arrhythmias causing symptoms of hemodynamic compromise
  - symptomatic severe valvular stenosis
  - uncontrolled symptomatic heart failure
  - active endocarditis or acute myocarditis or pericarditis
  - acute aortic dissection
  - acute pulmonary or systemic embolism
  - acute non-cardiac disorders that may affect exercise performance or may be aggravated by exercise
  - termination of exercise testing
    - patient's desire to stop
    - drop in systolic blood pressure of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
    - moderate to severe angina
    - ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
    - increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
    - signs of poor perfusion (cyanosis or pallor)
    - technical difficulties in monitoring ECG or systolic blood pressure
    - sustained ventricular tachycardia
- **risks:** death, myocardial infarction, arrhythmia, hemodynamic instability, and orthopedic injury (<1-5/10,000 supervised tests)

**NUCLEAR CARDIOLOGY**
- **description:** myocardial perfusion imaging (MPI) with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
  - evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously
  - predicts the likelihood of further cardiac event rates independent of the patient's history, examination, resting ECG, and stress ECG
  - often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi)
  - stress with either treadmill or IV vasodilator stress (dipyridamole, adenosine, regadenoson)
  - images of the heart obtained during stress and at rest 3-4 h later
  - tracers
    - Thallium-201 ($^{201}$TI, a K$^+$ analogue)
    - Technetium-99 ($^{99}$Tc)-labeled tracer (sestamibi/Cardiolite” or hexamibi/Myoview”)
- **indications**
  - exercise MPI
  - when ECG cannot be interpreted appropriately
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - in patients with previous imaging whose symptoms have changed
  - to diagnose ischemia
  - dipyridamole/adenosine MPI
  - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarkers
  - when ECG is cannot be interpreted appropriately due to LBBB or V-paced rhythm among patients unable to exercise, with the same indications as exercise MPI
- **contraindications**
  - contraindications to exercise testing
  - vasodilators (i.e. adenosine, regadenoson, and dipyridamole) are contraindicated in patients with hypotension, sick sinus syndrome, high-degree AV block (in the absence of backup pacemaker capability), and reactive airways disease
  - pregnancy
- **risks:** radiation exposure

**STRESS ECHOCARDIOGRAPHY**
- see Echocardiography, C12
Cardiac Catheterization and Angiography

Right Heart Catheterization (Swan-Ganz Catheter)

- **Description:** also known as pulmonary artery catheterization
  - obtain direct measurements of central venous, right-sided intracardiac, pulmonary artery, and pulmonary artery occlusion pressures
  - can estimate cardiac output, systemic and pulmonary vascular resistance as well as mixed venous oxyhemoglobin saturation, oxygen delivery, and oxygen uptake
  - right atrial, right ventricular, and pulmonary artery pressures are recorded
  - can also be used to measure the Cardiac Index (CI)
  - \( \text{CI} = \frac{\text{CO}}{\text{body surface area}} \)
  - cardic index is a measure of cardiac function
  - \(<1.8 \text{ L/min/m}^2\) usually means cardiogenic shock
  - \(2.6-4.2 \text{ L/min/m}^2\) is considered normal
  - pulmonary capillary wedge pressure (PCWP)
    - obtained by advancing the catheter to wedge in the distal pulmonary artery
    - records pressure measured from the pulmonary venous system
    - in the absence of pulmonary venous disease reflects left atrial pressure

- **Indications**
  - unexplained or unknown volume status in shock
  - severe cardiogenic shock (e.g. acute valvular disease, suspected pericardial tamponade)
  - suspected or known pulmonary artery hypertension
  - severe underlying cardiopulmonary disease (e.g. congenital heart disease, left-to-right shunt severe valvular disease, pulmonary hypertension) and undergoing corrective or other surgery

- **Contraindications**
  - lack of consent
  - infection at the insertion site
  - the presence of a right ventricular assist device
  - insertion during cardiopulmonary bypass

- **Risks**
  - complications for diagnostic catheterization <1%
  - inadequate diagnostic procedures occur in <1% of cases
  - complication of insertion: atrial and/or ventricular arrhythmias (~3% of patients)
  - catheter misplacement or knotting (uncommon)
  - perforation of a cardiac chamber and rupture of a cardiac valve or the pulmonary artery (rare)
  - complications of catheterization: pulmonary artery rupture, pulmonary infarction, thromboembolic events, infection, and data misinterpretation
  - within 24 h of catheterization: death, MI, or stroke (0.2% to 0.3% of patients)

![Swan-Ganz catheter placement](https://via.placeholder.com/150)
Left Heart Catheterization

- **description**
  - accomplished by introducing a catheter into the brachial or femoral artery and advancing it through the aorta, across the aortic valve, and into the left ventricle
  - evaluates mitral and aortic valvular defects and myocardial disease
  - systolic and end-diastolic pressure tracings recorded
  - LV size, wall motion and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
  - cardiac output (measured by the Fick oxygen method or the indicator dilution method)

- **indications**
  - identification of the extent and severity of CAD and evaluation of left ventricular function
  - assessment of the severity of valvular or myocardial disorders (e.g. aortic stenosis or insufficiency, mitral stenosis or insufficiency, and various cardiomyopathies) to determine the need for surgical correction
  - collection of data to confirm and complement noninvasive studies
  - determination of the presence of CAD in patients with confusing clinical presentations or chest pain of uncertain origin

- **contraindications**
  - severe uncontrolled hypertension
  - ventricular arrhythmias
  - acute stroke
  - severe anemia
  - active gastrointestinal bleeding
  - allergy to radiographic contrast
  - acute renal failure
  - uncontrolled congestive failure (so that the patient cannot lie flat)
  - unexplained febrile illness or untreated active infection
  - electrolyte abnormalities (e.g. hypokalemia)
  - severe coagulopathy

- **risks**
  - complications for diagnostic catheterization <1%
  - inadequate diagnostic procedures occur in <1% of cases
  - within 24 h of catheterization: death, MI, or stroke (0.2% to 0.3% of patients)

Coronary Angiography

- **description**
  - radiographic visualization of the coronary vessels after injection of radiopaque contrast media
  - coronary vasculature accessed via the coronary ostia

- **indications**
  - to define the coronary anatomy and the degree of luminal obstruction of the coronary arteries
  - to determine the presence and extent of obstructive CAD
  - to assess the feasibility and appropriateness of various forms of therapy, such as revascularization by percutaneous or surgical interventions
  - can also be used when the diagnosis of CAD is uncertain and CAD cannot be reasonably excluded by noninvasive techniques

- **contraindications**: severe renal failure (due to contrast agent toxicity – must check patient’s renal status)

- **risks**: major complications <2%, but increased in patients with pre-existing renal failure (especially in diabetic patients)

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**ACC/AHA 2011 Recommended Indications for Coronary Angiography**
- Disabling (CCS classes III and IV) chronic stable angina despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Serious ventricular arrhythmia or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing

**Coronary Angiography**
Gold standard for localizing and quantifying CAD

Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter

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Figure 18. Coronary angiogram schematic

AM = acute marginal; LAD = left anterior descending; OM = obtuse marginal; RCA = right coronary artery
Diagnostic Catheterization

- complications for diagnostic catheterization <1%
- inadequate diagnostic procedures occur in fewer than 1% of cases
- provocative pharmacological agents can be used to unmask pathology
  - fluid loading may unmask latent pericardial constriction
  - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in HCM
  - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  - a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, calcium channel blockers, adenosine, nitric oxide, or prostacyclin)

Contrast-Enhanced CT Coronary Angiography

- description: fast ECG synchronized multi-slice CT image acquisition in the heart to enable non-invasive imaging of the coronary arterial tree
- indications: often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
  - sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis
- contraindications: allergy to contrast dye; severe renal dysfunction
- risks: radiation exposure

Magnetic Resonance Imaging

- description: offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
- indications: valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, assessment of viable myocardium, and assessment of cardiomyopathies
- contraindications: metallic foreign bodies/implants
- risks: hazards posed by certain metallic devices inside patients

CAR DiEASE

Arrhythmias

Mechanisms of Arrhythmias

Alterations in Impulse Formation

A. Abnormal Automaticity

- automaticity is a property of certain cardiomyocytes to spontaneously depolarize to their threshold voltage to generate action potentials in a rhythmic fashion. Under normal circumstances only cells in the specialized conduction system (SA node, AV node, and ventricular conduction system) exhibit natural automaticity. These cells are pacemaking cells. The automaticity of these cells can become abnormally increased or decreased. In disease (e.g. post-MI ventricular ischemia) cells in the myocardium outside the conduction system may inappropriately acquire the property of automaticity and contribute to abnormal depolarization. If these ectopic generators depolarize at a rate greater than the SA node, they assume pacemaking control and become the source of abnormal rhythm. Automaticity can be influenced by:
  - neurohormonal tone (sympathetic and parasympathetic stimulation)
  - abnormal metabolic conditions (hypoxia, acidosis, hypothermia)
  - electrolyte abnormalities
  - drugs (e.g. digitalis)
  - local ischemia/infarction
  - other cardiac pathology

- this mechanism is responsible for the accelerated idioventricular rhythm and ventricular tachycardia that often occurs 24-72 h post MI

B. Triggered Activity due to Afterdepolarizations

1. Early Afterdepolarizations

- occur in the context of action potential prolongation
- consequence of the membrane potential becoming more positive during repolarization (e.g. not returning to baseline)
- result in self-maintaining depolarizing oscillations of action potential, generating a tachyarrhythmia (e.g. new baseline voltage is greater than threshold, which automatically triggers a new action potential after the refractory period ends)
- basis for the degeneration of QT prolongation, either congenital or acquired, into Torsades de Pointes

Sinus Arrhythmia (SA)

- Normal P waves, with variation of the P-P interval by >120 msec due to varying rate of SA node

Respiratory SA

- Seen more often in young adults (<30 yr old)
- Normal, results from changes in autonomic tone during respiratory cycle
- Rate increases with inspiration, slows with expiration

Non-Respiratory SA

- Seen more often in the elderly
- Can occur in the normal heart; it marked may be due to sinus node dysfunction (e.g. in heart disease, or after digitalis toxicity)
- Usually does not require treatment
2. Delayed Afterdepolarizations
   - occur after the action potential has fully repolarized, but before the next usual action potential, thus called a delayed afterdepolarization
   - commonly occurs in situations of high intracellular calcium (e.g. digitalis intoxication, ischemia) or during enhanced catecholamine stimulation (e.g. “twitchy” pacemaker cells)

Alterations in Impulse Conduction

A. Re-Entry Circuits
   - the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium (see Figure 26, C20, for an example in the context of AV nodal re-entrant tachycardia)
   - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits

B. Conduction Block
   - ischemia, fibrosis, trauma, and drugs can cause transient, permanent, unidirectional or bidirectional block
   - most common cause of block is due to refractory myocardium (cardiomyocytes are in refractory period or zone of myocardium unexcitable due to fibrosis)
   - if block occurs along the specialized conduction system distal zones of the conduction system can assume pacemaking control
   - conduction block can lead to bradycardia or tachycardia when impaired conduction leads to re-entry phenomenon

C. Bypass Tracts
   - normally the only conducting tract from the atria to the ventricles is the AV node into the His-Purkinje system
   - congenital/acquired accessory conducting tracts bypass the AV node and facilitate premature ventricular activation before normal AV node conduction
   - see Pre-Excitation Syndromes, C21

Figure 19. Clinical approach to arrhythmias
Bradyarrhythmias

1. SA NODAL DYSFUNCTION

A. Sinus Bradycardia

- P axis normal (P waves positive in I and aVF)
- Rate <60 bpm; marked sinus bradycardia (<50 bpm)
- May be seen in normal adults, particularly athletes, and in elderly individuals
- Increased vagal tone or vagal stimulation; drugs (β-blockers, calcium channel blockers, etc.); ischemia/infarction

- Atropine; pacing for sick sinus syndrome

Figure 20. Sinus bradycardia

2. AV CONDUCTION BLOCKS

A. First Degree AV Block

- Prolonged PR interval (>200 msec)
- Frequently found among otherwise healthy adults

- No treatment required

Figure 21. First degree AV block

B. Second Degree AV Block: Type I (Mobitz I)

- A gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
- AV block is usually in AV node (proximal triggers usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia

Figure 22. Second degree AV block with Wenckebach phenomenon (Mobitz I) (4:3 conduction) (lead V1)

B. Second Degree AV Block: Type II (Mobitz II)

- The PR interval is constant; there is an abrupt failure of conduction of a P wave
- AV block is usually distal to the AV node (i.e. bundle of His); increased risk of high grade or 3rd degree AV block

Figure 23. Second degree AV block (Mobitz II) (3:2 conduction) (lead V1)

B. Third Degree AV Block

- Complete failure of conduction of the supraventricular impulses to the ventricles; ventricular depolarization initiated by an escape pacemaker distal to the block
- Wide or narrow QRS, P-P and R-R intervals are constant, variable PR intervals; no relationship between P waves and QRS complexes (P waves “marching through”)

Management (see Electrical Pacing, C24)

Figure 24. Third degree AV block (complete heart block) (lead II)

Supraventricular Tachyarrhythmias

Presentation for SVT (and Pre-Excitation Syndromes)

- presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate CHF, hypotension, or ischemia in patients with underlying disease
- untreated tachycardias can cause cardiomyopathy (rare, potentially reversible with treatment of SVTs)
- includes supraventricular and ventricular rhythms

Supraventricular Tachyarrhythmias

- tachyarrhythmias that originate in the atria or AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS, unless there is pre-existing bundle branch block or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

1. Sinus Tachycardia

- sinus rhythm with rate >100 bpm
- occurs in normal subjects with increased sympathetic tone (e.g. exercise, emotions, pain), alcohol use, caffeinated beverages, drugs (e.g. β-adrenergic agonists, anticholinergic drugs, etc.)
- etiology: fever, hypotension, hypovolemia, anemia, thyrotoxicosis, CHF, MI, shock, PE, etc.
- treatment: treat underlying disease; consider β-blocker if symptomatic, calcium channel blocker if β-blockers contraindicated
2. Premature Beats
- premature atrial contraction
  - ectopic supraventricular beat originating in the atria
  - P wave morphology of the PAC usually differs from that of a normal sinus beat
  - junctional premature beat
  - ectopic supraventricular beat that originates in the vicinity of the AV node
  - P wave is usually not seen or an inverted P wave is seen and may be before or closely follow the QRS complex (referred to as a retrograde, or “traveling backward” P wave)
- treatment usually not required

3. Atrial Flutter
- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly the right atrium)
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (2:1, 3:1, 4:1, etc.) or variable
- etiology: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis
- ECG: sawtooth flutter waves (most common type of flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy); commonly seen as 2:1 block with HR of 150
- in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and bring out flutter waves
- treatment of acute atrial flutter
  - acute and if unstable (e.g. hypotension, CHF, angina) electrical cardioversion
  - if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable:
    1. rate control: β-blocker, diltiazem, verapamil, or digoxin
    2. chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
- anticoagulation guidelines same as for patients with AFib
- treatment of long-term atrial flutter: antiarrhythmics, catheter radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter – i.e. whether right-sided isthmus-dependent or left-sided origin)

4. Multifocal Atrial Tachycardia (MAT)
- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
- atrial rate 100-200 bpm – 3 or more distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
- occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline, or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics, or ablation

5. Atrial Fibrillation
- see CCS Atrial Fibrillation Guidelines 2016 for details (free mobile app – iCCS available on iOS and Android)
- most common sustained arrhythmia
- incidence increases with age (10% of population >80 yr old)
- symptoms: palpitations, fatigue, syncope, may precipitate or worsen heart failure
- classification
  - lone: occurs in persons younger than 60 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease, prosthetic heart valves, or valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: AFib sustained for more than 7 d or AFib that terminates only with cardioversion
  - permanent/chronic: continuous AFib that is unresponsive to cardioversion or in which clinical judgement has led to a decision not to pursue cardioversion
  - recurrent: two or more episodes of AFib
  - secondary: caused by a separate underlying condition or event (e.g. myocardial infarction, cardiac surgery, pulmonary disease, hyperthyroidism)
- may be associated with thromboembolic events (stroke risk can be assessed by CHADS2 score in nonvalvular AFib; CHA2DS2-VASc if the former gives a score of 0 or 1)
- initiation
  - single circuit re-entry and/or ectopic foci act as aberrant generators producing atrial tachycardia (350-600 bpm)
  - impulses conduct irregularly across the atrial myocardium to give rise to fibrillation
  - in some cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated
- maintenance
  - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AFib; the longer the patient is in AFib the more difficult it is to convert back to sinus rhythm
- consequences
  - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response of <200 bpm and the tachycardia leads to suboptimal cardiac output
  - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation – AFib is an important risk factor for stroke
Table 5. CHADS2 Risk Prediction for Non-Valvular AFib and Refer to AHA/ACC/HRS AFib Guidelines 2014 for more details

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS2 Score</th>
<th>Stroke Risk (%/Yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
<td>0</td>
<td>1.9 (low)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>2.8 (low-mod)</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>1</td>
<td>2-3</td>
<td>4.0-5.9 (mod)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>4-6</td>
<td>8.5-18.2 (high)</td>
</tr>
<tr>
<td>Stroke/TIA (prior)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 26. Atrial fibrillation (lead II)

- ECG findings
  - no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline
  - irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
  - wide QRS complexes due to aberrancy may occur following a long-short cycle sequence ("Ashman phenomenon")
  - loss of atrial contraction, thus no “a” wave seen in JVP no S4 on auscultation

- management (adapted from CCS Atrial Fibrillation Guidelines 2016)
  - major objectives (RACE): all patients with AFib (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk and for the risk of bleeding, and most patients should receive either an oral anticoagulant or ASA (see below)
    1. Rate control: β-blockers, diltiazem, verapamil (in patients with heart failure: digoxin, amiodarone)
       - digoxin can be considered as a therapeutic option to achieve rate control in patients whose response to beta-blockers and/or calcium channel blockers is inadequate or contraindicated
    2. Anticoagulation: use either warfarin or novel oral anticoagulant (NOACs) e.g. apixaban, dabigatran, rivaroxaban to prevent thromboembolism
       for patients with non-valvular AF (NV AF): oral anticoagulant (OAC) is recommended for most patients aged >65 yr or CHADS2 >= 1. ASA 81 mg is recommended only for patients with none of the risk outlined in the CCS algorithm (age <65 and no CHADS2: risk factors) who have arterial disease (coronary, aortic, or peripheral). Novel oral anticoagulant (NOAC) is to be used in preference to warfarin
    3. Cardioversion (electrical)
       - if AFib <24–48 h, can usually cardiovert without anticoagulation
       - if AFib >24–48 h, anticoagulate for 3 wk prior and 4 wk after cardioversion due to risk of unstable intra-atrial thrombus
       - if patient unstable (hypotensive, active angina due to tachycardia, uncontrolled heart failure) should cardiovert immediately
    4. Etiology
       - HTN, CAD, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, post-operative PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol ("holiday heart")
       - may present in young patients without demonstrable disease ("lone AFib") and in the elderly without underlying heart disease
  - studies of patients with AFib suggest that there is no difference in long-term survival when treating patients with a rhythm-control versus rate-control strategy
  - however, many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate AFib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible
  - newly discovered AFib
    - anticoagulants may be beneficial if high risk for stroke
    - if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
    - if AFib persists, 2 options
      1. rate control and anticoagulation (as indicated above)
      2. cardioversion (as above)
  - recurrent or permanent AFib
    - if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
    - patients who have undergone at least one attempt to restore sinus rhythm may remain in AFib after recurrence; permanent AFib may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations

 Lenient versus Strict Rate Control in Patients with Atrial Fibrillation
 NEJM 362:1263-1273
 Study: Randomized, multi-centre Netherlands prospective study, follow-up for at least 2 yr
 Population: 614 patients with permanent atrial fibrillation.
 Intervention: Lenient control (resting HR <110 bpm) or strict control (resting HR <80 bpm)
 Primary Outcomes: Death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events.
 Results: Goal of the study was to establish whether lenient control was equivalent to strict control for prevention of primary outcomes. Resulting hazard ratios were not significantly different between the treatment groups (P = 0.001). Frequencies of hospitalization and adverse effects were also similar. More patients were able to maintain lenient targets (97.3%) compared to strict targets (86%).
 Conclusion: Lenient control was equivalent to strict control for prevention of primary outcomes in patients with atrial fibrillation. Furthermore, lenient control was more easily achieved.

 Rivaroxaban for Stroke Prevention in AFib – ROCKET-AF Trial
 NEJM 2011;365:883-891
 Study: Prospective, non-inferiority, double blind, RCT, median follow-up of 1.9 yr.
 Population: n=14,264 patients with AF (mean CHADS=2.3), Patients either had previous thromboembolism or ≥3 risk factors.
 Intervention: Patients were randomized to receiving rivaroxaban or warfarin.
 Outcome: Composite of strokes and systemic thromboembolic event (STE).
 Results: The hazard ratio of the primary outcome for rivaroxaban compared to warfarin was 0.89; 95% CI 0.74-1.03; p < 0.001 for noninferiority; p = 0.12 for superiority. Furthermore, the hazard ratio for major and non-major, but clinically relevant, bleeding was 1.03; 95% CI 0.96-1.11; p = 0.44. There were also significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, p = 0.02) and fatal bleeding (0.2% vs. 0.5%, p = 0.003) for rivaroxaban.
 Conclusions: In patients with AFib, rivaroxaban is non-inferior to warfarin for stroke prevention and major and non-major bleeding.
6. **AV NODAL RE-ENTRANT TACHYCARDIA (AVNRT)**

- re-entrant circuit using dual pathways (fast conducting β-fibres and slow conducting α-fibres) within
  or near the AV node; often found in the absence of structural heart disease – cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset
- fast regular rhythm: rate 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex
  - treatment
    - acute: Valsalva maneuver or carotid sinus pressure technique, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina, or CHF)
    - long-term: 1st line – β-blocker, diltiazem, digoxin; 2nd line – flecainide, propafenone; 3rd line – catheter ablation

---

**Pre-Excitation Syndromes**

- refers to a subset of SVTs mediated by an accessory pathway which can lead to ventricular pre-excitation

**Wolff-Parkinson-White Syndrome**

- congenital defect present in 1.5-2/1,000 of the general population
- an accessory conduction tract (Bundle of Kent; can be in right or left atrium) abnormally allows early electrical activation of part of one ventricle
- impulses travel at a greater conduction velocity across the Bundle of Kent thereby effectively ‘bypassing’ AV node
- since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex – the so-called “delta wave”
- atrial impulses that conduct to the ventricles through both the Bundle of Kent and the normal AV node/His-Purkinje system generate a broad “fusion complex”
- ECG features of WPW
  - PR interval <120 msec
  - delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  - widening of the QRS complex due to premature activation
  - secondary ST segment and T wave changes
  - tachyarrhythmias may occur – most often AVRT and AFib
A Fib in WPW Patients
- A Fib is the index arrhythmia in up to 20% of patients with WPW syndrome
  - it is usually intermittent rather than persistent or permanent
  - rapid atrial depolarizations in A Fib are conducted through the bypass tract which is not able to filter impulses like the AV node can
  - consequently the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens
- treatment: electrical cardioversion, IV procainamide, or IV amiodarone
  - do not use drugs that slow AV node conduction (digoxin, β-blockers) as this may cause preferential conduction through the bypass tract and precipitate VF
  - long-term: ablation of bypass tract if possible

AV Re-Entrant Tachycardia
- re-entrant loop via accessory pathway and normal conduction system
- initiated by a premature atrial or ventricular complex
  - orthodromic AVRT: stimulus from a premature complex travels up the bypass tract (V to A) and down the AV node (A to V) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system)
  - comprises 95% of the reentrant tachycardias associated with WPW syndrome
    - antidromic AVRT: more rarely the stimulus goes up the AV node (V to A) and down the bypass tract (A to V); wide and abnormal QRS as ventricular activation is only via the bypass tract
    - treatment
      - acute: similar to AVNRT except avoid long-acting AV nodal blockers (e.g. digoxin and verapamil)
      - long-term: for recurrent arrhythmias ablation of the bypass tract is recommended
        - drugs such as flecainide and procainamide can be used

Ventricular Tachyarrhythmias

Premature Ventricular Contraction (PVC) or Ventricular Premature Beat (VPB)
- QRS width >120 msec, no preceding P wave, bizarre QRS morphology
  - origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
  - PVCs may be benign but are usually significant in the following situations
    - consecutive (≥3 = VT) or multiform (varied origin)
    - PVC falling on the T wave of the previous beat (“R on T phenomenon”): may precipitate ventricular tachycardia or VF

Accelerated Idioventricular Rhythm
- ectopic ventricular rhythm with rate 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute MI or other types of heart disease (cardiomyopathy, hypertensive, valvular) but it does not affect prognosis and does not usually require treatment

Ventricular Tachycardia (VT)
- 3 or more consecutive ectopic ventricular complexes
  - rate >100 bpm (usually 140-200)
  - ventricular flutter: if rate >200 bpm and complexes resemble a sinusoidal pattern
  - “sustained VT” if it lasts longer than 30 s
  - ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec)
  - AV dissociation; bizarre QRS pattern
  - also favour Dx of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
  - occasionally during VT supraventricular impulses may be conducted to the ventricles generating QRS complexes with normal or aberrant supraventricular morphology ("ventricular capture") or summation pattern ("fusion complexes")

- monomorphic VT
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - typically result from intraventricular re-entry circuit
  - potential causes: chronic infarct scarring, acute MI/ischemia, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances

- polymorphic VT
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm) vs. monomorphic VT
  - potential causes: acute MI, severe or silent ischemia, and predisposing factors for QT prolongation
  - treatment
    - sustained VT (>30 s) is an emergency, requiring immediate treatment
    - hemodynamic compromise: electrical cardioversion
    - no hemodynamic compromise: electrical cardioversion, lidocaine, amiodarone, type Ia agents (procainamide, quinidine)
**Table 6. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy**

<table>
<thead>
<tr>
<th>Clinical Clues</th>
<th>ECG Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms</td>
<td>AV dissociation</td>
</tr>
<tr>
<td>History of CAD and previous MI</td>
<td>Capture or fusion beats</td>
</tr>
<tr>
<td>Physical exam</td>
<td>QRS width &gt; 140 msec</td>
</tr>
<tr>
<td>Cannon “a” waves</td>
<td>Extreme axis deviation (left or right</td>
</tr>
<tr>
<td>Variable S1</td>
<td>superior axis)</td>
</tr>
<tr>
<td>Carotid sinus massage/adenosine</td>
<td>Capture or fusion beats</td>
</tr>
<tr>
<td>terminates arrhythmia</td>
<td>VT</td>
</tr>
<tr>
<td>Carotid sinus massage/adenosine</td>
<td>Capture or fusion beats</td>
</tr>
<tr>
<td>terminates arrhythmia</td>
<td>VT</td>
</tr>
</tbody>
</table>

*If patient >65 yr and previous MI or structural heart disease, then chance of VT >95%*

**May terminate VT in some patients with no structural heart disease**

**Torsades de Pointes**
- a variant of polymorphic VT that occurs in patients with baseline QT prolongation – "twisting of the points"
- looks like usual VT except that QRS complexes "rotate around the baseline" changing their axis and amplitude
- ventricular rate >100 bpm, usually 150-300 bpm
- etiology: predisposition in patients with prolonged QT intervals
  - congenital long QT syndromes
  - drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  - electrolyte disturbances: hypokalemia, hypomagnesemia
  - nutritional deficiencies causing above electrolyte abnormalities
- treatment: IV magnesium, temporary pacing, isoproterenol and correct underlying cause of prolonged QT, electrical cardioversion if hemodynamic compromise

**Ventricular Fibrillation (VFib)**
- chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology
- terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and cardiac output, and electrical defibrillation is carried out
- most frequent cause of sudden death
- refer to ACLS algorithm for complete therapeutic guidelines
Sudden Cardiac Arrest

Definition
- unanticipated, non-traumatic cardiac death in a stable patient which occurs within 1 h of symptom onset; Vfib is most common cause

Etiology
- primary cardiac pathology
  - ischemia/MI
  - LV dysfunction
  - severe ventricular hypertrophy
  - HCM
  - AS
- congenital heart disease e.g. arrhythmogenic right ventricular dysplasia
- mutations in cardiac ion channels e.g. long QT syndrome, Brugada syndrome

Management
- acute: resuscitate with prompt CPR and defibrillation
- investigate underlying cause (cardiac catheterization, electrophysiologic studies, echo)
- treat underlying cause
- antiarrhythmic drug therapy: amiodarone, β-blockers
- implantable cardioverter defibrillator (ICD)
- refer to ACLS guidelines (see Anesthesia and Perioperative Medicine, A31)

Electrophysiology Studies

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of SA node dysfunction and localize site of AV conduction block
- tachyarrhythmias: map for possible ablation or to assess inducibility of VT

Electrical Pacing

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia in the setting of heart disease

Pacemaker Indications
- SA node dysfunction (most common): symptomatic bradycardia ± hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

Pacemaker Complications
- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism) pacemaker leads (perforation, malposition), pocket hematomas and infection
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure pacemaker syndrome and pacemaker mediated tachycardia

Pacing Techniques
- temporary: transvenous (jugular, subclavian, femoral) or external (transcutaneous) pacing
- permanent: transvenous into RA, apex of RV, or both
- can sense and pace atrium, ventricle, or both
- new generation: rate responsive, able to respond to physiologic demand
- biventricular

Implantable Cardioverter Defibrillators

- sudden cardiac death (SCD) usually results from ventricular fibrillation (Vfib), sometimes preceded by monomorphic or polymorphic ventricular tachycardia (VT)
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/Vfib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention
- benefit seen in patients with ischemic and non-ischemic cardiomyopathy, depressed left ventricular ejection fraction (LVEF), prolonged QRS
- see Heart Failure, C34 for current treatment recommendations
Catheter Ablation

Techniques
- radiofrequency (RF) ablation: a low-voltage high-frequency form of electrical energy (similar to cautery); RF ablation produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth
- cryoablation: new technology which uses a probe with a tip that can decrease in temperature to 20°C and -70°C. Produces small, necrotic lesions similar to RF ablation; when brought to -20°C, the catheter tip reversibly freezes the area; bringing the tip down to -70°C for 5 min permanently scars the tissue
  - advantage: can "test" areas before committing to an ablation
  - disadvantage: takes much longer than RF (5 min per cryoablation vs. 1 min per RF ablation)

Indications
- paroxysmal SVT
  - AVNRT: accounts for more than half of all cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
  - re-entrant rhythm, with an accessory AV connection as the retrograde limb
  - corrected by targeting the accessory pathway
- atrial flutter: re-entry pathway in right atrium
- A Fib: potential role for pulmonary vein ablation
- ventricular tachycardia: focus arises from the right ventricular outflow tract and less commonly originates in the inferoseptal left ventricle near the apex (note: majority of cases of VT are due to scarring from previous MI and cannot be ablated)

Major Complications
- 1% of patients
- death: 0.1-0.2%
- cardiac: high grade AV block requiring permanent pacemaker (less risk with cryoablation), tamponade, pericarditis
- vascular: hematoma, vascular injury, thromboembolism, TIA/stroke
- pulmonary: PE

Ischemic Heart Disease

Epidemiology
- most common cause of cardiovascular morbidity and mortality
- Canadian-led INTERHEART study showed that 9 modifiable risk factors accounted for >90% of MI
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- M:F = 2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70
  - according to the Framingham Heart Study, men develop coronary heart disease at a rate double that of women for age <60; incidence in women triples shortly after menopause
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease see Family Medicine, FM7

Table 7. Risk Factors and Markers for Atherosclerotic Heart Disease

<table>
<thead>
<tr>
<th>Non-Modifiable Risk Factors</th>
<th>Modifiable Risk Factors</th>
<th>Markers of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Hyperlipidemia*</td>
<td>Elevated lipoprotein(a)</td>
</tr>
<tr>
<td>Male, postmenopausal female</td>
<td>HTN*</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Family history (FHx) of MI*</td>
<td>DM*</td>
<td>Elevated high-sensitivity C-reactive protein (hsCRP)</td>
</tr>
<tr>
<td>First degree male relative &lt;55</td>
<td>Cigarette smoking*</td>
<td>Carotid IMT/plaque</td>
</tr>
<tr>
<td>First degree female relative &lt;65</td>
<td>Psychosocial stress</td>
<td>Ankle-brachial index</td>
</tr>
<tr>
<td>Obesity</td>
<td>Sedentary lifestyle</td>
<td></td>
</tr>
<tr>
<td>Heavy alcohol intake</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Major risk factor
Chronic Stable Angina

**Definition**
- symptom complex resulting from an imbalance between oxygen supply and demand in the myocardium

**Etiology and Pathophysiology**
- factors that decrease myocardial oxygen supply:
  - decreased luminal diameter: atherosclerosis, vasospasm
  - decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - decreased hemoglobin: anemia
  - decreased SaO₂: hypoxemia
  - congenital anomalies
- factors that increase myocardial oxygen demand:
  - increased heart rate: hyperthyroidism
  - increased contractility: hyperthyroidism
  - increased wall stress: myocardial hypertrophy, aortic stenosis

**Signs and Symptoms**
- **typical**
  1. retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety
  2. predictably precipitated by the “3 Es”: exertion, emotion, eating
  3. brief duration, lasting <10-15 min and typically relieved by rest and nitrates
- atypical/probable angina (meets 2 of the above)
- non-cardiac chest pain (meets <1 of the above)
- Levine's sign: clutching fist over sternum when describing chest pain
- anginal equivalents: dyspnea, acute LV failure, flash pulmonary edema

**Clinical Assessment**
- history including directed risk factor assessment and physical exam
- labs: Hb, fasting glucose, fasting lipid profile
- ECG (at rest and during episode of chest pain if possible)
- CXR (suspected heart failure, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs or symptoms of pulmonary disease)
- stress testing (see Stress Testing, C13) or angiography
- echo
- to assess systolic murmur suggestive of aortic stenosis, mitral regurgitation, and/or HCM
- to assess LV function in patients with Hx of prior MI, pathological Q waves, signs or symptoms of CHF

**Differential Diagnosis**
- see Differential Diagnosis of Common Presentations, C4

---

**Figure 35. Pathophysiology of atherosclerosis**

- Hypertension
- Diabetes Mellitus
- Smoking
- Dyslipidemia
- Rheumatoid Arthritis

- Endothelial injury
- Monocyte recruitment
- Enhanced LDL permeability
  - Monocytes enter into initial space and differentiate into macrophages – LDL is converted into oxidized-LDL (OX-LDL)
  - Macrophages take up OX-LDL via scavenger receptors to become foam cells (‘fatty streak’ and lipid core of plaque)
- Cytokine and growth factor signaling from damaged endothelium and macrophages promote medial smooth muscle cell migration into the intima, proliferation (intimal hyperplasia), and release of matrix to form the fibrous cap of plaque – rupture depends on balance of pro- and anti-proteases, magnitude of necrosis and location of plaque (bifurcation sites are exposed to greater shear stress)
  - Calcification
  - Plaque rupture
  - Hemorrhage into plaque
  - Fragmentation
  - Wall weakening
- Increased vessel wall rigidity
- Thrombosis
- Lumen narrowing
- Emboli
- Aneurysm
Treatment of Chronic Stable Angina

1. General Measures
- goals: to reduce myocardial oxygen demand and/or increase oxygen supply
- lifestyle modification (diet, exercise)
- treatment of risk factors: statins (see Endocrinology, E5, Family Medicine, FM10 for target lipid guidelines), antihypertensives, etc.
- pharmacological therapy to stabilize the coronary plaque to prevent rupture and thrombosis

2. Antiplatelet Therapy (first-line therapy)
- ASA
- clopidogrel when ASA absolutely contraindicated

3. β-blockers (first-line therapy – improve survival in patients with hypertension)
- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β2 receptors)
- avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand

4. Nitrates (symptomatic control, no clear impact on survival)
- decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
- maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)

5. Calcium Channel Blockers (CCBs, second-line or combination)
- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- caution: verapamil/diltiazem combined with β-blockers may cause symptomatic sinus bradycardia or AV block

6. ACE Inhibitors (ACEI, not used to treat symptomatic angina)
- angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. HTN, DM, proteinuric renal disease, previous MI with LV dysfunction)
- benefit in all patients at high risk for CV disease (concomitant DM, renal dysfunction, or LV systolic dysfunction)

7. Invasive Strategies
- revascularization (see Coronary Revascularization, C31 and COURAGE trial sidebar)

VARIANT ANGINA (PRINZMETAL’S ANGINA)
- myocardial ischemia secondary to coronary artery vasospasm, with or without atherosclerosis
- uncommonly associated with infarction or LV dysfunction
- typically occurs between midnight and 8 am, unrelated to exercise, relieved by nitrates
- typically ST elevation on ECG
- diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
- treat with nitrates and CCBs

SYNDROME X
- typical symptoms of angina but normal angiogram
- may show definite signs of ischemia with exercise testing
- thought to be due to inadequate vasodilator reserve of coronary resistance vessels
- better prognosis than overt epicardial atherosclerosis

Acute Coronary Syndromes

Definition
- ACS includes the spectrum of UA, NSTEMI and STEMI; this distinction aids in providing the appropriate therapeutic intervention
- MI is defined by evidence of myocardial necrosis. It is diagnosed by a rise/fall of serum markers plus any one of:
  - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
  - ECG changes (ST-T changes, new BBB or pathological Q waves)
  - imaging evidence (myocardial loss of viability, wall motion abnormality, or intracoronary thrombus)
  - if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
- NSTEMI meets criteria for myocardial infarction without ST elevation or BBB
- STEMI meets criteria for myocardial infarction characterized by ST elevation or new BBB
Ischemic Heart Disease

Cardiology and Cardiac Surgery

Toronto Notes 2018

• UA is clinically defined by any of the following:
  ■ accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion decreased response to treatment
  ■ angina at rest
  ■ new-onset angina
  ■ angina post-MI or post-procedure (e.g. percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG])

Investigations

• history and physical
  ■ note that up to 30% of MIs are unrecognized or “silent” due to atypical symptoms – more common in women, DM, elderly, post-heart transplant (because of denervation)
• ECG
• CXR
• labs
  ■ serum cardiac biomarkers for myocardial damage (repeat 8 h later) (see Cardiac Biomarkers, C11)
  ■ CBC, INR/PTT electrolytes and magnesium, creatinine, urea glucose, serum lipids
  ■ draw serum lipids within 24-48 h because values are unreliable from 2-48 d post-MI

MANAGEMENT OF ACUTE CORONARY SYNDROMES

1. General Measures

• ABCs: assess and correct hemodynamic status first
• bed rest, cardiac monitoring, oxygen
• nitroglycerin SL followed by IV
• morphine IV

2. Anti-Platelet and Anticoagulation Therapy

• see also CCS Antiplatelet Guidelines 2012 for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
• ASA chewed
• NSTE MI
  ■ ticagrelor in addition to ASA or if ASA contraindicated, subcutaneous low molecular weight heparin or IV unfractionated heparin (UFH) (LMWH preferable, except in renal failure or if CABG is planned within 24 h)
  ■ clopidogrel used if patient ineligible for ticagrelor
  ■ if PCI is planned: ticagrelor or prasugrel and consider IV GP IIb/IIIa inhibitor (e.g. abciximab)
  ■ clopidogrel used if patient ineligible for ticagrelor and prasugrel
  ■ prasugel contraindicated in those with a history of stroke/TIA, and avoidance of or lower dose is recommended for those >75 yr old or weighing under 60 kg (TRITON-TIMI 38)
• anticoagulation options depend on reperfusion strategy:
  ■ primary PCI: UFH during procedure; bivalirudin is a possible alternative
  ■ thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
  ■ no reperfusion: LMWH (enoxaparin) until discharge from hospital
  ■ continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)

3. β-blockers

• STEMI contraindications include signs of heart failure low output states, risk of cardiogenic shock, heart block, asthma or airway disease; initiate orally within 24 h of diagnosis when indicated
• if β-blockers are contraindicated or if β-blockers/nitrates fail to relieve ischemia, non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (calcium channel blockers do not prevent MI or decrease mortality)

4. Invasive Strategies and Reperfusion Options

• UA/NSTEMI: early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  ■ recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  ■ CHF or LV dysfunction
  ■ hemodynamic instability
  ■ high (≥3) TIMI risk score (tool used to estimate mortality following an ACS)
  ■ sustained ventricular tachycardia
  ■ dynamic ECG changes
  ■ high-risk findings on non-invasive stress testing
  ■ PCI within the previous 6 mo
  ■ repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high risk features
  ■ note: thrombolysis is NOT administered for UA/NSTEMI

TIMI Risk Score for UA/NSTEMI

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Historical</strong></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 yr</td>
<td>1</td>
</tr>
<tr>
<td>≥3 risk factors for CAD</td>
<td>1</td>
</tr>
<tr>
<td>Known CAD (stenosis ≥50%)</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin* use in past 7 d</td>
<td>1</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td></td>
</tr>
<tr>
<td>Recent (≤24 h) severe angina</td>
<td>1</td>
</tr>
<tr>
<td>ST-segment deviation ≥0.5 mm</td>
<td>1</td>
</tr>
<tr>
<td>Increased cardiac markers</td>
<td>1</td>
</tr>
<tr>
<td><strong>Risk Score</strong> = Total Points</td>
<td></td>
</tr>
</tbody>
</table>

Note: more accurate risk quantification scores for UA/NSTEMI exist, such as the GRACE Risk Score; however, TIMI is still used most often
- STEMI
  - after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - goal is to re-perfuse artery: thrombolysis (“EMS-to-needle”) within 30 min or primary PCI (“EMS-to-balloon”) within 90 min (depending on capabilities of hospital and access to hospital with PCI facility)
  - thrombolysis
    - preferred if patient presents ≤12 h of symptom onset, and <30 min after presentation to hospital, has contraindications to PCI, or PCI cannot be administered within 90 min
- PCI
  - early PCI (≤12 h after symptom onset and <90 min after presentation) improves mortality vs. thrombolysis with fewer intra-cranial hemorrhages and recurrent MIs
  - primary PCI: without prior thrombolytic therapy – method of choice for reperfusion in experienced centres (JAMA 2004;291:736-739)
  - rescue PCI: following failed thrombolytic therapy (diagnosed when following thrombolysis, ST segment elevation fails to resolve below half its initial magnitude and patient still having chest pain)

![Diagram](image.png)

**Figure 36** Reperfusion strategy in STEMI

**Table 8. Contraindications for Thrombolysis in STEMI**

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior intracranial hemorrhage</td>
<td>Chronic, severe, poorly controlled HTN</td>
</tr>
<tr>
<td>Known structural cerebral vascular lesion</td>
<td>Uncontrolled HTN (sBP &gt;180, dBP &gt;110)</td>
</tr>
<tr>
<td>Known malignant intracranial neoplasm</td>
<td>Current anticoagulation</td>
</tr>
<tr>
<td>Significant closed-head or facial trauma (≤3 mo)</td>
<td>Noncompressible vascular punctures</td>
</tr>
<tr>
<td>Ischemic stroke (≥3 mo)</td>
<td>Ischemic stroke (≥3 mo)</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>Recent internal bleeding (≤2 4 wk)</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
<td>Prolonged CPR or major surgery (≤3 wk)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Active peptic ulcer disease</td>
</tr>
</tbody>
</table>

**Long-Term Management of ACS**
- risk of progression to MI or recurrence of MI or death is highest within 1 mo
- at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- pre discharge workup: ECG and echo to assess residual LV systolic function
- drugs required in hospital to control ischemia should be continued after discharge in all patients
- other medications for long-term management of ACS are summarized below

1. **General Measures**
   - education
   - risk factor modification

2. **Antiplatelet and Anticoagulation Therapy**
   - see also CCS Antiplatelet Guidelines 2012 for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
   - ECASA 81 mg daily
   - ticagrelor 90 mg twice daily or prasugrel 10 mg daily (at least 1 mo, up to 9-12 mo, if stent placed at least 12 mo)
   - clopidogrel 75 mg daily can be used as alternatives to ticagrelor and prasugrel when indicated
   - ± warfarin x 3 mo if high risk (large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)
3. **β-Blockers** (e.g. metoprolol 25-50 mg bid or atenolol 50-100 mg daily)

4. **Nitrates**
   - alleviate ischemia but do not improve outcome
   - use with caution in right-sided MI patients who have become preload dependent

5. **Calcium Channel Blockers** (NOT recommended as first line treatment, consider as alternative to β-blockers)

6. **Angiotensin-Converting Enzyme Inhibitors**
   - prevent adverse ventricular remodelling
   - recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
   - recommended for symptomatic CHF; reduced LVEF (<40%), anterior MI
   - use ARBs in patients who are intolerant of ACEI; avoid combining ACE and ARB

7. **± Aldosterone Antagonists**
   - if on ACEI and β-blockers and LVEF <40% and CHF or DM
   - significant mortality benefit shown with eplerenone by 30 d

8. **Statins** (early, intensive, irrespective of cholesterol level; e.g. atorvastatin 80 mg daily)

9. **Invasive Cardiac Catheterization if indicated** (risk stratification)

### Table 9: Complications of Myocardial Infarction

<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology</th>
<th>Presentation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arhythmia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Tachycardia</td>
<td>Sinus, A fib, VT, V fib</td>
<td>First 48 h</td>
<td>See Arhythmias, C 16</td>
</tr>
<tr>
<td>2. Bradycardia</td>
<td>Sinus, AV block</td>
<td>First 48 h</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial Rupture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. LV free wall</td>
<td>Transmural infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>2. Papillary muscle</td>
<td>Inferior infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>3. Ventricular septum</td>
<td>Septal infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td><strong>Shock/CHF</strong></td>
<td></td>
<td></td>
<td>Inotropes, intra-aortic balloon pump</td>
</tr>
<tr>
<td>1. Pericardial effusion</td>
<td>Infarction or aneurysm</td>
<td>Within 48 h</td>
<td>Inotropes, intra-aortic balloon pump</td>
</tr>
<tr>
<td><strong>Post-Infarct Angina</strong></td>
<td>Persistent coronary stenosis</td>
<td>Anytime</td>
<td>Aggressive medical therapy PCI or CABG</td>
</tr>
<tr>
<td><strong>Recurrent MI</strong></td>
<td>Multivessel disease</td>
<td>Anytime</td>
<td>Aggressive medical therapy PCI or CABG</td>
</tr>
<tr>
<td><strong>Thromboembolism</strong></td>
<td>Mural/epicard thrombus</td>
<td>1-10 d, up to 6 mo</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td><strong>Pericarditis</strong></td>
<td>Inflammatory</td>
<td>1-7 d</td>
<td>ASA</td>
</tr>
<tr>
<td><strong>Dressler’s Syndrome</strong></td>
<td>Autoimmune</td>
<td>2 8 wk</td>
<td></td>
</tr>
</tbody>
</table>
PERCUTANEOUS CORONARY INTERVENTION

- interventional cardiology technique aimed at relieving significant coronary stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

**Indications**
- medically refractory angina
- NSTEMI/UA with high risk features (e.g. high TIMI risk score, see sidebar C28)
- primary/rescue PCI for STEMI

**Balloon Angioplasty and Intracoronary Stenting**
- coronary lesions dilated with balloon inflation
- major complication is restenosis (approximately 15% at 6 mo), felt to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
- bare metal stent (BMS) versus drug-eluting stents: PRAMI trial demonstrated stenting non-culprit lesions results in 14% absolute risk reduction of cardiac death, nonfatal MI, or refractory angina
- coated with antiproliferative drugs (sirolimus, paclitaxel, everolimus)
- reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
- complication: late stent thrombosis (5 events per 1,000 stents implanted)
Adjunctive Therapies
- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
  - dual antiplatelet therapy (ASA and clopidogrel) for 1 mo with BMS or ≥12 mo with DES
  - DAPT study showed benefit of dual antiplatelet therapy beyond 12 mo
- ASA and prasugrel can be considered for those at increased risk of stent thrombosis

Procedural Complications
- mortality and emergency bypass rates <1%
- nonfatal MI: approximately 2-3%

CORONARY ARTERY BYPASS GRAFT SURGERY
- objective of CABG is complete reperfusion of the myocardium

Indications
- CABG
  - ≥50% diameter stenosis in the left main coronary artery
  - ≥70% diameter stenosis in three major coronary arteries
  - ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
  - survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery
- other
  - ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
  - ≥70% diameter stenosis in the proximal LAD artery and evidence of ischemia
  - multivessel CAD in patients with diabetes
  - LV systolic dysfunction (LVEF 35% to 50%) and significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization
- PCI
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG
  - CABG or PCI
    - one or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

Table 11. Conduits for CABG

<table>
<thead>
<tr>
<th>Graft</th>
<th>Occlusion/Patency Rate</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saphenous Vein Grafts</td>
<td>At 10 yr, 50% occluded, 25% stenotic, 25% angiographically normal</td>
<td>Used when arterial grafts are not available or many grafts are required, such as triple or quadruple bypass</td>
</tr>
<tr>
<td>Left Internal Thoracic/Mammary Artery (LITA/LIMA)</td>
<td>90-95% patency at 15 yr</td>
<td>Most preferred option because of excellent patency and decreased need for repeated revascularization procedures</td>
</tr>
<tr>
<td>Right Internal Thoracic/ Mammary Artery (RITA/RIMA)</td>
<td>Pedicled RIMA patency comparable to LIMA</td>
<td>Used in bilateral ITA/IMA grafting</td>
</tr>
<tr>
<td>Radial Artery (free graft)</td>
<td>85-90% patency at 5 yr</td>
<td>Prone to severe vasospasm post-operatively due to muscular wall</td>
</tr>
<tr>
<td>Right Gastroepiploic Artery</td>
<td>80-90% patency at 5 yr</td>
<td>Primarily used as an in situ graft to bypass the RCA.</td>
</tr>
<tr>
<td>Complete Arterial Revascularization</td>
<td>For younger patients (&lt;60 yr of age)</td>
<td>Is preferred due to longer term graft patency</td>
</tr>
<tr>
<td>Redo Bypass Grafting</td>
<td>Operative mortality 2.3x higher than first operation</td>
<td>10% perioperative MII rate</td>
</tr>
</tbody>
</table>

Table 10 Choice of Revascularization Procedure

<table>
<thead>
<tr>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td></td>
</tr>
<tr>
<td>Less invasive technique</td>
<td>Greater ability to achieve complete revascularization procedures</td>
</tr>
<tr>
<td>Decreased peri procedural morbidity and mortality</td>
<td>Decreased need for repeated revascularization procedures</td>
</tr>
<tr>
<td>Shorter peri procedural hospitalization</td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td></td>
</tr>
<tr>
<td>Single or double vessel disease</td>
<td>Triple vessel or left main disease</td>
</tr>
<tr>
<td>Inability to tolerate surgery</td>
<td>DM</td>
</tr>
</tbody>
</table>

Table 11. Conduits for CABG

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</tr>
</tbody>
</table>


Study: RCT comparing whether shortening the duration of clopidogrel therapy from 6 months to 6 weeks after DES implantation was associated with superior net clinical outcome in patients receiving concomitant aspirin and OAC.

Population: 514 patients from 3 European centres receiving DES implantation on OAC and aspirin.

Intervention: 6 week vs. 6 month clopidogrel therapy post-DES

Outcome: Death, myocardial infarction, definite stent thrombosis, stroke, thrombolysis in myocardial infarction major bleeding at 9 months

Results: Primary endpoint occurred in 8.9% in 6 week group vs. 27 patients in 6 month group (HR: 1.14; 95% CI: 0.88-1.91; p-0.63)

Conclusions: Six weeks of triple therapy is not superior to 6 months. Physician should weigh trade-off between ischemic and bleeding risk when choosing shorter or longer duration of triple therapy

Percutaneous Coronary Intervention vs. Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease: The SYNTAX Trial. NEJM 2009;360:961-972

Study: Prospective RCT.

Population: 1,800 patients with untreated three-vessel or left main coronary artery disease and anatomically equivalent for both Percutaneous Intervention (PCI) and Coronary Artery Bypass Graft (CABG).

Intervention: PCI vs. CABG.

Outcome: Composite of death from any cause, stroke, MI, or repeat revascularization in 12 mo post-intervention.

Results: Incidence of primary outcome was lower in the CABG intervention vs. PCI (12.4% vs. 17.8%, p=0.002, NNT=19). PCI was associated with significantly higher rates of repeat revascularization (13.5% vs. 5.9%, p<0.001) and cardiac death (13.7% vs. 2.1%, p=0.009), while CABG had higher rates of stroke (2.2% vs. 0.6%, p=0.03).

Conclusions: In patients with three-vessel or left main coronary artery disease CABG is superior to PCI in preventing major adverse cardiac, cerebrovascular events within 12 mo of intervention.
Operative Issues
- Left ventricular (LV) function is an important determinant of outcome of all heart diseases
- Patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- Assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, stress echocardiography, PET scanning, or MRI

CABG and Antiplatelet Regimens
- Please refer to CCS guidelines – 2012 update on antiplatelet therapy – for more information if possible
- Prior to CABG, clopidogrel, and ticagrelor should be discontinued for 5 days and prasugrel for 7 days before surgery
- Dual antiplatelet therapy should be continued for 12 months in patients with ACS within 48–72 hours after CABG
- ASA (81 mg) continued indefinitely (can be started 6 hours after surgery)
- Patients requiring CABG after PCI should continue their dual antiplatelet therapy as recommended in the post-PCI guidelines

Table 12. Risk Factors for CABG Mortality and Morbidity (decreasing order of significance)

<table>
<thead>
<tr>
<th>Risk Factors for CABG Mortality</th>
<th>Risk Factors for CABG Post-Operative Morbidity or Increased Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency of surgery (emergent or urgent)</td>
<td>Reoperation</td>
</tr>
<tr>
<td>Reoperation</td>
<td>Emergent procedure</td>
</tr>
<tr>
<td>Older age</td>
<td>Pre-operative intra-aortic balloon pump (IABP)</td>
</tr>
<tr>
<td>Poor left ventricular function (see below)</td>
<td>CHF</td>
</tr>
<tr>
<td>Female gender</td>
<td>CABG + valve surgery</td>
</tr>
<tr>
<td>Left main disease</td>
<td>Older age</td>
</tr>
<tr>
<td>Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, DM, cereb ovascular disease, and peripheral vascular disease</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
</tbody>
</table>

Procedural Complications
- CABG using cardiopulmonary bypass (CPB)
  - Stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
  - Immunosuppression
  - Systemic inflammatory response leading to
    - Myocardial dysfunction
    - Renal dysfunction
    - Neurological injury
    - Respiratory dysfunction
    - Coagulopathies

OFF-PUMP CORONARY ARTERY BYPASS SURGERY

Procedure
- Avoids the use of CPB by allowing surgeons to operate on a beating heart
  - Stabilization devices (e.g., Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
  - Procedure is safe and well tolerated by most patients; however, this surgery remains technically more demanding

Indications
- Used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe peripheral vascular disease (PVD), severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g., Jehovah's Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- **Absolute contraindications**: hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels, and calcified coronary vessels
- **Relative contraindications**: cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

Outcomes
- OPCAB decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
- No significant difference in terms of survival at 2 years, frequency of cardiac events (MI, PCI, CHF, recurrent angina, redo CABG), or medication usage compared to on-pump CABG

Safety and Efficacy of Drug-Eluting and Bare Metal Stents
Circulation 2009; 119:3193-3206
Study: Meta-analysis of RCTs and observational studies. 22 RCTs and 34 observational studies.
Population: 8,470 and 182,901 patients in RCTs and observational studies respectively who underwent percutaneous coronary intervention.
Intervention: Drug-Eluting Stents (DES) versus Bare Metal Stents (BMS).
Outcome: All-cause mortality, myocardial infarction (MI), and target vessel revascularization (TVR).
Result: No difference in mortality was found between DES vs. BMS by RCTs, while observational studies showed significantly lower mortality rates in DES-treated patients (hazard ratio [HR] 0.79, p<0.001). No difference in MI incidence was found in RCTs, while lower incidences of MI were found in observational studies (HR 0.87, p=0.014). DES has a significantly lower TVR rate in both RCT (HR 0.45, p<0.001) and observational studies (HR 0.46, p<0.001).
Conclusions: DES significantly reduces rates of TVR compared to BMS. Although there is no difference in mortality or MI incidence as found by RCTs, observational studies suggest lower mortality and MI rates in patients with DES over BMS.
Heart Failure

- see also CCS Heart Failure Guidelines 2012 for details (free mobile apps available on iOS and Android platforms in the CCS app stores) as well as the CCS Heart Failure Guidelines Compendium available at CCS.ca

Congestive Heart Failure

Low-Output HF

due to decreased cardiac output

Systolic Dysfunction

Injury and ischemia in myocardium
Infarction and inflammation

Diastolic Dysfunction

Infiltration and fibrosis
Thick, stiffened myocardium

High-Output HF

due to increased cardiac demand

Increased Cardiac Workload

- Myocardial stress
- Volume overload
- Pressure overload

Compensation

- Increased heart rate and myocardial contractility
- Increased blood volume

Decompensation

- Deterioration of heart function
- Heart unable to maintain blood circulation

Increased venous congestion

Pulmonary vascular congestion
- Fluid accumulation in lungs, apnea, shortness of breath, fatigue, weakness

Does this Dyspneic Patient in the Emergency Department have Congestive Heart Failure?

<table>
<thead>
<tr>
<th>Test</th>
<th>LR + (95% CI)</th>
<th>LR – (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial clinical judgment</td>
<td>4.4 (1.8-10.0)</td>
<td>0.45 (0.28-0.73)</td>
</tr>
<tr>
<td>Past Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>5.9 (4.1-8.0)</td>
<td>0.45 (0.38-0.53)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.1 (2.0-4.9)</td>
<td>0.69 (0.58-0.82)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.8 (1.1-2.9)</td>
<td>0.68 (0.48-0.96)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>2.6 (1.5-4.5)</td>
<td>0.7 (0.54-0.91)</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>2.2 (1.2-3.9)</td>
<td>0.65 (0.45-0.92)</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>1.3 (1.2-1.6)</td>
<td>0.48 (0.35-0.67)</td>
</tr>
<tr>
<td>Physical Exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JVP with abdominojugular reflux, and Kussmaul’s sign</td>
<td>5.1 (3.2-7.9)</td>
<td>0.66 (0.57-0.77)</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>5.1 (3.2-7.9)</td>
<td>0.66 (0.57-0.77)</td>
</tr>
<tr>
<td>Rales</td>
<td>2.8 (1.9-4.1)</td>
<td>0.51 (0.41-0.63)</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>2.3 (1.5-3.7)</td>
<td>0.64 (0.47-0.87)</td>
</tr>
<tr>
<td>Chest Radiograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary venous congestion</td>
<td>12 (6.8-21)</td>
<td>0.48 (0.29-0.83)</td>
</tr>
<tr>
<td>Interstitial edema</td>
<td>12 (6.8-21)</td>
<td>0.68 (0.44-1.06)</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>3.3 (2.4-4.7)</td>
<td>0.33 (0.23-0.48)</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.8 (1.7-8.8)</td>
<td>0.79 (0.65-0.96)</td>
</tr>
<tr>
<td>Any abnormal finding</td>
<td>2.2 (1.6-3.1)</td>
<td>0.64 (0.47-0.88)</td>
</tr>
</tbody>
</table>

Table 13. Signs and Symptoms of Left vs. Right Heart Failure

<table>
<thead>
<tr>
<th>Left Failure</th>
<th>Right Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Cardiac Output (Forward)</td>
<td>Fatigue  Syncope  Systemic hypotension  Cool extremities  Slow capillary refill  Peripheral cyanosis  Pulsus alternans  Precordial heave</td>
</tr>
<tr>
<td>Venous Congestion (Backward)</td>
<td>Dyspnea, orthopnea, PND  Cough  Crackles</td>
</tr>
<tr>
<td>Left failure symptoms if decreased RV output leads to LV underfilling Tricuspid regurgitation S3 (right-sided)</td>
<td></td>
</tr>
<tr>
<td>Peripherial edema  Elevated JVP with abdominojugular reflux, and Kussmaul’s sign  Hepatomegaly  Pulsatile liver</td>
<td></td>
</tr>
</tbody>
</table>

Figure 39. Congestive Heart Failure

Dichotomies of Heart Failure

- Forward vs. backward
- Left-sided vs. right-sided
- Systolic vs. diastolic dysfunction
- Low output vs. high output

Use Ejection Fraction to Grade LV Dysfunction

- Grade I (EF >60%) (Normal)
- Grade II (EF = 40-59%)
- Grade III (EF = 21-39%)
- Grade IV (EF ≤20%)
Pathophysiology
- most common causes are ischemic heart disease, hypertension and valvular heart disease
- myocardial insult causes pump dysfunction/impaired filling leading to myocardial remodelling
  - pressure overload (e.g. AS or HTN) leads to compensatory hypertrophy (concentric remodelling) and eventually interstitial fibrosis
  - volume overload (e.g. AI) leads to dilatation (eccentric remodelling)
  - both processes lead to maladaptive changes contributing to disease process
  - results in decreased volume cardiac output resulting in activation of the SNS and RAAS
- Na\(^+\) and water retention, increasing preload and afterload, tachycardia perpetuates cycle of increasing cardiac demand and decompensation

Heart Failure with Reduced Ejection Fraction
- impaired myocardial contractile function \(\rightarrow\) decreased LVEF and SV \(\rightarrow\) decreased CO

Volume Overload and Eccentric Remodelling is the Typical Phenotype
- findings: apex beat displaced, S3, cardiothoracic ratio >0.5, decreased LVEF, LV dilatation
- causes
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - alcohol (and other toxins)
    - myocarditis
    - dilated cardiomyopathy (multiple causes – see Dilated Cardiomyopathy, C40)

Heart Failure with Preserved Ejection Fraction
- previously known as “diastolic heart failure”
- concentric remodelling with a “stiff” left ventricle is the typical phenotype
- 1/2 of patients with heart failure have preserved EF; confers similar prognosis to HRF; more common in the elderly and females
- reduced LV compliance causes increased LV filling pressures, increased LA pressure/volume, and pulmonary congestion
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal EF
- causes
  - transient ischemia (relaxation of myocardium is active and requires ATP)
  - permanent
    - severe hypertrophy (HTN, aortic stenosis, HCM)
    - restrictive cardiomyopathy (e.g. amyloid)
  - MI

High-Output Heart Failure
- caused by demand for increased cardiac output
- often exacerbates existing heart failure or decompensates a patient with other cardiac pathology
- differential diagnosis: anemia, thiamine deficiency (beriberi), hyperthyroidism, A-V fistula or L-R shunting, Paget’s disease, renal disease, hepatic disease

Precipitants of Symptomatic Exacerbations
- consider natural progression of disease vs. new precipitant
- always search for reversible cause
- differential diagnosis can also be organized as follows:
  - new cardiac insult/disease: MI, arrhythmia, valvular disease
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection, etc.
  - medication non-compliance
  - dietary indiscretion e.g. salt intake
  - obstructive sleep apnea

Investigations
- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), BUN, creatinine, fasting blood glucose, HbA1c, lipid profile, liver function tests, serum TSH ± ferritin, BNP, uric acid
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchial alveolar cuffing
- echo: systolic function (LVEF), diastolic function (E/A ratio, E’e), cardiac dimensions, wall motion abnormalities, RVSP (from TR jet), valvular disease, pericardial effusion
- radionuclide angiography: LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

A Validated Clinical and Biochemical Score for the Diagnosis of Acute Heart Failure: the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Acute Heart Failure Score

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Possible Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 yr</td>
<td>1</td>
</tr>
<tr>
<td>Orthopnea present</td>
<td>2</td>
</tr>
<tr>
<td>Lack of cough</td>
<td>1</td>
</tr>
<tr>
<td>Current loop diuretic use (before presentation)</td>
<td>1</td>
</tr>
<tr>
<td>Rales on lung exam</td>
<td>1</td>
</tr>
<tr>
<td>Lack of fever</td>
<td>2</td>
</tr>
<tr>
<td>Elevated NT-proBNP</td>
<td>4</td>
</tr>
<tr>
<td>(&gt;450 pg/mL if &lt;50 yr, &gt;900 pg/mL if &gt;50 yr)</td>
<td>2</td>
</tr>
<tr>
<td>Interstitial edema on chest x-ray</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
</tr>
</tbody>
</table>

Likelihood of heart failure
- Low = 0-5
- Intermediate = 6-8
- High = 9-14

Brain natriuretic peptide (BNP) is secreted by ventricles due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into ventricles, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP. The above scoring algorithm developed by Ridgway et al. is commonly used. A score of <6 has a negative predictive value of 98%, while scores ≥6 had a sensitivity of 96% and specificity of 84% (p = 0.001) for the diagnosis of acute heart failure.

New York Heart Association (NYHA)

Functional Classification of Heart Failure
- Class I: ordinary physical activity does not cause symptoms of HF
- Class II: comfortable at rest, ordinary physical activity results in symptoms
- Class III: marked limitation of ordinary activity; less than ordinary physical activity results in symptoms
- Class IV: inability to carry out any physical activity without discomfort; symptoms may be present at rest

Toronto Notes 2018
Acute Treatment of Pulmonary Edema

- treat acute precipitating factors (e.g., ischemia, arrhythmias)
- L – Lasix (furosemide) 40–500 mg IV
- M – morphine 2–4 mg IV; decreases anxiety and preload (venodilation)
- N – nitroglycerin: topical/IV/SI – use with caution in preload-dependent patients (e.g., right HF or RV infarction) as it may precipitate CV collapse
- O – oxygen: in hypoxemic patients
- P – positive airway pressure (CPAP/BiPAP); decreases preload and need for ventilation when appropriate
- P – position: sit patient up with legs hanging down unless patient is hypotensive
- in ICU setting or failure of LMNOPP, other interventions may be necessary
  - nitroprusside IV
  - hydralazine PO
  - sympathomimetics
    - dopamine
      - low dose: selective renal vasodilation (high potency D1 agonist)
      - medium dose: inotropic support (medium potency β1 agonist)
      - high dose: increases SVR (low potency β1 agonist) which is undesirable
  - dobutamine
    - β1-selective agonist causing inotropy, tachycardia, hypotension (low dose) or hypertension (high dose); most serious side effect is arrhythmia, especially AF
  - phosphodiesterase inhibitors (milrinone)
    - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
- consider pulmonary artery catheter to monitor pulmonary capillary wedge pressure (PCWP) if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
  - intra-aortic balloon pump (IABP) - reduces afterload via systemic unloading and improves coronary perfusion via diastolic augmentation
  - left or right ventricular assist device (LVAD/RVAD)
  - cardiac transplant

Long-Term Management

- overwhelming majority of evidence-based management applies to HFREF
- currently no proven pharmacologic therapies shown to reduce mortality in HFPEF; control risk factors (e.g., hypertension)

Conservative Measures

- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease alcohol consumption, patient education, sodium and fluid restriction
- multidisciplinary heart failure clinics: for management of individuals at higher risk, or with recent hospitalization

Non-Pharmacological Management

- from CCS guidelines (2013 update)
- cardiac rehabilitation: participation in a structured exercise program for NYHA class I-III after clinical status assessment to improve quality of life (HF-ACTION trial)

Pharmacological Therapy

1. Renin-angiotensin-aldosterone blockade

   - ACEI: standard of care – slows progression of LV dysfunction and improves survival
   - all asymptomatic patients functional class II IV
   - all asymptomatic patients with LVEF <40%
   - post-MI
   - angiotensin II receptor blockers
     - second-line to ACEI if not tolerated, or as adjunct to ACEI if β-blockers not tolerated
     - combination with ACEI is not routinely recommended and should be used with caution as it may precipitate hyperkalemia, renal failure, the need for dialysis and increase (CHARM, ONTARGET)
   - combination angiotensin II receptor blockers with nephrilysin inhibitors (ARNI) is a new class of medication that has morbidity and mortality benefit over ACEI alone; it has been recommended to replace ACEI or ARBs for patients who have persistent symptoms (PARADIGM HF)

2. β-blockers: slow progression and improve survival

   - class I-III with LVEF <40%
   - stable class IV patients
   - carvedilol improves survival in class IV HF (COMET)
   - note: should be used cautiously, titrate slowly because may initially worsen CHF

Can the Clinical Examination Diagnose Left-Sided Heart Failure in Adults?

From The Rational Clinical Examination JAMA 2009. http://www.jamaevidence.com/content/3471892
Study: Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of CHF.
Results: The diagnosis of left ventricular dysfunction in patient after an MI based on the presence of radiographic pulmonary venous congestion with edema, rales, and third heart sound had a positive likelihood ratio (+LR) of 3.1 (95% CI 1.7–5.8) and a negative likelihood ratio (–LR) of 0.41 (95% CI 0.30–0.56). Female sex was -LR of 1.8 (95% CI 1.2–2.2) and SBP ≥160 mmHg (+LR, 1.8 [95% CI 1.3–2.4]) were the most indicative for diastolic dysfunction. Heart rate ≥100/min (+LR 0.43 [95% CI 0.29–0.63]) and left atrial ECG abnormality (+LR 0.42 [95% CI 0.26–0.63]) were most indicative for systolic dysfunction.
Conclusions: Patients with signs, symptoms, and risk factors for systolic dysfunction should receive an ECG and CPR. Female sex and SBP ≥160 mmHg are suggestive of diastolic dysfunction; heart rate ≥100/min and left atrial ECG abnormality suggest systolic dysfunction.
3. **Mineralocorticoid receptor (aldosterone) antagonists**: mortality benefit in symptomatic heart failure and severely depressed ejection fraction
   - spironolactone or eplerenone symptomatic heart failure in patients already on ACEI, beta blocker and loop diuretic
   - note: potential for life threatening hyperkalemia
   - monitor K⁺ after initiation and avoid if Cr >220 µmol/L or K⁺ >5.2 mmol/L

4. **Diuretics**: symptom control, management of fluid overload
   - furosemide (40-500 mg daily) for potient diuresis
   - metolazone may be used with furosemide to increase diuresis
   - furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by β-blockers, ACEI, ARBs, and aldosterone antagonists

5. **Digoxin and cardiac glycosides**: digoxin improves symptoms and decreases hospitalizations, no effect on mortality
   - indications: patient in sinus rhythm and symptomatic on ACEI, or CHF and AFlb
   - patients on digitalis glycosides may worsen if these are withdrawn.

6. **Antiarrhythmic drugs**: for use in CHF with arrhythmia
   - can use amiodarone, β-blocker, or digoxin

7. **Anticoagulants**: warfarin for prevention of thromboembolic events
   - prior thromboembolic event or AFlb, presence of LV thrombus on echo

### Procedural Interventions
- resynchronization therapy: symptomatic improvement with biventricular pacemaker
- consider if QRS >130 msec, LVEF <35%, and persistent symptoms despite optimal therapy
- greatest benefit likely with marked LV enlargement, mitral regurgitation, QRS >150 msec
- ICD: mortality benefit in 1st prevention of sudden cardiac death
- prior MI, optimal medical therapy, LVEF <30%, clinically stable
- prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
- LVAD/RVAD (see Ventricular Assist Devices, C38)
- cardiac transplantation (see Cardiac Transplantation, C38)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see Valvular Heart Disease, C43)

### Sleep-Disordered Breathing
- 45-55% of patients with CHF have sleep disturbances, including Cheyne-Stokes breathing and sleep apnea (central or obstructive)
- associated with a worse prognosis and greater LV dysfunction
- nasal continuous positive airway pressure (CPAP) is effective in treating symptoms of sleep apnea with secondary beneficial effects in cardiac function and symptoms

### Influence of Ejection Fraction on Cardiac Outcomes

<table>
<thead>
<tr>
<th>LVEF</th>
<th>CHF Hospitalization</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>22%</td>
<td>14.9%</td>
<td>15.4%</td>
</tr>
<tr>
<td>23-32%</td>
<td>10.9%</td>
<td>10.6%</td>
</tr>
<tr>
<td>33-42%</td>
<td>7.2%</td>
<td>7.4%</td>
</tr>
<tr>
<td>43-52%</td>
<td>5.7%</td>
<td>5.2%</td>
</tr>
<tr>
<td>&gt;52%</td>
<td>6.9%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

### Higher New York Heart Association Classes and Increased Mortality and Hospitalization in Patients with Heart Failure and Preserved Left Ventricular Function

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Proportion of All-Cause Hospitalization</th>
<th>Proportion of All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>60.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>I</td>
<td>65.2%</td>
<td>21.3%</td>
</tr>
<tr>
<td>III</td>
<td>77.7%</td>
<td>35.9%</td>
</tr>
<tr>
<td>IV</td>
<td>75.0%</td>
<td>59.3%</td>
</tr>
</tbody>
</table>

### Chronic Treatment of CHF
- ACEI
- β-blockers
- Mineralocorticoid receptor antagonists
- Diuretic
- Inotrope
- Antiarrhythmic
- Anticoagulant

*Mortality benefit*
**Cardiac Transplantation**

- treatment for end-stage heart disease; due to ischemic or non-ischemic cardiomyopathy
- worldwide 1 yr survival is 85-90%, 3 yr survival about 60%, annual mortality rate of 4%
- matching is according to blood type, body size and weight (should be within 25%), and HLA tissue matching (if time allows)

**Indications for Surgery**
- severe cardiac disability despite maximal medical therapy (e.g. recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 mL/kg/min in absence of β-blocker)
- symptomatic cardiac ischemia refractory to conventional treatment (e.g. unstable angina not amenable to CABG or PCI with LVEF <30%; recurrent, symptomatic ventricular arrhythmias)
- exclusion of all surgical alternatives to cardiac transplantation

**Relative Contraindications**
- incurable malignancy
- major systemic illness
- irreversible major organ disease
- active systemic infection
- obesity
- irreversible pulmonary HTN (pulmonary vascular resistance [PVR] >6 Wood units)
- severe COPD (FEV₁ <1 L)
- active drug addiction or alcoholism

**Prerequisites**
- psychosocial stability
- medically compliant and motivated

**Complications**
- rejection
  - common, <5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
  - risk of acute rejection is greatest during the first 3 mo after transplant
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
  - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft CAD
  - approximately 50% develop graft CAD within 5 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
  - second most common cause of late death following transplantation
  - cutaneous neoplasms most common, followed by non-Hodgkin’s lymphoma and lung cancer
  - immunosuppressive medication side effects (prednisone, cyclosporine, tacrolimus, sirolimus)

**Ventricular Assist Devices**
- work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD), or both ventricles (BiVAD)
- indications:
  - bridge to transplantation, bridge to decision (for transplant), or long term permanent therapy (“destination therapy”)
  - post-operative mechanical support when unable to separate from cardiopulmonary bypass despite inotropic and intra-aortic balloon pump (IABP) support
    - IABP is a catheter based device inserted into the femoral artery and advanced to the descending aorta that decreases myocardial O₂ demand and increases blood flow to coronary arteries
    - inflation of the balloon occurs during diastole to increase ascending aorta and coronary artery perfusion pressure; deflation occurs at systole to reduce intra-aortic pressure thus reducing afterload
  - post-operative cardiogenic shock

**REMATCH Trial**

**Canadian Cardiovascular Society Focused Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive: Fitness following Left Ventricular Assist Device Implantation**

**Effects of Donor Pre-Treatment with Dopamine on Survival After Heart Transplantation: A Cohort Study of Heart Transplant Recipients Nestled in a Randomized Controlled Multicentre Trial**

**REMATCH Trial:**

Increased survival of 23% vs. 8% with LVAD vs. medical management of heart failure after 2 yr. Heartmate VAD has a biologic surface, the efore, does not require long-term anticoagulation but higher risk of infection.

**Canadian Cardiovascular Society Focused Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive: Fitness following Left Ventricular Assist Device Implantation:**

Patients with a continuous flow, NYHA class I-II, LVAD that are stable 2 mo post LVAD implantation qualify for private driving only and are disqualified from commercial driving.
Myocardial Disease

Definition of Cardiomyopathy
- intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
- functional classification: dilated, hypertrophic, or restrictive
- LV dysfunction 2º to MI often termed "ischemic cardiomyopathy", is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD

Table 14. Summary Table for CHF and Myocardial Disease

<table>
<thead>
<tr>
<th>Heart Failure Reduced Ejection Fraction</th>
<th>Heart Failure Preserved Ejection Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated Cardiomyopathy</td>
<td>Secondary Causes</td>
</tr>
<tr>
<td>Idiopathic, infectious (e.g. myocarditis) alcohol, familial, collagen vascular disease, etc</td>
<td>CAD, MI, DM, valvular (e.g. AR, MR)</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>Genetic disorder affecting cardiac sarcomeres (most common cause of sudden cardiac death in young athletes)</td>
</tr>
<tr>
<td>Restrictive Cardiomyopathy</td>
<td>Amyloidosis, sarcoidosis, sclerosis, hemochromatosis, Fabry’s, Pompe’s Disease, Loeffler’s, etc.</td>
</tr>
<tr>
<td>Secondary Causes</td>
<td>HTN, DM, valvular (e.g. AS), post-MI, transiently by ischemia, etc.</td>
</tr>
</tbody>
</table>

Myocarditis

Definition
- inflammatory process involving the myocardium ranging from acute to chronic; an important cause of dilated cardiomyopathy

Etiology
- idiopathic
- infectious
  - viral (most common): parvovirus B19, influenza, coxsackie B, echovirus, poliovirus, HIV, mumps
  - bacterial: S. aureus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia
  - fungi
  - spirochetal (Lyne disease – Borrelia burgdorferi)
  - Chagas disease (Trypanosoma cruzi), toxoplasmosis
- toxic: catecholamines, chemotherapy, cocaine
- hypersensitivity/eosinophilic: drugs (antibiotics, diuretics, lithium, clozapine), insect/snake bites
- systemic diseases: collagen vascular diseases (SLE, rheumatoid arthritis, others), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

Signs and Symptoms
- constitutional symptoms
- acute CHF - dyspnea, tachycardia, elevated JVP
- chest pain – due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- pre-syncpe/syncope/sudden death

Investigations
- ECG: non-specific ST-T changes ± conduction defects
- blood work
  - increased CK, troponin, LDH, and AST with acute myocardial necrosis ± increased WBC, ESR, ANA, rheumatoid factor, complement levels
  - blood culture, viral titres and cold agglutinins for Mycoplasma
- CXR: enlarged cardiac silhouette
- echo: dilated, hypokinetic chambers, segmental wall motion abnormalities
- cardiovascular magnetic resonance: functional and morphological abnormalities as well as tissue pathology (gadolinium enhancement)
- myocardial biopsy

Management
- supportive care
- restrict physical activity
- treat CHF
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible
Prognosis
- often unrecognized, and may be self-limited
- myocarditis treatment trial showed 5 yr mortality between 25-50%
- giant cell myocarditis, although rare can present with fulminant CHF and be rapidly fatal, with 5 yr mortality >80%
- sudden death in young adults
- may progress to dilated cardiomyopathy

Dilated Cardiomyopathy

Definition
- unexplained dilation and impaired systolic function of one or both ventricles

Etiology
- idiopathic (presumed viral or idiopathic) ~50% of DCM
- alcohol
- familial/genetic
- uncontrolled tachycardia (e.g. persistent rapid AFib)
- collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
- infectious: viral (coxsackie B, HIV), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever toxoplasmosis
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), anti-retrovirals, chloroquine, clozapine, TCA
- radiation

Signs and Symptoms
- may present as:
  - CHF
  - systemic or pulmonary emboli
  - arrhythmias
  - sudden death (major cause of mortality due to fatal arrhythmia)

Investigations
- blood work: CBC, electrolytes, Cr, bicarbonate, BNP CK, troponin, LFTs, TSH, TIBC
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (non-sustained VT)
- CXR: global cardiomegaly (globular heart), signs of CHF, pleural effusion
- echo: chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- coronary angiography: in selected patients to exclude ischemic heart disease

Management
- treat underlying disease: e.g. abstinence from alcohol
- treat CHF: see Heart Failure, C34
- thromboembolism prophylaxis: anticoagulation with warfarin
  - indicated for: AFib, history of thromboembolism or documented thrombus
- treat symptomatic or serious arrhythmias
- immunize against influenza and S. pneumoniae
- consider surgical options (e.g. LVAD, transplant, volume reduction surgery) in appropriate candidates with severe, drug refractory disease
- consider ICD among patients with a LVEF <30%

Prognosis
- depends on etiology
- better with reversible underlying cause, worst with infiltrative diseases, HIV, drug-induced
- cause of death usually CHF (due to pump failure) or sudden death 2° to ventricular arrhythmias
- systemic emboli are significant source of morbidity
- 20% mortality in 1st yr, 10% per year after
Hypertrophic Cardiomyopathy

- see 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy for details

Definition
- defined as unexplained ventricular hypertrophy
- various patterns of HCM are classified, but most causes involve pattern of septal hypertrophy

Etiology and Pathophysiology
- histopathologic features include myocyte disarray, myocyte hypertrophy, and interstitial fibrosis
- cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins (>400 mutations associated with autosomal dominant inheritance, incomplete penetrance)
- prevalence of 1/500-1/1,000 in general population
- generally presents in early adulthood

Hemodynamic Classification
- hypertrophic obstructive cardiomyopathy (HOCM): dynamic LV outflow tract (LVOT) obstruction, either at rest or with provocation, defined as LVOT gradient of at least 30 mmHg
  - dynamic i.e. obstruction (and the murmur) is reduced with maneuvers that increase preload, and augmented with maneuvers that reduce preload
- non-obstructive HCM: no LVOT obstruction
- many patients have diastolic dysfunction (impaired ventricular filling secondary to LV hypertrophy which decreases compliance)

Signs and Symptoms
- clinical manifestations: asymptomatic (common, therefore screening is important), SOB on exertion, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
- pulses: rapid upstroke, “spike and dome” pattern in carotid pulse (in HCM with outflow tract obstruction)
- precordial palpation: PMI localized, sustained, double impulse, ‘triple ripple’ (triple apical impulse in HOCM), LV lift
- precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLQS or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOT obstruction as compared to AS); often with pansystolic murmur due to mitral regurgitation

Investigations
- ECG/Holter monitor: LVH, high voltages across precordium, prominent Q waves (leads I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- transthoracic echocardiography and echo-Doppler study: asymmetric septal hypertrophy (less commonly apical), systolic anterior motion (SAM) of mitral valve and MR; LVOT gradient can be estimated by Doppler measurement
genetic studies (± magnetic resonance imaging) can be helpful when echocardiography is inconclusive for diagnosis
- cardiac catheterization (only when patient being considered for invasive therapy)

Management
- avoid factors which increase obstruction (e.g. volume depletion)
  - avoidance of all competitive sports
- treatment of obstructive HCM
  - medical agents: β blockers, disopyramide, verapamil (started only in monitored setting), phenylephrine (in setting of cardiogenic shock)
  - avoid nitrates, diuretics, and ACEI as they increase LVOT gradient and worsen symptoms
- patients with obstructive HCM and drug-refractory symptoms
  - surgical myectomy
  - alcohol septal ablation - percutaneous Intervention that ablates the hypertrophic septum with 100% ethanol via the septal artery
  - dual chamber pacing (rarely done)
- treatment of patients at high risk of sudden death : ICD
- first-degree relatives (children, siblings, parents) of patients with HCM should be screened (physical, ECG, 2D echo) every 12-18 mo during adolescence, then serially every 5 yr during adulthood

Prognosis
- potential complications: AFib, VT, CHF, sudden cardiac death (1% risk/yr; most common cause of SCD in young athletes)
  - major risk factors for sudden death (consider ICD placement)
  - history of survived cardiac arrest/sustained VT
  - family history of multiple premature sudden deaths
  - other factors associated with increased risk of sudden cardiac death
    - syncope (presumed to be arrhythmic in origin)
    - non-sustained VT on ambulatory monitoring
    - marked ventricular hypertrophy (maximum wall thickness ≥30 mm)
    - abnormal BP in response to exercise (in patients <40 yr old with HCM)

RCM vs. Constrictive Pericarditis (CP)
Present similarly but CP is treatable with surgery
Restrictive Cardiomyopathy

**Definition**
- impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)

**Etiology**
- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis
- storage diseases: hemochromatosis, Fabry's disease, Gaucher's disease, glycogen storage diseases
- endomyocardial
  - endomyocardial fibrosis, Loeffler's endocarditis, or eosinophilic endomyocardial disease
  - radiation heart disease
  - carcinoïd syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)

**Clinical Manifestations**
- CHF (usually with preserved LV systolic function), arrhythmias
- elevated JVP with prominent x and y descents, Kussmaul's sign
- S3, S4, MR, TR
- thromboembolic events

**Investigations**
- ECG: low voltage, non-specific, diffuse ST-T wave changes ± non-ischemic Q waves
- CXR: mild cardiac enlargement
- Echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
- cardiac catheterization: increased end-diastolic ventricular pressures
- endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

**Management**
- exclude constrictive pericarditis
- treat underlying disease: control HR, anticoagulate if AFib
- supportive care and treatment for CHF, arrhythmias
- cardiac transplant: might be considered for CHF refractory to medical therapy, see Cardiac Transplantation, C38

**Prognosis**
- depends on etiology
Valvular Heart Disease

- see Guidelines on the Management of Valvular Heart Disease. JACC Jun 10;63(22):2438-88 for details

Infective Endocarditis
- see Infectious Diseases, ID16
- American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  • only for patients with:
    - prosthetic valve material
    - past history of IE
    - certain types of congenital heart disease
    - cardiac transplant recipients who develop valvulopathy
  • only for the following procedures:
    - dental
    - respiratory tract
    - procedures on infected skin/skin structures/MSK structures
    - not GI/GU procedures specifically

Rheumatic Fever
- see Pediatrics, P53

Prognosis
- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease – fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
- onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
- mitral valve most commonly affected

Valve Repair and Valve Replacement
- indication for valve repair or replacement depends on the severity of the pathology; typically recommended when medical management has failed to adequately improve the symptoms or reduce the risk of morbidity and mortality
- pathologies that may require surgical intervention include congenital defects, infections, rheumatic heart disease as well as a variety of valve diseases associated with aging
- valve repair: balloon valvuloplasty, surgical valvuloplasty (commissurotomy, annuloplasty), chordae tendineae shortening, tissue patch
- valve replacement: typically for aortic or mitral valves only; mitral valve repair is favoured in younger individuals; percutaneous techniques being established

Choice of Valve Prosthesis

<table>
<thead>
<tr>
<th>Table 15. Mechanical Valve vs Bioprosthetic Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical Valve</td>
</tr>
<tr>
<td>Good durability</td>
</tr>
<tr>
<td>Less preferred in small aortic root sizes</td>
</tr>
<tr>
<td>Increased risk of thromboembolism (1-3%/yr): requires long-term anticoagulation with coumadin</td>
</tr>
<tr>
<td>Target INR Aortic valves: 2.0-3.0 (mean 2.5) Mitral valves: 2.5-3.5 (mean 3.0)</td>
</tr>
<tr>
<td>Increased risk of hemorrhage: 1-2%/yr</td>
</tr>
</tbody>
</table>

Mitrval Valve Repair vs. Replacement for Severe Ischemic Mitral Regurgitation
NEJM 2014;370:23-32

Purpose: Ischemic mitral regurgitation is associated with significant mortality. The purpose of this study was to compare the effectiveness and safety of repairing versus replacing the mitral valve in patients with severe chronic ischemic mitral regurgitation.

Study Design: RCT with 251 patients with severe ischemic mitral regurgitation were randomly assigned to mitral valve repair or chordal-sparing replacement. The primary endpoint was the left ventricular end-systolic volume index (LVEFVR) at 12 mo.

Results: There were no significant between-group differences in LVEFVR, in the rate of major adverse cardiac or cerebrovascular events, in functional status, or in quality of life at 12 mo. The rate of moderate or severe mitral regurgitation recurrence at 12 mo was significantly higher in the repair group than in the replacement group (32.8% vs. 2.3%, respectively).

Conclusions: No significant difference in left ventricular reverse remodeling or survival at 12 mo between patients who underwent mitral valve repair or replacement. Replacement provided more durable correction of mitral regurgitation, but there were no significant differences in clinical outcomes.
Table 16. Valvular Heart Disease

<table>
<thead>
<tr>
<th>Aortic Stenosis (AS)</th>
<th>Aortic Regurgitation (AR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Supravalvular: aortic root disease (Marfan’s, atherosclerosis and dissecting aneurysm, connective tissue disease)</td>
</tr>
<tr>
<td>Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease</td>
<td>Valvular: congenital (bicuspid aortic valve, large VSD), IE</td>
</tr>
<tr>
<td><strong>Definition</strong></td>
<td>Acute Onset: IE, aortic dissection, trauma, failed prosthetic valve</td>
</tr>
<tr>
<td>Normal aortic valve area = 3-4 cm²</td>
<td><strong>Pathophysiology</strong></td>
</tr>
<tr>
<td>Mild AS &gt; 1.5 cm²</td>
<td>Volume overload → LV dilatation → increased SV, high sBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)</td>
</tr>
<tr>
<td>Moderate AS 1.0 to 1.5 cm²</td>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Severe AS &lt; 1.0 cm²</td>
<td>Usually only becomes symptomatic late in disease when LV failure develops</td>
</tr>
<tr>
<td>Critical AS &lt; 0.5 cm²</td>
<td>Dyssynergia, orthopnea, PND, syncope, anghia</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td><strong>Physical Exam</strong></td>
</tr>
<tr>
<td>Outflow obstruction → increased EDP → concentric LVH → LV failure → CHF, subendocardial ischemia</td>
<td>Waterhammer pulse, bifemoral pulse, femoral-brachial sBP &gt; 20 (Hill’s test wide pulse pressure), hyperdynamic apex, displaced PML, heaving apex</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Auscultation: early decrescendo diastolic murmur at LLNB (cusp pathology) or RLSB (aortic root pathology), best heard sitting, leaning forward, on full expiration, soft S1, absent S2, S3 (late)</td>
</tr>
<tr>
<td>Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema</td>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td>ECG: LVH, LAE, LVEF and/or LVF &lt; 50%</td>
</tr>
<tr>
<td>Narrow pulse pressure, brachial-radial delay, pulesus parvus et tardus sustained PMI</td>
<td>ECG: LVH, LAE, aortic root dilatation</td>
</tr>
<tr>
<td>Auscultation: crescendo-decrescendo SEM radiating to R clavicle and carotid, musical noise at apex (Gallavardin phenomenon), S4, soft S2 with paradoxical splitting, S3 (late)</td>
<td>ECG: LVH, LAE, LVEF and/or LVF &lt; 50%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Echo/TTE: quantify AR, leaflet or aortic root anomalies</td>
</tr>
<tr>
<td>ECG: LVH, stran, LBBB, LAE, AFib</td>
<td><strong>Cath:</strong> if &gt; 40 yr and surgical candidate – to assess for ischemic heart disease</td>
</tr>
<tr>
<td>CXR: post-stenotic aortic root dilatation, calcified valve, LAE, CHF</td>
<td>Exercise testing: hypotension with exercise</td>
</tr>
<tr>
<td>Echo: reduced valve area, pressure gradient, LWH, reduced LV function</td>
<td><strong>Auscultation</strong></td>
</tr>
<tr>
<td><strong>Auscultation</strong></td>
<td>Asymptomatic: serial echos, avoid exertion</td>
</tr>
<tr>
<td>Asymptomatic: serial echos, avoid exertion</td>
<td>Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS</td>
</tr>
<tr>
<td>Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS</td>
<td><strong>Surgical Options</strong></td>
</tr>
<tr>
<td><strong>Surgical Options</strong></td>
<td>Valve replacement: most patients</td>
</tr>
<tr>
<td>Valve replacement: aortic rheumatic valve disease and trileaflet valve</td>
<td>Valve repair: most limited role</td>
</tr>
<tr>
<td>– prior to pregnancy (if AS significant)</td>
<td>Aortic root replacement (Bentall procedure): when ascending aortic aneurysm present ()valved conduit used</td>
</tr>
<tr>
<td>– balloon valvuloplasty (in very young)</td>
<td><strong>Interventional Options</strong></td>
</tr>
<tr>
<td>Percutaneous valve replacement (transfemoral or transapical approach) is an option in selected patients who are not considered good candidates for surgery</td>
<td><strong>Symptomatic</strong>: avoid nitrates/arterial dilators and ACEI in severe AS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mitral Stenosis (MS)</th>
<th>Mitral Regurgitation (MR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Valvular: congenital cleft leaflets () LV dilatation/aneurysms (CHF, DCM, myocarditis), IE abscess, Marfan’s syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease</td>
</tr>
<tr>
<td>Rheumatic disease most common cause, congenital (rare)</td>
<td><strong>Pathophysiology</strong></td>
</tr>
<tr>
<td>Severe MS is mitral valve area (MVA) &lt; 1.5 cm²</td>
<td>Reduced CO → increased LV and LA pressure → LV dilatation → LV failure → CHF and pulmonary HTN</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF; worse with AFib (no atrial kick) tachycardia (decreased atrial emptying time) and pregnancy (increased preload)</td>
<td>Dyspnea, PND, syncope, palpitations, rapid RBBB, diaphoresis, angina</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td><strong>Physical Exam</strong></td>
</tr>
<tr>
<td>SDB on exertion, orthopnea fatigue, palpitations, periperal edema, malar flush, pinched and blue facies (severe MS)</td>
<td>Displaced hyperdynamic apex, left parasternal lift, apical thrill</td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td>Auscultation: holosystolic murmur at apex, best heard with bell in left lateral decubitus position following exertion, loud S1, OS following loud P2 (heard best during expiration), loud grade 4 systolic murmur and short A2-OS interval correlate with worse MS</td>
</tr>
<tr>
<td>AFib, no “a” wave on JVP, left parasternal lift, palpable diastolic thrill at apex</td>
<td>ECG: NSR/AFib, LAE, P mitrale, RHV, RAD</td>
</tr>
<tr>
<td>Auscultation: mid-diastolic rumble at apex, best heard with bell in left lateral decubitus position following exertion, loud S1, OS following loud P2 (heard best during expiration), long diastolic murmur and short A2-OS interval correlate with worse MS</td>
<td>ECG: LVH, LAE, LVEF and/or LVF &lt; 50%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Echo/TTE: shows restricted opening of mitral valve</td>
</tr>
<tr>
<td>ECG: NSR/AFib, LAE, P mitrale, RHV, RAD</td>
<td>Echocardiography: quantitative AR, leaflet or aortic root abnormalities</td>
</tr>
<tr>
<td>CXR: LAE, CHF, mitral valve calcification</td>
<td>Swann-Ganz Catheter: prominent LA “v” wave</td>
</tr>
<tr>
<td>Echocardiography: shows restricted opening of mitral valve</td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td><strong>Cath:</strong> indicated in concensus CAD if &gt; 60 yr (male) or &gt; 50 yr (female)</td>
<td>Asymptomatic: serial echos</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Symptomatic: decrease preload (diuretics), decrease afterload (ACEI) for severe MR and poor surgical candidates; stabilize acute MR with vasodilators before surgery</td>
</tr>
<tr>
<td>Avoid exertion, fever (increased LA pressure), treat AFib and CHF, increase diastolic filling time (β-blockers, digitalis)</td>
<td><strong>Surgery</strong></td>
</tr>
<tr>
<td>Surgery if: NYHA class III-IV CHF, LV dilatation and/or LVF &lt; 50% with/without symptoms</td>
<td>Valve repair: &gt; 75% of pts with MR and myxomatous mitral valve prolapse – annuloplasty, leaflet repair, chordae transfers/shorten/replacement</td>
</tr>
<tr>
<td><strong>Invasive Options</strong></td>
<td>Valve replacement: most patients</td>
</tr>
<tr>
<td>Percutaneous balloon valvuloplasty: young rheumatic pts and good leaflet morphology can be determined by echo, asymptomatic pts with moderate-severe MS, pulmonary HTN</td>
<td>Valve repair: &gt; 75% of pts with MR and myxomatous mitral valve prolapse – annuloplasty, leaflet repair, chordae transfers/shorten/replacement</td>
</tr>
<tr>
<td>Contraindication: left atrial thrombus, moderate MR</td>
<td>Valve replacement: failure of repair, heavily calcified annulus</td>
</tr>
<tr>
<td>Open Mitral Commisurotomy: if mild calcification + leaflet/chordal thickening</td>
<td>Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation</td>
</tr>
<tr>
<td>– restenosis in 50% pts in 9 yr</td>
<td>Valve replacement: failure of repair, heavily calcified annulus</td>
</tr>
</tbody>
</table>
| Valve replacement: indicated in moderate-severe calcification and severely scarred leaflets | }
Table 16. Valvular Heart Disease (continued)

**Mitral Valve Prolapse (MVP)**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Myxomatous degeneration of chordae, thick, bulky leaflets that crowd orifice, associated with Marfan’s syndrome, pectus excavatum, straight back syndrome, other MSK abnormalities; &lt;3% of population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>Auscultation: mid-systolic click (due to billowing of mitral leaflet into LA); tending of redundant valve tissue; mid to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers</td>
</tr>
<tr>
<td>Investigations</td>
<td>ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy</td>
</tr>
<tr>
<td>Echo</td>
<td>Systolic displacement of thickened mitral valve leaflets into LA</td>
</tr>
<tr>
<td>Treatment</td>
<td>Asymptomatic: no treatment; reassurance</td>
</tr>
<tr>
<td>Surgical Options</td>
<td>β-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if AFib</td>
</tr>
<tr>
<td>Surgical Options</td>
<td>Mitral valve surgery (repair favoured over replacement) if symptomatic and significant MR</td>
</tr>
</tbody>
</table>

**Pulmonary Stenosis (PS)**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Usually congenital, rheumatic disease (rare), carcinoid syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>Increased RV pressure → RV hypertrophy → right heart failure</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Chest pain, syncope, fatigue, peripheral edema</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>Systolic murmur at 2nd left intercostal space accentuated by inspiration, pulmonary ejection click, right s/d 64</td>
</tr>
<tr>
<td>Investigations</td>
<td>ECG: RAE</td>
</tr>
<tr>
<td>CXR</td>
<td>prominent pulmonary arteries enlarged RV</td>
</tr>
<tr>
<td>Echo</td>
<td>diagnostic</td>
</tr>
<tr>
<td>Treatment</td>
<td>Balloon valvuloplasty if severe symptoms</td>
</tr>
<tr>
<td>Surgical Options</td>
<td>Percutaneous or open balloon valvuloplasty</td>
</tr>
</tbody>
</table>

**Pulmonary Regurgitation (PR)**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Pulmonary HTN, IE, rheumatic disease, tetrology of Fallot (post-repair)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>Increased RV volume → increased wall tension → RV hypertrophy → right heart failure</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Chest pain, syncope, fatigue, peripheral edema</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>Early diastolic murmur at LLSSB, Graham Steell (diastolic) murmur 2nd and 3rd left intercostal space increasing with inspiration</td>
</tr>
<tr>
<td>Investigations</td>
<td>ECG: RAE</td>
</tr>
<tr>
<td>CXR</td>
<td>prominent pulmonary arteries if pulmonary HTN; enlarged RV</td>
</tr>
<tr>
<td>Echo</td>
<td>diagnostic</td>
</tr>
<tr>
<td>Treatment</td>
<td>Rarely requires treatment; valve replacement (rarely done)</td>
</tr>
<tr>
<td>Surgical Options</td>
<td>Pulmonary valve replacement</td>
</tr>
</tbody>
</table>

**Tricuspid Stenosis (TS)**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS (in RHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>Increased RA pressure → right heart failure → decreased CO and fixed on exertion</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Peripheral edema, fatigue, palpitations</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>Prominent “a” waves in JVP; +ve abdominojugular reflux, Kussmaul’s sign, diastolic rumble 4th left intercostal space</td>
</tr>
<tr>
<td>Investigations</td>
<td>ECG: RAE</td>
</tr>
<tr>
<td>CXR</td>
<td>dilatation of RA without pulmonary artery enlargement</td>
</tr>
<tr>
<td>Echo</td>
<td>diagnostic</td>
</tr>
<tr>
<td>Treatment</td>
<td>Preload reduction (diuretics), slow HR</td>
</tr>
<tr>
<td>Surgical Options</td>
<td>Valve Replacement: — if severely diseased valve — bioprosthesi s preferred</td>
</tr>
</tbody>
</table>

**Tricuspid Regurgitation (TR)**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>RV dilatation, IE (particularly due to IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>RV dilatation → TR further RV dilatation → right heart failure</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Peripheral edema, fatigue, palpitations</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>“cv” waves in JVP; +ve abdominojugular reflux, Kussmaul’s sign, holosystolic murmur at LLSSB accentuated by inspiration, left parasternal lift</td>
</tr>
<tr>
<td>Investigations</td>
<td>ECG: RAE, RVH, AFib</td>
</tr>
<tr>
<td>CXR</td>
<td>RV enlargement</td>
</tr>
<tr>
<td>Echo</td>
<td>diagnostic</td>
</tr>
<tr>
<td>Treatment</td>
<td>Preload reduction (diuretics)</td>
</tr>
<tr>
<td>Surgical Options</td>
<td>Rarely requires treatment; valve replacement (rarely done)</td>
</tr>
<tr>
<td>Surgical Options</td>
<td>Annuloplasty (i.e. repair, rarely replacement)</td>
</tr>
</tbody>
</table>
Figure 41. Hemodynamics of aortic stenosis
Stenosis across the aortic valve results in the generation of a significant pressure gradient between the left ventricle and the aorta and a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure hence diminishing S2.

Figure 42. Hemodynamics of aortic regurgitation
Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2 is audible). The presence of regurgitant blood from the aorta increases left-ventricular end-diastolic volume.

Figure 43. Hemodynamics of acute mitral regurgitation
During systolic contraction, blood regurgitates from the left ventricle into the left atrium across the incompetent mitral valve resulting in an audible holosystolic murmur between S1 and S2. The portion of left ventricular end-diastolic volume that regurgitates into the left atrial myocardium increases left atrial pressures resulting in a tall V-wave (in the JVP).

Figure 44. Hemodynamics of mitral stenosis
First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to mitral stenosis and the consequent generation of a pressure gradient across the left atrium and left ventricle. In diastole the stenotic mitral valve opens which corresponds to the opening snap (OS) and the passage of blood across the mitral stenosis results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible.
Pericardial Disease

Acute Pericarditis

Etiology of Pericarditis/Pericardial Effusion
- idiopathic is most common: presumed to be viral
- infectious
  - viral: Coxsackie virus A, B (most common), echovirus
  - bacterial: S. pneumoniae, S. aureus
  - TB
- fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma
- collagen vascular disease: SLE, polyarteritis, rheumatoid arthritis, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (sarcoid)

Signs and Symptoms
- diagnostic triad: chest pain, friction rub and ECG changes (diffuse ST elevation and PR depression with reciprocal changes in aVR)
- pleuritic chest pain: alleviated by sitting up and leaning forward
- pericardial friction rub: may be uni-, bi-, or triphasic; evanescent and rare
- ± fever, malaise

Investigations
- ECG: initially diffuse elevated ST segments ± depressed PR segment, the elevation in the ST segment is concave upwards → 2-5 d later ST isoelectric with T wave flattening and inversion
- CXR: normal heart size, pulmonary infiltrates
- Echo: performed to assess for pericardial effusion

Treatment
- treat the underlying disease
- anti-inflammatory agents (high dose NSAIDs/ASA, steroids use controversial), analgesics

Complications
- recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

Pericardial Effusion

Etiology
- transudative (serous)
- CHF, hypoalbuminemia/hypoproteinemia, hypothyroidism
- exudative (serosanguinous or bloody)
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
- physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

Signs and Symptoms
- may be asymptomatic or similar to acute pericarditis
- dyspnea, cough
- extra-cardiac (esophageal/recurrent laryngeal nerve/tracheo-bronchial/phrenic nerve irritation)
- JVP increased with dominant "x" descent
- arterial pulse normal to decreased volume, decreased pulse pressure
- auscultation: distant heart sounds ± rub
- Ewart's sign

Investigations
- ECG: low voltage, flat T waves, electrical alternans (classic, but not sensitive to exclude effusion)
  - be cautious in diagnosing STEMI in a patient with pericarditis and an effusion - antiplatelets may precipitate hemorrhagic effusion
- CXR: cardiomegaly, rounded cardiac contour
- ER: bedside ultrasound with subxiphoid view showing fluid in pericardial sac
- Echo (procedure of choice): fluid in pericardial sac
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, neoplastic involvement
Pericardial Disease

C48  Cardiology and Cardiac Surgery

Toronto Notes 2018

Treatment
• mild: frequent observation with serial echos, treat underlying cause, anti-inflammatory agents
• severe: treat as in tamponade (see Cardiac Tamponade)

Cardiac Tamponade

Etiology
• major complication of rapidly accumulating pericardial effusion
• cardiac tamponade is a clinical diagnosis
• any cause of pericarditis but especially trauma, malignancy, uremia, proximal aortic dissection with rupture

Pathophysiology
• high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

Signs and Symptoms
• tachypnea, dyspnea, shock, muffled heart sounds
• pulsus paradoxus (inspiratory fall in systolic BP >10 mmHg during quiet breathing)
• JVP “x” descent only, blunted “y” descent
• hepatic congestion/peripheral edema

Investigations
• ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
• echo: pericardial effusion, compression of cardiac chambers (RA and RV) in diastole
• cardiac catheterization

Treatment
• pericardiocentesis: Echo-guided
• pericardiotomy
• avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO)
• IV fluid may increase CO
• treat underlying cause

Constrictive Pericarditis

Etiology
• chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
• any cause of acute pericarditis may result in chronic pericarditis
• major causes are idiopathic, post-infectious (viral, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease

Signs and Symptoms
• dyspnea, fatigue, palpitations
• abdominal pain
• may mimic CHF (especially right-sided HF)
  • ascites, hepatosplenomegaly, edema
• increased JVP, Kussmaul's sign (paradoxic increase in JVP with inspiration), Friedreich's sign (prominent “y” descent)
• BP usually normal (and usually no pulsus paradoxus)
• precordial examination: ± pericardial knock (early diastolic sound)
• see Table 17 for differentiation from cardiac tamponade

Investigations
• ECG: non-specific – low voltage, flat T wave, ± AFib
• CXR: pericardial calcification, effusions
• echo/CT/MRI: pericardial thickening, ± characteristic echo-Doppler findings
• cardiac catheterization: equalization of end-diastolic chamber pressures (diagnostic)

Treatment
• medical: diuretics, salt restriction
• surgical: pericardectomy (only if refractory to medical therapy)
• prognosis best with idiopathic or infectious cause and worst in post-radiation; death may result from heart failure

Classic Quartet of Tamponade
• Hypotension
• Increased JVP
• Tachycardia
• Pulsus paradoxus

Beck's Triad
• Hypotension
• Increased JVP
• Muffled heart sounds

DDx Pulsus Paradoxus
• Constrictive pericarditis (rarely)
• Severe obstructive pulmonary disease (e.g. asthma)
• Tension pneumothorax
• PE
• Cardiogenic shock
• Cardiac tamponade

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Table 17. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Constrictive Pericarditis</th>
<th>Cardiac Tamponade</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP</td>
<td>&quot;y&quot; &gt; &quot;x&quot;</td>
<td>&quot;x&quot; &gt; &quot;y&quot;</td>
</tr>
<tr>
<td>Kussmaul’s sign</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Uncommon</td>
<td>Always</td>
</tr>
<tr>
<td>Pericardial knock</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Variable</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Table 18. Commonly Used Cardiac Therapeutics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)</td>
<td>enalapril (Vasotec®), perindopril (Coveryl®), lisinopril (Zestril®)</td>
<td>Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis</td>
<td>HTN, CAD, CHF, post-MI, DM</td>
<td>Bilateral renal artery stenosis, pregnancy, caution n decreased GFR</td>
<td>Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema</td>
</tr>
<tr>
<td>ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)</td>
<td>candesartan, irbesartan, valsartan</td>
<td>Block AT II receptors, causing similar effects to ACEI</td>
<td>Same as ACEI, although evidence is generally less for ARBs; often used when ACEI are not tolerated</td>
<td>Same as ACEI</td>
<td>Similar to ACEI, but do not cause dry cough</td>
</tr>
<tr>
<td>DIRECT RENIN INHIBITORS (DRIs)</td>
<td>aliskiren</td>
<td>Directly blocks renin thus inhibiting the conversion of angiotensinogen to angiotensin I; this also causes a decrease in AT II</td>
<td>HTN (exact role of this drug remains unclear)</td>
<td>Pregnancy, severe renal impairment</td>
<td>Diarrhea, hyperkalemia (higher risk if used with an ACEI), rash, cough, angioedema, reflux, hypotension, rhabdomyolysis, seizure</td>
</tr>
<tr>
<td>β-BLOCKERS</td>
<td>atenolol, metoprolol, bisoprolol</td>
<td>Block β-adrenergic receptors, decreasing HR, BP contractility, and myocardial oxygen demand, slow conduction through the AV node</td>
<td>HTN, CAD, acute MI, post-MI, CHF (start low and go slow), Afib, SVT</td>
<td>Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW. Caution in asthma, claudication, Raynaud’s phenomenon and desensitization of CHF</td>
<td>Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud’s phenomenon and claudication</td>
</tr>
<tr>
<td>CAUCIAL CHANNEL BLOCKERS (CCBs)</td>
<td>diltiazem</td>
<td>Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers Also vasodilate</td>
<td>HTN, CAD, SVT, diastolic dysfunction</td>
<td>Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW, CHF</td>
<td>Hypotension, bradycardia, edema Negative inotrope</td>
</tr>
<tr>
<td>Phenylalkylamines (non-dihydropyridines)</td>
<td>amlodipine (Norvasc®), nifedipine (Adalat®), felodipine (Plendil®)</td>
<td>Block smooth muscle calcium channels causing peripheral vasodilation</td>
<td>HTN, CAD</td>
<td>Severe aortic stenosis and liver failure</td>
<td>Hypotension, edema, flushing, headache, light-headedness</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>hydrochlorothiazide, chlorothalidone, metolazone</td>
<td>Reduce Na⁺ reabsorption in the distal convoluted tubule (DCT)</td>
<td>HTN (drugs of choice for uncomplicated HTN)</td>
<td>Sulfa allergy, pregnancy</td>
<td>Hypotension, hypokalemia, polyuria</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>furosemide (Lasix®)</td>
<td>Blocks Na⁺/K⁺/ATPase in thick ascending limb of the loop of Henle</td>
<td>CHF, pulmonary or peripheral edema</td>
<td>Hypovolemia, hypokalemia</td>
<td>Hypovolemia, hypokalemic metabolic alkalosis</td>
</tr>
<tr>
<td>Aldosterone receptor antagonists</td>
<td>spironolactone, eplerenone</td>
<td>Antagonize aldosterone receptors</td>
<td>HTN, CHF, hypokalemia</td>
<td>Renal insufficiency, hypokalemia, pregnancy</td>
<td>Edema, hyperkalemia, gynecomastia</td>
</tr>
<tr>
<td>DIURETICS</td>
<td>digoxin (Lanoxin®)</td>
<td>Inhibit Na⁺/K⁺/ATPase, leading to increased intracellular Na⁺ and Ca²⁺ concentration and increased myocardial contractility Also slows conduction through the AV node</td>
<td>CHF AFib</td>
<td>2nd or 3rd degree AV block, hypokalemia, WPW</td>
<td>AV block, tachyarrhythmias, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, N/V</td>
</tr>
<tr>
<td>INOTROPES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 18. Commonly Used Cardiac Therapeutics (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumarins</td>
<td>warfarin (Coumadin®)</td>
<td>Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X</td>
<td>Atrial fibrillation, left ventricular dysfunction, prosthetic valves</td>
<td>Recent surgery or bleeding, bleeding diathesis, pregnancy</td>
<td>Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis</td>
</tr>
<tr>
<td>Heparins</td>
<td>Unfractionated heparin</td>
<td>Antithrombin III agonist, leading to decreased clotting factor activity</td>
<td>Acute MI or ACS; when immediate anticoagulant effect needed</td>
<td>Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)</td>
<td>Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs)</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>dabigatran, melagatran</td>
<td>Competitive, direct thrombin inhibitor; thrombin enables fibrinogen conversion to fibrin during the coagulation cascade, thereby preventing thrombus development</td>
<td>Atrial fibrillation</td>
<td>Severe renal impairment, recent surgery, active bleeding</td>
<td>Bleeding, GI upset</td>
</tr>
<tr>
<td><strong>ANTIPLATELETS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td>ASA (Aspirin®)</td>
<td>Irreversibly acetylates platelet COX-1 preventing thromboxane A2-mediated platelet aggregation</td>
<td>Coronary artery disease, acute MI, post-MI, post-PCI, CABG</td>
<td>Active bleeding or PUD</td>
<td>Bleeding, GI upset, ulceration, impaired renal perfusion</td>
</tr>
<tr>
<td>Thienopyridines</td>
<td>clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®)</td>
<td>P2Y12 antagonist (block platelet ADP receptors)</td>
<td>Acute MI, post-MI, post-PCI, CABG</td>
<td>Active bleeding or PUD</td>
<td>Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)</td>
</tr>
<tr>
<td>Nucleoside analogues</td>
<td>ticagrelor (Brilinta®)</td>
<td>P2Y12 antagonist (but different binding site than thienopyridines)</td>
<td>Acute MI, particularly if PCI is planned</td>
<td>Recent surgery or bleeding, bleeding diathesis</td>
<td>Bleeding</td>
</tr>
<tr>
<td>GPIIb/IIIa inhibitors</td>
<td>eptifibatide, tirofiban, abciximab</td>
<td>Block binding of fibrinogen to Gp IIb/IIIa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>THROMBOLYTICS</strong></td>
<td>alteplase, reteplase, tenecteplase, streptokinase</td>
<td>Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin</td>
<td>Acute STEMI</td>
<td>See Table 8, C29</td>
<td>Bleeding</td>
</tr>
<tr>
<td><strong>NITRATES</strong></td>
<td>nitroglycerin</td>
<td>Relax vascular smooth muscle, producing venous and arteriolar dilation</td>
<td>Coronary artery disease, CHF (isosorbide dinitrate plus hydralazine)</td>
<td>Concurrent use of cGMP phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure</td>
<td>Headache, dizziness, weakness, postural hypotension</td>
</tr>
<tr>
<td><strong>LIPID LOWERING AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Mevacor®)</td>
<td>Inhibit HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis</td>
<td>Dyslipidemia (1st prevention of CAD), CAD, post-MI (2nd prevention of CV events)</td>
<td>Liver or muscle disease</td>
<td>Myalgia, rhabdomyolysis, abdominal pain</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor</td>
<td>ezetimibe (Zetia®)</td>
<td>Inhibits gut absorption of cholesterol</td>
<td>Decreases LDL but does not reduce mortality</td>
<td>Liver or renal impairment</td>
<td>Myalgia, rhabdomyolysis, abdominal pain</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>fibrates, bile acid sequestrates, nicotinic acid</td>
<td>Primarily in familial hypercholesterolemia</td>
<td></td>
<td></td>
<td>GI side effects common</td>
</tr>
<tr>
<td>Investigational</td>
<td>PSCK9 inhibitor</td>
<td>Monoclonal antibody</td>
<td></td>
<td>Hypercholesterolemia</td>
<td></td>
</tr>
</tbody>
</table>
Figure 45. Representative cardiac action potential

### Table 19. Antiarrhythmic* Drugs (Vaughan-Williams Classification)

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>quinidine procainamide disopyramide</td>
<td>SVT, VT Torsades de Pointes (all Ia), diarrhea Lupus-like syndrome Antiarrhythmic effects</td>
<td>Moderate Na⁺ channel blockade Slows phase 0 upstroke Prolongs repolarization, slowing conduction</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>lidocaine mexiteline</td>
<td>VT Confusion, stupor, seizures GI upset, tremor</td>
<td>Mild Na⁺ channel blockade Shortens phase 3 repolarization</td>
<td></td>
</tr>
<tr>
<td>Ic</td>
<td>propafenone flecainide encainide</td>
<td>SVT, VT AFib Exacerbation of VT (all Ic) Negative inotropy (all Ic) Bradycardia and heart block (all Ic)</td>
<td>Marked Na⁺ channel blockade Markedly slows phase 0 upstroke</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>propranolol metoprolol, etc.</td>
<td>SVT, AFib Bronchospasm, negative inotropy, bradyarrhythmias AV block, impotence, fatigue</td>
<td>β-blocker Decreases phase 4 depolarization</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>amiodarone** sotalol</td>
<td>SVT, VT AFib Amiodarone: Photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR Amiodarone and Sotalol: Torsades de Pointes, bradyarrhythmias heart block, β-blocker side effects</td>
<td>Blocks K⁺ channel Prolongs phase 3 repolarization, which prolongs refractory period</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>verapamil diltiazem</td>
<td>SVT AFib Bradycardia AV block Hypotension</td>
<td>Calcium channel blocker Slows phase 4 spontaneous depolarization, slowing AV node conduction</td>
<td></td>
</tr>
</tbody>
</table>

*All antiarrhythmics have potential to be proarrhythmic **Amiodarone has class I, II, III, and IV properties

### Table 20. Actions of α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>α RECEPTORS</th>
<th>β RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target System</td>
<td>α1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Constriction of vascular smooth muscle Constriction of skin, skeletal muscle, and splanchnic vessels Increased myocardial contractility Decreased heart rate</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>Dermal</td>
<td>Pilomotor smooth muscle contraction Apocrine constriction</td>
</tr>
<tr>
<td>Ocular</td>
<td>Radial muscle contraction</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Inhibition of myenteric plexus Anal sphincter constriction</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Pregnant uterine contraction Penile and seminal vesicle ejaculation Urinary bladder contraction</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Stimulate liver gluconeogenesis and glycogenolysis at the liver Same as α1 Fat cell lipolysis</td>
</tr>
</tbody>
</table>

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)
## Table 21. Commonly Used Drugs that Act on α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>α RECEPTORS</th>
<th>β RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>α1</td>
<td>β1</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>α1 and α2</td>
<td>β1 and β2</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>α2</td>
<td>β2</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norpinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Antagonist**      |             |             |
| Prazosin            | α1          | β1          |
| Phenoxybenzamine    | α1 and α2   | β1 and β2   |
| Phentolamin         | α2          | β2          |
| Yohimbine           |             |             |
| Metoprolol          |             |             |
| Acebutolol          |             |             |
| Alprenolol          |             |             |
| Atenolol            |             |             |
| Esmolol             |             |             |
| Metoprolol          |             |             |
| Acebutolol          |             |             |
| Alprenolol          |             |             |
| Atenolol            |             |             |
| Esmolol             |             |             |
| Propranolol         |             |             |
| Timolol             |             |             |
| Nadolol             |             |             |
| Pindolol            |             |             |
| Carvedilol          |             |             |

Adapted from the Family Practice Notebook (http://www.fpnotebook.com/NEU194.htm)

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### Landmark Cardiac Trials

#### ISCHEMIC HEART DISEASE

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>Lancet 2003;361:1149-58</td>
<td>In hypertensive patients with risk factors for CHD and average or below-average cholesterol, atorvastatin reduced nonfatal MI, fatal CHD, fatal/nonfatal stroke, coronary events but not all-cause mortality</td>
</tr>
<tr>
<td>CAPRIE</td>
<td>Lancet 1996;348:1329-39</td>
<td>In atherosclerotic vascular disease, clopidogrel reduced the primary combined endpoint of stroke, MI, or vascular death and improved PAD compared to ASA</td>
</tr>
<tr>
<td>CARE</td>
<td>NEJM 1996;335:1001-9</td>
<td>Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol</td>
</tr>
<tr>
<td>COURAGE</td>
<td>NEJM 2007;356:1503-16</td>
<td>Compared with optimal medical therapy alone, PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events</td>
</tr>
<tr>
<td>CURE</td>
<td>NEJM 2001;345:494-502</td>
<td>Clopidogrel plus ASA reduced death from CV causes, non fatal MI, or stroke but increased bleeding complications</td>
</tr>
<tr>
<td>EUROPA</td>
<td>Lancet 2003;362:782-88</td>
<td>With stable CAD and no CHF, perindopril reduced cardiovascular death, MI, and total mortality</td>
</tr>
<tr>
<td>HOPE</td>
<td>NEJM 2000;342:154-60</td>
<td>In high-risk patients without low LVEF or CHF, ramipril reduced rates of death, MI, stroke, revascularization, new diagnosis of DM and complications due to DM; vitamin E had no effect on outcomes</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002;360:7-22</td>
<td>In high-risk patients with various cholesterol values, simvastatin reduced all-cause mortality, coronary deaths, and major vascular events</td>
</tr>
<tr>
<td>INTERHEART</td>
<td>Lancet 2004;364:937-52</td>
<td>Nine modifiable risk factors account for 90% of myocardial infarction</td>
</tr>
<tr>
<td>JUPITER</td>
<td>NEJM 2008;359:2195-2207</td>
<td>With low to normal LDL-C and elevated hsCRP treatment with rosuvastatin significantly reduced major cardiovascular events; NNT with rosuvastatin for 2 yr to prevent one primary endpoint = 95</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>NEJM 2009;360:961-972</td>
<td>CABG has lower rate of ma or cardiac or cerebrovascular events; the rate of stroke was increased with CABG, whereas the rate of repeat revascularization was increased with PCI</td>
</tr>
<tr>
<td>TNT</td>
<td>NEJM 2005;352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d</td>
</tr>
<tr>
<td>WHI</td>
<td>JAMA 2002;288:321-333</td>
<td>Estrogen plus progestin therapy is associated with increased risks of cardiovascular disease and breast cancer but decreased risks of hip fracture and colorectal cancer in postmenopausal women</td>
</tr>
</tbody>
</table>

#### MYOCARDIAL INFARCTION

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHAT</td>
<td>JAMA 1982;247:1707-14</td>
<td>In acute MI, propranolol reduced all-cause mortality, cardiovascular death, and sudden death from atherosclerotic heart disease</td>
</tr>
<tr>
<td>COURAGE</td>
<td>NEJM 2007;356:1503-16</td>
<td>Compared with optimal medical therapy alone, PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events</td>
</tr>
<tr>
<td>DAPT</td>
<td>NEJM 2014;371:2155-66</td>
<td>Dual antiplatelet therapy beyond one year confers additional benefit</td>
</tr>
<tr>
<td>ISIS-2</td>
<td>Lancet 1988;2:349-80</td>
<td>Early therapy with str. plrokinase and ASA in patients with MI individually and in combination significantly reduced all-cause mortality and in combination demonstrated additive effect</td>
</tr>
</tbody>
</table>

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This content is adapted from the Family Practice Notebook (http://www.fpnotebook.com/NEU194.htm).
<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MYOCARDIAL INFARCTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-4</td>
<td><em>Lancet</em> 1995;345:669-85</td>
<td>In patients with suspected or definite acute MI, early treatment with captopril reduced all-cause mortality at 35 d and during long-term follow-up</td>
</tr>
<tr>
<td>OASIS-5</td>
<td><em>NEJM</em> 2006;354:1464-76</td>
<td>Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 and MI at 30 and 180 d</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td><em>NEJM</em> 2015 EPUB</td>
<td>Ticagrelor on top of ASA reduces CV events and in patients with a history of MI</td>
</tr>
<tr>
<td>PLATO</td>
<td><em>NEJM</em> 2009;361:1045-57</td>
<td>ACS patients with either STEMI or NSTEMI, regardless of reperfusion strategy, ticagrelor reduced mortality, MI and stroke without increased bleeding compared to clopidogrel</td>
</tr>
<tr>
<td>PROVE IT – TIMI 22</td>
<td><em>NEJM</em> 2004;350:1495-1504</td>
<td>In patients hospitalized for ACS, high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td><em>NEJM</em> 2007;357:2001-15</td>
<td>In ACS patients scheduled for PCI, prasugrel reduced ischemic events but increased major bleeding compared to clopidogrel; no change in mortality</td>
</tr>
<tr>
<td><strong>HEART FAILURE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIRE</td>
<td><em>Lancet</em> 1993;342:821-8</td>
<td>Ramipril commenced 3-10 d after MI and continued for a mean 15 mo period significantly reduced all-cause mortality in patients with non-severe CHF</td>
</tr>
<tr>
<td>CIBIS II</td>
<td><em>Lancet</em> 1999;353:9-13</td>
<td>Bisoprolol reduced all-cause mortality, cardiovascular death, all-cause hospitalization, and CHF hospitalization</td>
</tr>
<tr>
<td>COMET</td>
<td><em>Lancet</em> 2003;362:7-13</td>
<td>Carvedilol was associated with a reduction in all cause mortality compared with metoprolol</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td><em>NEJM</em> 1987;316:1429-35</td>
<td>Enalapril reduced all-cause mortality, death due to progression of heart failure</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td><em>NEJM</em> 2001;344:1651-8</td>
<td>Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td><em>NEJM</em> 2008;359:2456-2467</td>
<td>In patients with CHF and normal LVEF treatment with ARB (irbesartan) did not improve mortality or cardiovascular morbidity compared to placebo</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td><em>Lancet</em> 1999;353:2001-7</td>
<td>Metoprolol CR/XL daily in addition to optimum standard therapy improved survival in clinically stable patients equating to prevention of 1 death per 27 patients treated per year</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td><em>NEJM</em> 2014;371:993-1004</td>
<td>Novel drug (LCZ696 containing valsartan and a neprilysin inhibitor [prevents degradation of natriuretic peptides]) reduces hospitalization and mortality</td>
</tr>
<tr>
<td>RALES</td>
<td><em>NEJM</em> 1999;341:709-17</td>
<td>In severe CHF (class III/IV) and LVEF &lt;35%, spironolactone reduced all-cause mortality, sudden death, and death due to progression of heart failure</td>
</tr>
<tr>
<td>SAVE</td>
<td><em>NEJM</em> 1992;327:669-77</td>
<td>Patients with LV dysfunction post-MI long-term captopril over 3.5 yr reduced the risk of death due to cardiovascular causes recurrent MI, development of severe CHF, and CHF hospitalization</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td><em>NEJM</em> 2005;352:225-237</td>
<td>In mild-to-moderate CHF shock-only ICD significantly reduces risk of death; amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF</td>
</tr>
<tr>
<td>SOLVD</td>
<td><em>NEJM</em> 1991;325:293-302</td>
<td>In stable chronic CHF with decreased LVEF (&lt; 0.35), long-term enalapril reduced death due to all causes and death or hospitalization due to CHF</td>
</tr>
<tr>
<td>TRACE</td>
<td><em>NEJM</em> 1995;333:1670-6</td>
<td>In patients with LV dysfunction post-MI, long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td><em>NEJM</em> 1991; 325:303-10</td>
<td>In chronic CHF, enalapril reduced mortality more than hydralazine-isosorbide for at least 2 yr; treatment with either enalapril or hydralazine-isosorbide increased LVEF</td>
</tr>
<tr>
<td><strong>DIABETES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDS</td>
<td><em>Lancet</em> 2004;264:685-96</td>
<td>Atorvastatin reduces the risk of cardiovascular events in patients with type 2 DM</td>
</tr>
<tr>
<td>ONTARGET</td>
<td><em>NEJM</em> 2008;358:1547-59</td>
<td>In patients with vascular disease or DM without CHF, telmisartan is equally as effective as ramipril, with telmisartan causing a reduced risk of cough and angioedema, and an increased risk of hypertensive symptoms; combination therapy offers no advantage</td>
</tr>
<tr>
<td>Trial</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>NEJM 2002;347:1825-33</td>
<td>No significant difference in mortality rates between rate or rhythm control of AFib</td>
</tr>
<tr>
<td>AF CHF</td>
<td>NEJM 2008;358:2667-77</td>
<td>In patients with AFib and CHF, there is no significant difference in mortality rates from cardiovascular causes between rate and rhythm control</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>NEJM 2011:365:981-92</td>
<td>AFib patients treated with apixaban had a lower incidence of stroke, major bleeding and mortality compared to warfarin</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI48</td>
<td>NEJM 2013:369:2093-2104</td>
<td>AFib patients treated with edoxaban had similar rates of stroke and lower rates of major bleeding compared to warfarin</td>
</tr>
<tr>
<td>RE-LY</td>
<td>NEJM 2009:361:1139-51</td>
<td>AFib patients treated with dabigatran had a lower incidence of stroke compared to warfarin, with similar rates of major bleeding</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>NEJM 2011:365:883-891</td>
<td>In patients with AFib rivoxabarin is non-inferior to warfarin for stroke prevention, and major and non-major bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HYPERTENSION</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYVET</td>
<td>NEJM 2008;358:1887-98</td>
<td>In hypertensive patients &gt;80 yr treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non-fatal stroke</td>
</tr>
<tr>
<td>SIPlicity-HTN 3</td>
<td>NEJM 2014:370:1393-1401</td>
<td>Renal denervation does not reduce blood pressure in patients with resistant hypertension compared to sham procedure</td>
</tr>
<tr>
<td>SPRINT</td>
<td>NEJM 2015:373:2103-2116</td>
<td>In patients with high risk of cardiovascular events excluding diabetes, strict systolic BP control (&lt;120 mmHg) is associated with fewer cardiovascular events and lower all-cause mortality</td>
</tr>
<tr>
<td>UKHDS (UKPDS)</td>
<td>BMJ 1998;317:703-13</td>
<td>Hypertensive patients with DM and tight BP control at &lt;150/85 mmHg by use of ACEI or β-blocker reduced risk of diabetic complications and death related to DM and reduced risk of end-organ damage</td>
</tr>
<tr>
<td>VALUE</td>
<td>Lancet 2004;363:2022-2031</td>
<td>Valsartan group had higher incidence of MI than amlodipine group, whereas amlodipine had a higher incidence of new-onset DM</td>
</tr>
</tbody>
</table>
Acronyms                      2

General Principles              2
Drug Nomenclature
Phases of Clinical Drug Testing
Drug Administration

Pharmacokinetics                3
Absorption
Distribution
Metabolism (Biotransformation)
Elimination
Pharmacokinetic Calculation

Pharmacodynamics                7
Dose-Response Relationship
Effects of Drugs on Receptors
Effectiveness and Safety
Therapeutic Indices

Therapeutic Drug Monitoring     9

Adverse Drug Reactions          9
Approach to Suspected Adverse Drug Reactions

Variability in Drug Response    10

Drug Interactions               10

Autonomic Pharmacology          10
Parasympathetic Nervous System
Sympathetic Nervous System
Opioid Therapy and Chronic Non-Cancer Pain

Common Drug Endings             12

References                     12

For more information on medical pharmacology, please refer to our new textbook product, Pharmacology You See
### Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
<td></td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
<td></td>
</tr>
<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
<td></td>
</tr>
<tr>
<td>BBB</td>
<td>blood brain barrier</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>clearance</td>
<td></td>
</tr>
<tr>
<td>Cr</td>
<td>creatinine</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
<td></td>
</tr>
<tr>
<td>CSFa</td>
<td>certain safety factor</td>
<td></td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450 protein</td>
<td></td>
</tr>
<tr>
<td>DIN</td>
<td>drug identification number</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>bioavailability</td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
<td></td>
</tr>
<tr>
<td>HH</td>
<td>Henderson Hasselbalch</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>pharmacodynamics</td>
<td></td>
</tr>
<tr>
<td>PDE</td>
<td>phosphodiesterase</td>
<td></td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Po/w</td>
<td>partition coefficient of a drug</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
<td></td>
</tr>
<tr>
<td>TBW</td>
<td>total body water</td>
<td></td>
</tr>
<tr>
<td>TDM</td>
<td>therapeutic drug monitoring</td>
<td></td>
</tr>
<tr>
<td>TI</td>
<td>therapeutic index</td>
<td></td>
</tr>
<tr>
<td>Vd</td>
<td>volume of distribution</td>
<td></td>
</tr>
</tbody>
</table>

### General Principles

#### Drug Nomenclature

- **chemical name**: describes chemical structure; consistent in all countries (e.g. N-(4-hydroxyphenyl)acetamide is acetaminophen)
- **DIN or NDC**: DIN assigned by Health Canada; NDC assigned by FDA (US)
- **non-proprietary name**: approved name (post-phase III trial), official name (listed in pharmacopeia), or generic name (off-patent) such as acetaminophen
- **proprietary (trade) name**: the brand name or registered trademark (e.g. Tylenol®)

### Phases of Clinical Drug Testing

- **pre-clinical**: testing a drug in a controlled environment (lab) on animal or human cells before human testing to discern the PK and toxicological profile
- **phase I**: first administration to healthy human volunteers, following animal studies; to determine PK and PD
- **phase II**: first administration to patients, small sample sizes; to determine initial safety and efficacy, dose range, PK, and PD
- **phase III**: large sample sizes, often double-blinded RCT; comparative (new drug vs. placebo or standard of care) to establish safety and efficacy
- **phase IV**: post-marketing surveillance, wide distribution; to determine effects of long-term use, rare ADRs, ideal dosing, and effects in real-world practice

### Drug Administration

- choice of route of administration depends on: drug properties, local and systemic effects, desired onset and/or duration of action, and patient characteristics

**Table 1. Routes of Drug Administration**

<table>
<thead>
<tr>
<th>Route</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (PO)</td>
<td>Convenient, easy to administer</td>
<td>Incomplete absorption</td>
</tr>
<tr>
<td></td>
<td>Large surface area for absorption</td>
<td>Hepatic first-pass effect</td>
</tr>
<tr>
<td></td>
<td>Inexpensive relative to parenteral administration</td>
<td>Potential GI irritation</td>
</tr>
<tr>
<td>Bucal/Sublingual (SL)</td>
<td>Rapid onset of action</td>
<td>Must be lipid-soluble, non-irritating</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Short duration of action</td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>Almost no hepatic first-pass effect</td>
<td>Inconvenient, irritation at site of application</td>
</tr>
<tr>
<td></td>
<td>Use when NPO, vomiting, or unconscious</td>
<td>Erratic absorption</td>
</tr>
<tr>
<td>Intravenous (IV)</td>
<td>No hepatic first-pass effect</td>
<td>Hard to remove once administered</td>
</tr>
<tr>
<td></td>
<td>Slow infusion or rapid onset of action</td>
<td>Risk of infection, bleeding, vascular injury</td>
</tr>
<tr>
<td></td>
<td>Easy to inject dose</td>
<td>Extravasation</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>Depot storage if oil-based = slow release of drug</td>
<td>Pain/hematoma at site of injection</td>
</tr>
<tr>
<td></td>
<td>Aquous solution = rapid onset of action</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>Non-irritating drugs, small volumes</td>
<td>Pain at site of injection</td>
</tr>
<tr>
<td></td>
<td>Constant, even absorption</td>
<td>Smaller volumes than IM</td>
</tr>
<tr>
<td></td>
<td>Alternative to IV</td>
<td>May have tissue damage from multiple injections</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Direct into CSF</td>
<td>Risk of infection</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Immediate action in lungs</td>
<td>Must be gas, vapour, or aerosol</td>
</tr>
<tr>
<td>Topical</td>
<td>Easy to administer</td>
<td>Effects are mainly limited to site of application</td>
</tr>
<tr>
<td></td>
<td>Localized (limited systemic absorption)</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>Drug absorption through intact skin</td>
<td>Irritation at site of application</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Delayed onset of action</td>
</tr>
<tr>
<td></td>
<td>Hydrophilic drugs not easily absorbed</td>
<td></td>
</tr>
<tr>
<td>Others (Intrapерitoneal, Intra-Articular)</td>
<td>Local effect</td>
<td>Risk of infection</td>
</tr>
</tbody>
</table>
Pharmacokinetics

- **study of “what the body does to a drug”**
- **definition**: relationship between drug administration, time-course/rate of absorption and distribution, concentration changes in the body compartments, and the drug’s removal from the body

## Absorption

- **definition**: movement of the drug from the site of administration into plasma

### Mechanisms of Drug Absorption

- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms include active transport, facilitated diffusion, and pinocytosis/phagocytosis

### Factors Affecting the Rate and Extent of Drug Absorption

- **P<sub>ow</sub>**
  - local blood flow at the site of administration (e.g. sublingual vessels facilitate rapid absorption of sublingual medications)
- **molecular size** (e.g. drugs with smaller molecular weight absorb faster)
- **pH and drug ionization**
  - drugs are usually weak acids (e.g. ASA) or weak bases (e.g. ketoconazole) and thus exist in ionized and non-ionized forms
  - non-ionized forms cross cell membranes much faster than ionized (charged) forms
  - the ratio of ionized to non-ionized forms is determined by body compartment pH and drug pKa (HH equation)
- total surface area for absorption
- small intestinal villi are the primary site of absorption for most oral drugs

Bioavailability (F)

- **definition**: proportion of dose that reaches systemic circulation in an unchanged state
- decreased by limited drug absorption or first-pass effect
- IV dose has 100% bioavailability (F = 1)

### First-Pass Effect

- **definition**: drug metabolism by the liver and/or the gut before it reaches systemic circulation, resulting in reduced F
- occurs with PO administration of a drug: GI tract (absorption) → portal vein to liver (first-pass metabolism) → systemic circulation
- occurs less with PR administration because drug absorbed in colon bypasses the portal system

### Efflux Pump

- Pgp is a protein found in various parts of the body that acts as a multidrug efflux pump involved in the transport of drugs out of cells
- for example, opposes intestinal absorption (e.g. dabigatran etexilate) and also enhances renal elimination of certain drugs (e.g. digoxin, etoposide, paclitaxel, tacrolimus, cyclosporine)
- some drugs (e.g. macrolide antibiotics) inhibit Pgp function, leading to increased serum levels of drugs transported by Pgp. Pgp inducers (e.g. St. John’s wort) do the opposite
- some tumours overexpress Pgp leading to multidrug resistance to chemotherapeutic agents

## Distribution

- **definition**: movement of drugs between different body compartments and to the site of action

### Factors Affecting the Rate and Extent of Drug Distribution

- physiochemical properties of the drug (e.g. P<sub>ow</sub> and pKa)
- pH of fluid
- plasma protein binding
- binding within compartments (i.e. depots)
- regional blood flow

---

**Figure 1. Distribution of total body water (TBW)**

- **Total Body Water**: 60% of body weight
- **Extracellular Fluid**: 16-20%
- **Intercellular Fluid**: 40-44%
- **Intravascular Plasma**: 4%
- **Interstitial Fluid**: 12-15%
Volume of Distribution

- $V_d$ the apparent volume of fluid into which a drug distributes
- maximum actual $V_d$ (anatomic fluid volume accessible to drug) = TBW (TBW~40 L for average adult)
  - a calculated value $(V_d) = \text{amount of drug in body} ÷ \text{plasma drug concentration}$
  - a theoretical value that does not correspond to an anatomic space (i.e. can exceed TBW)
  - small $V_d$ corresponds to a drug that concentrates in plasma and/or binds plasma proteins to a high degree
  - large $V_d$ corresponds to a drug that distributes into tissues (fat, muscle, etc.); most is not in blood (measured space).
  - it therefore “appears” to distribute in a large volume
- $V_d$ of plasma protein bound drugs can be altered by liver and kidney disease
- example: amiodarone distributes into TBW (actual $V_d = 40$ L), but it also concentrates in fat tissues giving instead a large apparent $V_d$ of 400 L; therefore, to achieve a given plasma concentration of amiodarone, we dose as though the drug distributes into 400 L of body fluid

 Plasma Protein Binding

- drug molecules in the blood exist in an equilibrium of two forms:
  1. bound to plasma protein: acidic drugs bind to albumin, basic drugs bind to α1-acid glycoprotein
  2. free or unbound: can leave the circulation to distribute into tissues and exert an effect, subject to metabolism and elimination
  - bound fraction is determined by drug concentration, binding affinity, and plasma protein concentration (number of binding sites)
  - reduced number of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in increased concentration of free drug, which is often metabolized with no harmful effects, although toxicity is possible

Depots

- a body compartment in which drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wk)

 Barriers (relative)

- body structures that limit or prevent diffusion of drug molecules, such as the placenta or BBB (a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. Pgp), which serve as a natural defense mechanism against drugs and xenobiotics
- need to consider dosing route if drugs are meant to cross these barriers

Metabolism (Biotransformation)

- definition: chemical transformation of a drug in vivo to enhance elimination
- sites of biotransformation include liver (main), GI tract, lung, plasma, kidney
- as a result of the process of biotransformation:
  - an inactive prodrug may be activated (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be changed to another active metabolite (e.g. diazepam to oxazepam)
  - a drug may be changed to a toxic metabolite (e.g. meperidine to normeperidine)
  - a drug may be inactivated (most drugs)

Drug Metabolizing Pathways

- phase I (P450) reactions
  - minor molecular changes introduce or unmask polar groups on a parent compound to increase water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation); the change in $P_{ow}$ is typically minimal compared to phase II, and often phase I places a polar ‘handle’ on a lipophilic drug to allow for phase II
  - mediated by CYPs found in the endoplasmic reticulum
  - product of the reaction can be excreted or undergo further phase II reactions
- phase II (conjugation) reactions
  - conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
  - dramatically increases water solubility and renal elimination
  - can result in biologically active metabolites (e.g. glucuronides of morphine)
  - can occur independently of phase I reactions
Factors Affecting Drug Biotransformation

- **genetic polymorphisms** of metabolizing enzymes
  - individual genotypes may determine rate of drug metabolism (e.g. poor, intermediate, extensive, or ultrarapid metabolizers)
  - may lead to toxicity or ineffectiveness of a drug at a normal dose
  - tamoxifen and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas overactive/duplicated alleles impart “ultrarapid metabolizer” phenotype)
  - warfarin is metabolized by CYP2C9 (nonfunctional alleles lead to greater effect and lower dose requirements)
- **enzyme inhibition** may sometimes be due to other drugs
  - CYP inhibition leads to an increased concentration and bioavailability of the substrate drug (e.g. erythromycin [CYP3A4 inhibitor] can predispose patients to simvastatin toxicity [metabolized by CYP3A4])
- **enzyme induction**
  - certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
  - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCPs) by inducing the CYP system
- **liver dysfunction** (e.g. hepatitis, alcoholic liver, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but this may not be clinically significant due to the liver's reserve capacity
- **renal disease** often results in decreased drug clearance
- **extremes of age** (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
- **nutrition**: insufficient protein and fatty acid intake decreases CYP biotransformation, and vitamin/mineral deficiencies may also impact other metabolizing enzymes
- **alcohol**: while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1 and increase risk of hepatocellular damage from acetaminophen by increasing the generation of acetaminophen's toxic metabolite
- **smoking** can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. theophylline, antipsychotics)

**Elimination**

- **definition**: removal of drug from the body

**Routes of Drug Elimination**

- **kidney** (main organ of elimination)
  - two mechanisms:
    1. **glomerular filtration**
       - a passive process, so that only the free drug fraction can be eliminated
       - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
    2. **tubular secretion**
       - an active process that is saturable allowing both protein-bound and free drug fractions to be excreted
       - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
       - drugs may competitively block mutual secretion if both use the same secretion system (e.g. probenecid can reduce the excretion of penicillin)
- **tubular reabsorption**: drugs can be passively reabsorbed back to the systemic circulation, countering elimination mechanisms
- **renal function** (assessed using serum Cr levels) decreases with age and is affected by many disease states such as diabetes
- **stool**: some drugs and metabolites are actively excreted in the bile or directly into the GI tract
  - enterohepatic reabsorption counteracts stool elimination, and can prolong the drug's duration in the body
  - some glucuronide conjugates that are excreted in bile may be hydrolyzed in the intestines by bacteria back to their original form and can be systemically reabsorbed
- **lungs**: elimination of anesthetic gases and vapours by exhalation
- **saliva**: saliva concentrations of some drugs parallel their plasma levels (e.g. rifampin)

**Cytochrome P450 System**

The CYPs are a superfamily of heme proteins that are grouped into families and subfamilies according to their amino acid sequence. These proteins are responsible for the metabolism of drugs, chemicals, and other substances.

**Nomenclature:** CYP = cytochrome P450 protein
- 1st number = family
- letter = subfamily
- 2nd number = isoform

The CYP1, CYP2, and CYP3 families metabolize most drugs in humans. The most important isoforms are CYP3A4 and CYP2D6; therefore, anticipate drug interactions if prescribing drugs using these enzymes.

**Examples of CYP Substrates, Inhibitors and Inducers**

http://www.medicine.iupui.edu/CLINPHARM/ddis/main-table

**The Cockcroft-Gault Equation can Estimate CrCl in Adults 20 yr of Age and Older**

- For males
  \[
  \text{CrCl (mL/min)} = \left( \frac{140 - \text{age in yr}}{\text{Wt} \times 1.2} \right) \times \text{serum Cr (µmol/L)}
  \]
- For females, multiply above equation x 0.85

Note, only applies when renal function is at steady state.

Avoid toxicity from drug or metabolite accumulation by adjusting a drug’s dosage according to the elimination characteristics of the patient.
Pharmacokinetic Calculation

- **definition:** the quantitative description of the rates of the various steps of drug disposition (i.e. how drugs move through the body)
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism, and elimination) can be graphically represented on a concentration vs. time graph

**Time Course of Drug Action**
- many kinetic parameters are measured using IV dosing, such that absorption is immediate and distribution for most drugs is rapid; thus elimination is the main process being measured
- the concentration axis is converted to a log10 concentration to allow for easier mathematical calculations
- drugs such as warfarin can exhibit hysteresis (for a single drug concentration, there may be two different response levels)

**Half-Life**
- **definition:** time taken for the serum drug level to fall 50% during elimination
- drugs with first order kinetics require five half-lives to reach steady state with repeated dosing or for complete drug elimination once dosing is stopped

**Steady State**
- drug concentration remains constant when amount of drug entering the system is eliminated from the system
- drug levels in therapeutic drug monitoring are of greatest utility when the steady state has been reached
  - special situations
    - use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
    - use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, insulin, unfractionated heparin)

**Clearance**
- a quantitative measurement of the body fluid volume from which a substance is removed per unit time
  - CI = rate of elimination of drug/plasma drug concentration
- must consider CI from a specific part of the body and total body CI

**Elimination Kinetics**
- first-order kinetics (most common type)
  - constant fraction of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the CI is less than would be predicted for a given concentration
  - shows linear relationship when plotted to a log (concentration) vs. time graph
- zero-order kinetics (less common, associated with overdose, e.g. alcohol)
  - drug is eliminated at a constant rate regardless of concentration; concept of half-life does not apply
  - the concentration axis is converted to a log (concentration) to allow for easier mathematical calculations

**Table 2. Half-Life**
<table>
<thead>
<tr>
<th># of Half-Lives</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>3.3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Steady State Concentration</td>
<td>50</td>
<td>75</td>
<td>87.5</td>
<td>90</td>
<td>93.8</td>
<td>96.9</td>
</tr>
</tbody>
</table>

**Clearance**
- a quantitative measurement of the body fluid volume from which a substance is removed per unit time
  - CI = rate of elimination of drug/plasma drug concentration
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  - the concentration axis is converted to a log (concentration) to allow for easier mathematical calculations

**Table 3. Loading vs. Maintenance Dosing**

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use when you need an IMMEDIATE effect</td>
<td>After a loading dose OR beginning with maintenance doses</td>
</tr>
<tr>
<td>Often parenteral medication</td>
<td>Steady-state levels achieved after ~5 half-lives</td>
</tr>
<tr>
<td>Rationale: give large dose of medication to &quot;fill up&quot; the volume of distribution</td>
<td>Can be given as either a continuous infusion (relatively rare, short half-life drug) OR much more commonly as intermittent doses</td>
</tr>
</tbody>
</table>

"Use when you need an IMMEDIATE effect" | "After a loading dose OR beginning with maintenance doses" | "Often parenteral medication" | "Steady-state levels achieved after ~5 half-lives" | "Rationale: give large dose of medication to "fill up" the volume of distribution" | "Can be given as either a continuous infusion (relatively rare, short half-life drug) OR much more commonly as intermittent doses" |
Pharmacodynamics

• study of “what the drug does to the body”

Dose-Response Relationship

• graded dose-response relationships: relates dose to intensity of effect

Efficacy

• the maximum biological response produced by a drug
• measured by E_{max} (the maximal response that a drug can elicit in a RCT or under optimal circumstances)

Potency

• measured by EC_{50} (the concentration of a drug needed to produce 50% of E_{max})
• a drug that reaches its EC_{50} at a lower dose is more potent

Figure 5. Log(dose)-response curve illustrating efficacy and potency

Effects of Drugs on Receptors

Agonists

• drugs that mimic the effects of the endogenous ligand and evoke a response when bound to the receptor
  • affinity: the ability of the agonist to bind to the receptor (e.g. the β2-agonist salbutamol has greater affinity for β2-receptors than β1-receptors)
  • efficacy: the ability to recapitulate endogenous response via the receptor interaction (e.g. binding of salbutamol to β2-receptors results in smooth muscle relaxation)
  • full agonists: can elicit a maximal effect at a receptor
  • partial agonists: can only elicit a partial effect, no matter the concentration at the receptor (i.e. reduced efficacy compared to full agonists)

Antagonists

• drugs that block the action of an agonist or of an endogenous ligand
  • chemical antagonism: direct chemical interaction between agonist and antagonist prevents agonist-receptor binding (e.g. chelating agents for removal of heavy metals)
  • functional antagonism: two agonists that act independently at different receptors and have opposite physiological effects (e.g. acetylcholine at the muscarinic receptor compared to epinephrine at the adrenergic receptor)
  • reversible and irreversible competitive antagonism
    • drugs that exert no direct effect upon binding to a given receptor
    • reversible competitive antagonists reversibly bind to the same receptor as the agonist, thus displacing it (e.g. naloxone is an antagonist to morphine or heroin)
    • irreversible antagonists form a covalent bond with the receptor, thus irreversibly blocking substrates from binding (e.g. phenoxybenzamine forms a covalent bond with adrenergic receptors preventing adrenaline and NE from binding)
  • non-competitive antagonism
    • antagonist binds to an alternate site near the agonist site, producing allosteric effects that change the ability of the agonist to bind (e.g. organophosphates irreversibly bind acetylcholinesterase)

Efficacy vs. Potency

• Efficacy measures the maximal effect of a drug
• Potency measures the concentration of a drug needed to produce a certain effect

Figure 6. The log(dose)-response curve for competitive reversible antagonism

Figure 7. The log(dose)-response curve for irreversible antagonism
Effectiveness and Safety

Effectiveness
- **ED50** (effective dose): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

Safety
- **LD50** (lethal dose): the dose of a drug needed to cause death in 50% of a test population of subjects
- **TD50** (toxic dose): the dose needed to cause a harmful effect in 50% of a test population of subjects

Therapeutic Indices

Therapeutic Index: **TD50/ED50**
- reflects the “margin of safety” for a drug – the likelihood of a therapeutic dose to cause serious toxicity or death
- the larger the TI, the safer a drug (e.g. warfarin has a narrow TI and requires drug monitoring)
- factors that can change the TI
  - presence of interacting drugs
  - changes in drug ADME

Certain Safety Factor: **TD1/ED99**
- >1 translates to a dose effective in at least 99% of the population and toxic in less than 1% of the population

Drugs with a narrow TI have a high likelihood of causing toxicity and need close therapeutic monitoring

The two most clinically relevant properties of any drug are effectiveness and safety
Therapeutic Drug Monitoring

• Definition: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance) serum drug samples are usually taken when the drug has reached steady state (after approximately 5 half-lives)

• TDM is often used for drugs that have: narrow TIs, unpredictable dose-response relationships, significant consequences associated with therapeutic failure or toxicity, and wide inter-patient PK variability

Adverse Drug Reactions

Table 4. Characteristics of Type A-E Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Augmented)</td>
<td>Dose related</td>
<td>Predictable extension of drug’s pharmacologic effect (e.g. β-blockers causing bradycardia) &gt;80% of all ADRs</td>
</tr>
<tr>
<td>B (Bizarre)</td>
<td>Non-dose related</td>
<td>Reactions unrelated to the known pharmacological actions of the drug Examples include: drug hypersensitivity syndromes, immunologic reactions (penicillin hypersensitivity), and idiosyncratic reactions (malignant hyperthermia)</td>
</tr>
<tr>
<td>C (Chronic)</td>
<td>Dose and time related</td>
<td>Related to cumulative doses Effects are well-known and can be anticipated (e.g. atypical femoral fracture from bisphosphonates)</td>
</tr>
<tr>
<td>D (Delayed)</td>
<td>Time related</td>
<td>Occurs some time after use of drug (e.g. carcinogen) May also be dose-related</td>
</tr>
<tr>
<td>E (End of use)</td>
<td>Withdrawal</td>
<td>Occurs after cessation of drug use (e.g. opiate withdrawal)</td>
</tr>
</tbody>
</table>

Approach to Suspected Adverse Drug Reactions

• History and physical exam: signs and symptoms of reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, de-challenge (response when drug is removed), and re-challenge (response when drug is given again)

• Differentiate between drug therapy vs. disease pathophysiology

• Treatment: stop the drug, supportive care, symptomatic relief

• Resources: check recent literature, Health Canada, and FDA; contact the pharmaceutical company; call Poison Control (1-888-268-9017) if overdose or poisoning suspected; check with Motherisk (www.motherisk.org) in cases involving pregnant or breastfeeding women

• Report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity
  - Canadian Adverse Drug Reaction Monitoring Program available for online reporting
Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
- possible causes of individual variability in drug response include problems with:
  - intake: patient adherence
  - PK
  - absorption: vomiting, diarrhea, or steatorrhea; first pass effect increased due to enzyme induction or decreased due to liver disease
  - drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, and fluoroquinolones)
  - distribution: very high or low percentage body fat; intact or disrupted BBB; patient is elderly or a neonate, or has liver dysfunction
  - biotransformation and elimination: certain genetic polymorphisms or enzyme deficiencies related to drug metabolism (e.g. acetylcholinesterase deficiency, CYP polymorphism); kidney or liver dysfunction
  - PD: genetic variability in drug response (e.g. immune-mediated reactions); diseases that affect drug PD; drug tolerance or cross-tolerance

Drug Interactions

- concomitant prescriptions: one drug alters the effect of another by changing its PK and/or PD
- PK interactions involve changes in drug concentration
  - absorption: alterations in gastrointestinal pH, gastric emptying, intestinal motility, gut transporters
  - metabolism: alterations in drug metabolizing enzymes (e.g. CYP)
  - excretion: alterations in renal elimination
- PD interactions are due to two drugs that exert similar effects (additive) or opposing effects (subtractive)
- drug interactions can also involve herbal medications (e.g. St. John’s wort) and food (e.g. grapefruit)

Autonomic Pharmacology

- most organs are innervated by both sympathetic and parasympathetic nerves, which have opposing effects (see Neurology, N8)
- ACh and NE are the main neurotransmitters of the autonomic NS
- ACh binds to cholinergic receptors, which include nicotinic and muscarinic receptors
- NE binds to adrenergic receptors, which principally include β1, β2, α1, and α2
- ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase
- acetylcholinesterase inhibitors (pyridostigmine, donepezil, galantamine, rivastigmine) can be used to increase ACh levels in conditions such as myasthenia gravis or Alzheimer’s disease
- NE action is terminated by reuptake at the presynaptic membrane, diffusion from the synaptic cleft and degradation at monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT)

Parasympathetic Nervous System

- blood vessels, adrenals, sweat glands, spleen capsule, and adrenal medulla do NOT have parasympathetic innervation
- parasympathetic pre-ganglionic fibres originate in the lower brainstem from cranial nerves III, VII, IX, X, and in the sacral spinal cord at levels S2-S4 and connect with post-ganglionic fibres via nicotinic receptors in ganglionic cells located near or within the target organ
- post-ganglionic fibres connect with effector tissues via:
  - M1 muscarinic receptors located in the CNS
  - M2 muscarinic receptors located in smooth muscle, cardiac muscle, and glandular epithelium
**Sympathetic Nervous System**

- sympathetic pre-ganglionic fibres originate in the spinal cord at spinal levels T1-L2/L3
- pre-ganglionic fibres connect with post-ganglionic fibres via nicotinic receptors located in one of two groups of ganglia:
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. pre-vertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- post-ganglionic fibres connect with effector tissues via:
  - β1 receptors in cardiac tissue
  - β2 receptors in smooth muscle of bronchi and GI tract
  - α1 receptors in vascular smooth muscle
  - α2 receptors in vascular smooth muscle
  - M3 muscarinic receptors located in sweat glands

**Table 5. Direct Effects of Autonomic Innervation on the Cardiorespiratory System**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic NS</th>
<th>Parasympathetic NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Receptor</td>
<td>Action</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sinoatrial</td>
<td>β1</td>
<td>Increased HR</td>
</tr>
<tr>
<td>2. At ionventricular node</td>
<td>β1</td>
<td>Increased conduction</td>
</tr>
<tr>
<td>3. Atria</td>
<td>β1</td>
<td>Increased contractility</td>
</tr>
<tr>
<td>4. Ventricles</td>
<td>β1</td>
<td>Increased contractility</td>
</tr>
<tr>
<td>Blood Vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Skin, splanchnic</td>
<td>α1, β2</td>
<td>Constriction</td>
</tr>
<tr>
<td>2. Skeletal muscle</td>
<td>α</td>
<td>Constriction</td>
</tr>
<tr>
<td>3. Coronary</td>
<td>α2 (large muscles)</td>
<td>Dilatation</td>
</tr>
<tr>
<td></td>
<td>α1, β2</td>
<td>Constriction</td>
</tr>
<tr>
<td>Lungs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bronchiolar smooth muscle</td>
<td>β2</td>
<td>Relaxation</td>
</tr>
<tr>
<td>2. Bronchiolar glands</td>
<td>α1, β2</td>
<td>Increased secretion</td>
</tr>
</tbody>
</table>

**Figure 11. Autonomic nervous system efferent tracts**

**Opioid Therapy and Chronic Non-Cancer Pain**

**Who?**

- for patients without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized non-opioid therapy, add a trial of opioids rather than continued therapy without opioids (weak recommendation)
- for patients with an active substance use disorder, use of opioids is not recommended (strong recommendation)
- for patients with chronic non-cancer pain with a history of substance use disorder, whose non-opioid therapy has been optimized, and who have persistent problematic pain, continue non-opioid therapy rather than a trial of opioids (weak recommendation)
- for patients with an active psychiatric disorder whose non-opioid therapy has been optimized, and who have persistent problematic pain, stabilize the psychiatric disorder before a trial of opioids is considered (weak recommendation)

**General Management Principles**

- when first considering therapy for patients with chronic non-cancer pain, optimize non-opioid pharmacotherapy and non-pharmacologic therapy, rather than a trial of opioids (strong recommendation)
- for patients with chronic non-cancer pain beginning opioid therapy, restrict the prescribed dose to less than 90 mg morphine equivalents daily, rather than having no upper limit or a higher limit on dosing (strong recommendation)
- for patients with chronic non-cancer pain who are currently using 90 mg morphine equivalents of opioids per day or more, taper opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy (weak recommendation)
- for patients with chronic non-cancer pain who are beginning opioid therapy, restrict the prescribed dose to less than 50 mg morphine equivalents daily (weak recommendation)
- for patients with chronic non-cancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects, rotate to other opioids rather than keeping the opioid the same (weak recommendation)
- for patients with chronic non-cancer pain who are using opioids and experiencing serious challenges in tapering, formal multidisciplinary program is suggested (strong recommendation)
# Common Drug Endings

## Table 6. Common Drug Endings

<table>
<thead>
<tr>
<th>Ending</th>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>-afil</td>
<td>5-PDE inhibitor</td>
<td>sildenafil</td>
</tr>
<tr>
<td>-ane</td>
<td>Inhaled general anesthetic</td>
<td>halothane</td>
</tr>
<tr>
<td>-azepam</td>
<td>Benzodiazepine</td>
<td>lorazepam</td>
</tr>
<tr>
<td>-azole</td>
<td>Antifungal</td>
<td>ketoconazole</td>
</tr>
<tr>
<td>-caine</td>
<td>Local anesthetic</td>
<td>lidocaine</td>
</tr>
<tr>
<td>-clol</td>
<td>β-blocker</td>
<td>propranolol</td>
</tr>
<tr>
<td>-prazole</td>
<td>Proton pump inhibitor</td>
<td>omeprazole</td>
</tr>
<tr>
<td>-pril</td>
<td>ACE inhibitor</td>
<td>captopril</td>
</tr>
<tr>
<td>-sartan</td>
<td>ARB</td>
<td>candesartan</td>
</tr>
<tr>
<td>-statin</td>
<td>HMG-CoA inhibitor</td>
<td>atorvastatin</td>
</tr>
<tr>
<td>-terol</td>
<td>β2 agonist</td>
<td>albuterol</td>
</tr>
<tr>
<td>-tidine</td>
<td>H2 antagonist</td>
<td>cimetidine</td>
</tr>
<tr>
<td>-tropin</td>
<td>Pituitary hormone</td>
<td>somatotropin</td>
</tr>
<tr>
<td>-vir</td>
<td>Antiviral</td>
<td>acyclovir</td>
</tr>
<tr>
<td>-zosin</td>
<td>α1 antagonist</td>
<td>prazosin</td>
</tr>
</tbody>
</table>

Note: Some medications are exceptions to the rule, e.g. methimazole (antithyroid)

For more information on medical pharmacology, please refer to our textbook product, Pharmacology You See

## References

**Principles of Clinical Pharmacology**

**Adverse Drug Reactions**
- Lewis T. Using the NO TEARS tool for medication review. BMAJ 2004;329:434.

**Drug Interactions**

**Opioid Guidelines**
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronyms</td>
<td>2</td>
</tr>
<tr>
<td><strong>Introduction to Skin</strong></td>
<td>2</td>
</tr>
<tr>
<td>Skin Anatomy</td>
<td></td>
</tr>
<tr>
<td>Skin Function</td>
<td></td>
</tr>
<tr>
<td><strong>Definitions</strong></td>
<td>3</td>
</tr>
<tr>
<td>Primary Morphological Lesions</td>
<td></td>
</tr>
<tr>
<td>Secondary Morphological Lesions</td>
<td></td>
</tr>
<tr>
<td>Other Morphological Lesions</td>
<td></td>
</tr>
<tr>
<td>Patterns and Distribution</td>
<td></td>
</tr>
<tr>
<td><strong>Differential Diagnoses of Common Presentations</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Common Skin Lesions</strong></td>
<td>5</td>
</tr>
<tr>
<td>Cysts</td>
<td></td>
</tr>
<tr>
<td>Fibrous Lesions</td>
<td></td>
</tr>
<tr>
<td>Hyperkeratotic Lesions</td>
<td></td>
</tr>
<tr>
<td>Keloids</td>
<td></td>
</tr>
<tr>
<td>Pigmented Lesions</td>
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<tr>
<td>Vascular Lesions</td>
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</tr>
<tr>
<td>Lipoma</td>
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<tr>
<td><strong>Acneiform Eruptions</strong></td>
<td>11</td>
</tr>
<tr>
<td>Acne Vulgaris/Common Acne</td>
<td></td>
</tr>
<tr>
<td>Perioral Dermatitis</td>
<td></td>
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<tr>
<td>Rosacea</td>
<td></td>
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<tr>
<td><strong>Dermatitis (Eczema)</strong></td>
<td>13</td>
</tr>
<tr>
<td>Asteatotic Dermatitis</td>
<td></td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td></td>
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<tr>
<td>Contact Dermatitis</td>
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<tr>
<td>Dyshidrotic Dermatitis</td>
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<td>Nummular Dermatitis</td>
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<td>Seborrheic Dermatitis</td>
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<td>Stasis Dermatitis</td>
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</tr>
<tr>
<td>Lichen Simplex Chronicus</td>
<td></td>
</tr>
<tr>
<td><strong>Papulosquamous Diseases</strong></td>
<td>16</td>
</tr>
<tr>
<td>Lichen Planus</td>
<td></td>
</tr>
<tr>
<td>Pityriasis Rosea</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td><strong>Vesiculobullous Diseases</strong></td>
<td>19</td>
</tr>
<tr>
<td>Bullous Pemphigoid</td>
<td></td>
</tr>
<tr>
<td>Pemphigus Vulgaris</td>
<td></td>
</tr>
<tr>
<td>Dermatitis Herpetiformis</td>
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<tr>
<td>Porphyria Cutanea Tarda</td>
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</tr>
<tr>
<td><strong>Drug Eruptions</strong></td>
<td>21</td>
</tr>
<tr>
<td>Exanthematous</td>
<td></td>
</tr>
<tr>
<td>Urticarial</td>
<td></td>
</tr>
<tr>
<td>Pustular</td>
<td></td>
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<tr>
<td>Bullous</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td><strong>Heritable Disorders</strong></td>
<td>23</td>
</tr>
<tr>
<td>Ichthyosis Vulgaris</td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis (Type I; von Recklinghausen’s Disease)</td>
<td></td>
</tr>
<tr>
<td>Vitiligo</td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>25</td>
</tr>
<tr>
<td>Bacterial Infections</td>
<td></td>
</tr>
<tr>
<td>Dermatophytoeses</td>
<td></td>
</tr>
<tr>
<td>Parasitic Infections</td>
<td></td>
</tr>
<tr>
<td>Viral Infections</td>
<td></td>
</tr>
<tr>
<td>Yeast Infections</td>
<td></td>
</tr>
<tr>
<td>Sexually Transmitted Infections</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-Malignant Skin Conditions</strong></td>
<td>33</td>
</tr>
<tr>
<td>Actinic Keratosis (Solar Keratosis)</td>
<td></td>
</tr>
<tr>
<td>Leukoplaik</td>
<td></td>
</tr>
<tr>
<td><strong>Malignant Skin Tumours</strong></td>
<td>34</td>
</tr>
<tr>
<td>Non-Melanoma Skin Cancers</td>
<td></td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td></td>
</tr>
<tr>
<td>Other Cutaneous Cancers</td>
<td></td>
</tr>
<tr>
<td><strong>Diseases of Hair Density</strong></td>
<td>37</td>
</tr>
<tr>
<td>Hair Growth</td>
<td></td>
</tr>
<tr>
<td>Non-Scarring (Non-Cicatricial) Alopecia</td>
<td></td>
</tr>
<tr>
<td>Scarring (Cicatricial) Alopecia</td>
<td></td>
</tr>
<tr>
<td><strong>Nails and Disorders of the Nail Apparatus</strong></td>
<td>39</td>
</tr>
<tr>
<td><strong>Skin Manifestations of Systemic Disease</strong></td>
<td>40</td>
</tr>
<tr>
<td><strong>Pediatric Exanthems</strong></td>
<td>P50</td>
</tr>
<tr>
<td><strong>Miscellaneous Lesions</strong></td>
<td>41</td>
</tr>
<tr>
<td>Angioedema and Urticaria</td>
<td></td>
</tr>
<tr>
<td>Erythema Nodosum</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
</tr>
<tr>
<td>Wounds and Ulcers</td>
<td></td>
</tr>
<tr>
<td>Sunscreens and Preventative Therapy</td>
<td></td>
</tr>
<tr>
<td>Topical Steroids</td>
<td></td>
</tr>
<tr>
<td>Dermatologic Therapies</td>
<td></td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>46</td>
</tr>
</tbody>
</table>
Acronyms

Skin Anatomy

Skin
- divided anatomically into epidermis, dermis, and subcutaneous tissue
- **epidermis**
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale
  - cells progress from stratum basale to stratum corneum in about 4 wk
    - stratum basale (germinativum): mitotic figures that give rise to keratinocytes
    - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
    - stratum granulosum: flat cells containing basophilic granules which characterize skin
    - stratum lucidum: transparent layers of packed dead cells
    - stratum corneum: flat scales of the water-resistant protein keratin
  - cells of the epidermis
    - keratinocytes: located in all layers of the epidermis, except the stratum corneum; connected to each other by desmosomes
    - melanocytes: located in the stratum basale; keratinocyte to melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races; produce melanosomes containing melanin, which are transferred to keratinocytes
    - Langerhans cells: dendritic cells which are important for immune surveillance
    - Merkel cells: located in the basal layer; involved in touch sensation
- **dermis**: comprises of connective tissue divided into two regions
  - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
  - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages
- **cells of dermis**
  - fibroblasts: produce collagen, elastin, and ground substance
  - mast cells: release histamines which mediate type 1 hypersensitivity
  - other components of dermis include: blood vessels, nerves, pilosebaceous units, and sweat glands
- **subcutaneous tissue** (hypodermis)
  - consists primarily of adipose cells, larger calibre vessels, nerves, and fascia
Epidermal Appendages
- epidermal in origin, can extend into the dermis; includes hair, nails, and cutaneous glands
- pilosebaceous unit = hair + hair follicle + sebaceous gland + arrector pili muscle

Cutaneous Glands
- sebaceous gland: part of pilosebaceous unit, produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
  - sebum has some antifungal properties
  - these glands cover entire skin surface and are absent only in non-hair bearing areas (e.g. palms, soles, lips)
- apocrine sweat gland: apocrine duct empties into hair follicle above sebaceous gland
  - found in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)
- eccrine sweat gland: not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds, and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface

Skin Function
- protection
  - due to continuous recycling and avascularity of epidermis
  - barrier to UV radiation (melanin), mechanical/chemical insults (sensory/mechanoreceptors), pathogens (immune cells), and dehydration (lipid rich barrier)
- thermal regulation
  - insulation to maintain body temperature in cool environments via peripheral vasoconstriction, hair, and subcutaneous adipose tissue
  - dissipation of heat in warm environments via increased activity of sweat glands and increased blood flow within dermal vascular networks
- sensation
  - touch, pain, and temperature sensation
- metabolic function
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

Definitions

Primary Morphological Lesions
Definition
- an initial lesion that has not been altered by trauma or manipulation, and has not regressed

Table 1. Types of Primary Morphological Lesions

<table>
<thead>
<tr>
<th>Profile</th>
<th>&lt;1 cm Diameter</th>
<th>≥1 cm Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat Lesion</td>
<td>Macule (e.g. freckle)</td>
<td>Patch (e.g. vitiligo)</td>
</tr>
<tr>
<td>Raised Superficial Lesion</td>
<td>Papule (e.g. wart)</td>
<td>Plaque (e.g. psoriasis)</td>
</tr>
<tr>
<td>Deep Palpable (dermal or subcutaneous) Lesion</td>
<td>Nodule (e.g. dermatofibroma)</td>
<td>Tumour (e.g. lipoma)</td>
</tr>
<tr>
<td>Elevated Fluid-Filled Lesion</td>
<td>Vesicle (e.g. HSV)</td>
<td>Bulla (e.g. bullous pemphigoid)</td>
</tr>
</tbody>
</table>

Secondary Morphological Lesions
Definition
- develop during the evolutionary process of skin disease, or created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)
- crust: dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- scale: excess keratin (e.g. seborrheic dermatitis)
- lichenification: thickening of the skin and accentuation of normal skin markings (e.g. chronic atopic dermatitis)
- fissure: a linear slit-like cleavage of the skin
- excoriation: a scratch mark
- erosion: a disruption of the skin involving the epidermis alone; heals without scarring
- ulcer: a disruption of the skin that extends into the dermis or deeper; may heal with scarring
- xerosis: pathologic dryness of skin (xeroderma), conjunctiva (xerophthalmia), or mucous membranes (xerostomia)
- atrophy: histological decrease in size or number of cells or tissues, resulting in thinning or depression of the skin
Other Morphological Lesions

- **cyst**: an epithelial-lined collection containing semi-solid or fluid material
- **pustule**: an elevated lesion containing purulent fluid (white, grey, yellow, green)
- **scar**: replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- **wheal**: a special form of papule or plaque that is transient (<24 h) and blanchable, often with a halo and central clearing, formed by edema in the dermis (e.g. urticaria)
- **comedone**: a special collection of sebum and keratin
  - open comedo (blackhead)
  - closed comedo (whitehead)
- **petechiae**: pinpoint extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, <3 mm in size
- **purpura**: larger than petechia, 3 mm-1 cm in size
- **ecchymosis**: larger than purpura, >1 cm in size (i.e. a "bruise")
- **telangiectasia**: dilated superficial blood vessels; blanchable, reticulated, and of small calibre, can be associated with benign or malignant entities

Patterns and Distribution

- **acral**: relating to the hands and feet (e.g. perniosis, secondary syphilis)
- **annular**: ring-shaped (e.g. granuloma annulare)
- **follicular**: involving hair follicles (e.g. folliculitis)
- **guttate**: lesions following a "drop-like" pattern (e.g. guttate psoriasis)
- **Koebner phenomenon**: i.e. isomorphic response, appearance of lesions at an injury site (e.g. lichen planus, psoriasis, vitiligo)
- **morbilliform**: literally means "measles-like", an eruption composed of macules and papules with truncal predominance
- **reticular**: lesions following a net-like pattern (e.g. livedo reticularis)
- **satellite**: small lesions scattered around the periphery of a larger lesion (e.g. candida diaper dermatitis)
- **serpiginous**: lesions following a snake-like pattern (e.g. cutaneous larva migrans)
- **target/targetoid**: concentric ring lesions, like a dartboard (e.g. erythema multiforme)
- **other descriptive terms**: discrete, clustered, linear, confluent, dermatitic, indurated (i.e. hard or firm)
### Differential Diagnoses of Common Presentations

**Table 2. Differential Diagnosis of Common Presenting Problems**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Infectious</th>
<th>Inflammatory</th>
<th>Drug/Toxin</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hyper-pigmentation</td>
<td></td>
<td>Neoplasia: lentigo maligna, MM, pigmented BCC</td>
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<td></td>
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<td></td>
<td>Other: melasma/cholema (“mask of pregnancy”)</td>
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<tr>
<td>Discrete Red Popule</td>
<td>Folliculitis</td>
<td>Acne vulgaris, Rosacea, Psoriasis, Urticaria</td>
<td>Bites/stings</td>
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<tr>
<td></td>
<td>Furuncle</td>
<td></td>
<td>Autoimmune: lichen planus; see Papulosquamous Diseases, D16</td>
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<td></td>
<td>Scabies</td>
<td></td>
<td>Vascular: hemangioma, pyogenic granuloma</td>
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<td></td>
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<td></td>
<td>Other: dermatofibroma, milia nula</td>
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<tr>
<td>Red Scales</td>
<td>Psychosis rosea</td>
<td>Dermatitis (atopic, contact, nummular, seborrheic) Discoid lupus Psoriasis Yellow subepidermal papules</td>
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<td></td>
<td>Secondary syphilis</td>
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<td>Gold</td>
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<tr>
<td></td>
<td>Syphilis</td>
<td></td>
<td>Autoimmune: lichen planus; see Papulosquamous Diseases, D16</td>
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<tr>
<td></td>
<td>Tinea</td>
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<td>Neoplastic: mycosis fungoides</td>
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<tr>
<td>Vesicle</td>
<td>Cat scratch disease</td>
<td>Acute contact dermatitis Dyshidrotic eczema</td>
<td>Other: dermatitis herpetiformis, porphyria cutanea tarda</td>
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<tr>
<td>Bulla</td>
<td>Bullous impetigo</td>
<td>Acute dermatitis EM, SLE, SJS/TEN</td>
<td>Fixed drug eruption SJS/TEN</td>
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<td></td>
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<td></td>
<td>Autoimmune: bullous pemphigoid, pemphigus vulgaris</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Other: dermatitis herpetiformis, porphyria cutanea tarda</td>
<td></td>
</tr>
<tr>
<td>Pustule</td>
<td>Candida</td>
<td>Acne vulgaris, Rosacea, Dyshidrotic dermatitis Psoriasis, Pustular folliculitis Pastoral psoriasis</td>
<td>Acute generalized exanthematous pustulosis (usually secondary to drug reaction)</td>
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<td></td>
<td>Dermatophyte</td>
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<td>Impetigo</td>
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<td>Sepsis</td>
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<td>Varicella</td>
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<td>CMV</td>
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<td>Coxsackie</td>
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<td>Cryptococcosis</td>
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<td>HSV/HZV</td>
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<td></td>
<td>HIV, TB</td>
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<tr>
<td>Skin Ulcer</td>
<td>Plague</td>
<td>RA, SLE, vacculitis, UC (pyoderma gangrenosum)</td>
<td>Autoimmune: necrobiosis lipodica diabeticum (e.g. DM) Congenital: XXV Hematologic: sickle cell disease Neoplasia: SCC</td>
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<tr>
<td></td>
<td>Syphilis</td>
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<td>TB</td>
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<td></td>
<td>Tularemia</td>
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</table>

### Common Skin Lesions

#### Cysts

**Table 3. Cysts**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Clinical Course</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal Cyst</td>
<td>Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris May be post-traumatic, rarely syndromic</td>
<td>Most common cutaneous cyst in youth – middle age</td>
<td>Central punctum may rupture (foul, cheesy odour, creamy colour) and produce inflammatory reaction Can increase in size and number over time</td>
<td>No treatment, Elective excision</td>
</tr>
<tr>
<td>Pilar Cyst (Trichilemmal)</td>
<td>Thick-walled cyst lined with stratified squamous epithelium and filled with dense keratin</td>
<td>2nd most common cutaneous cyst F&gt;M</td>
<td>Rupture causes pain and inflammation</td>
<td>No treatment, Elective excision</td>
</tr>
<tr>
<td>Dermoid Cyst</td>
<td>Rare congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick-walled cyst filled with dense keratin</td>
<td>Rare</td>
<td>If nasal midline, risk of extension into CNS</td>
<td>No treatment, Elective excision</td>
</tr>
<tr>
<td>Ganglion Cyst</td>
<td>Cystic lesion that originates from joint or tendon sheath, called a digital mucous cyst when found on fingertip Associated with osteoarthritis</td>
<td>Older age</td>
<td>Stable</td>
<td>No treatment Incision and expression of contents Elective excision</td>
</tr>
<tr>
<td>Milium</td>
<td>Small epidermoid cyst, primarily ar singing from pluripotential cells in epidermal or adnexal epithelium Can be secondary to blistering, ulceration, trauma, topical corticosteroid atrophy, or cosmetic procedures</td>
<td>Any age 40-50% of infants</td>
<td>In newborns, spontaneously resolves in first 4 wk of life</td>
<td>No treatment Incision and expression of contents Electrodessication Topical retinoid therapy</td>
</tr>
</tbody>
</table>
Fibrous Lesions

DERMATOFIGIBROMA

Clinical Presentation
- button-like, firm dermal papule or nodule, skin-coloured to red-brown
- majority are asymptomatic but may be pruritic and/or tender
- site: legs > arms > trunk
- dimple sign (Fitzpatrick’s sign): lateral compression causes dimpling of the lesion

Pathophysiology
- benign tumour due to fibroblast proliferation in the dermis

Etiology
- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibroma can be associated with SLE

Epidemiology
- adults, F>M

Differential Diagnosis
- dermatofibrosarcoma protuberans, malignant melanoma, Kaposi’s sarcoma, blue nevus

Investigations
- biopsy if diagnosis is uncertain

Management
- no treatment required
- excision if bothersome

SKIN TAGS

Clinical Presentation
- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axil, inframammary, and groin

Pathophysiology
- benign outgrowth of skin

Epidemiology
- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

Differential Diagnosis
- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma, fibroepithelioma of Pinkus (rare variant of BCC)

Management
- excision, electrodessication, cryosurgery

Hyperkeratotic Lesions

SEBORRHEIC KERATOSIS

Clinical Presentation
- known as ‘wisdom spots,’ ‘age spots,’ or ‘barnacles of life’
- well-demarcated waxy papule/plaque with classic “stuck on” appearance
- rarely pruritic
- over time lesions appear more warty, greasy and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

Pathophysiology
- very common benign epithelial tumour due to proliferation of keratinocytes and melanocytes

Epidemiology
- unusual <30 yr old
- M>F
- autosomal dominant inheritance
- Leser-Trelat sudden appearance of SK that can be associated with malignancy, commonly gastric adenocarcinomas

Skin Phototypes (Fitzpatrick)

<table>
<thead>
<tr>
<th>Phototype</th>
<th>Colour of Skin</th>
<th>Skin’s Response to Sun Exposure (without SPF protection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>White</td>
<td>Always burns, never tans</td>
</tr>
<tr>
<td>II</td>
<td>White</td>
<td>Always burns, little tan</td>
</tr>
<tr>
<td>III</td>
<td>White</td>
<td>Slight burn, slow tan</td>
</tr>
<tr>
<td>IV</td>
<td>Pale brown</td>
<td>Slight burn, faster tan</td>
</tr>
<tr>
<td>V</td>
<td>Brown</td>
<td>Rarely burns, dark tan</td>
</tr>
<tr>
<td>VI</td>
<td>Dark brown or black</td>
<td>Never burns, dark tan</td>
</tr>
</tbody>
</table>
Differential Diagnosis
- malignant melanoma (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented AK

Investigations
- biopsy only if diagnosis uncertain

Management
- none required, for cosmetic purposes only
- cryotherapy, electrodesiccation, excision

ACTINIC KERATOSIS (SOLAR KERATOSIS)
- see Pre-Malignant Skin Conditions, D33

KERATOACANTHOMA
- see Malignant Skin Tumours, D34

CORNS (HELOMATA)

Clinical Presentation
- firm papule with a central, translucent, cone-shaped, hard keratin core
- painful with direct pressure
- sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

Pathophysiology
- localized hyperkeratosis induced by pressure on hands and feet

Epidemiology
- F>M, can be caused by chronic microtrauma

Differential Diagnosis
- calluses, plantar warts

Management
- relieve pressure with padding or alternate footwear, orthotics
- paring, topical salicylic acid

Keloids

Clinical Presentation
- firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
- extends beyond the margins of the original injury, and may continue to expand in size for years with claw-like extensions
- can be pruritic and painful
- sites: earlobes, shoulders, sternum, scapular area, angle of mandible

Pathophysiology
- excessive deposition of randomly organized collagen fibres following trauma to skin

Epidemiology
- most common in black patients, followed by those of Asian descent (predilection for darker skin)
- M=F, all age groups

Management
- intralesional corticosteroid injections
- silicone compression
Pigmented Lesions

CONGENITAL NEVOMELANOCYTIC NEVI (CNMN)

Clinical Presentation
- sharply demarcated pigmented papule or plaque with regular borders ± coarse hairs
  - classified by size: small (<1.5 cm), medium M1: 1.5-10 cm, M2: >10-20 cm), large (L1: >20-30 cm, L2 >30-40 cm), giant (G1: >40-60 cm, G2: >60 cm)
  - may be surrounded by smaller satellite nevi

Pathophysiology
- nevomelanocytes in epidermis (clusters) and dermis (strands)

Epidemiology
- present at birth or develops in early infancy to childhood
- malignant transformation is rare (1-5%) and more correlated with size of the lesion
- neurocutaneous melanosis can occur in giant CNMN (melanocytes in the central nervous system)

Management
- take a baseline photo and observe lesion for change in shape, colour, or size out of proportion of growth
- surgical excision if suspicious, due to increased risk of melanoma
- MRI if suspicious for neurological involvement

OTHER CONGENITAL PIGMENTED LESIONS

Table 4. Comparison of Other Congenital Pigmented Lesions

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Differential Diagnosis</th>
<th>Clinical Course and Management</th>
</tr>
</thead>
</table>
| Café-au-lait Macule   | Flat light brown lesions with smooth or jagged borders | Areas of increased melanogenesis | 6 or more is suggestive of neurofibromatosis type I Also associated with McCune Albright syndrome | Flat congenital nevomelanocytic nevus, speckled lentiginous nevus
|                       |                 |              |                        | Enlarge in proportion to the child No effective treatment |
| Speckled Lentiginous Nevus (nevus spilus) | Brown pigmented macular background (café-au-lait macule-like) with dark macular or papular speckles | Increased melanocyte concentration | Risk of melanoma similar to that of a CNMN of the same size | Café-au-lait macule, agminated lentigines, Becker’s nevus Usually the light macular background is present at birth and speckles develop over time. Management is similar to that of CNMNs |
| Dermal Melanocytosis (historically known as Mongolian Spot) | Congenital grey-blue solitary or grouped macules commonly on lumbosacral area | Ectopic melanocytes in dermis | 99% occurs in Asian and Indigenous infants | Ecchymosis Usually fades in early childhood but may persist into adulthood |

ACQUIRED NEVOMELANOCYTIC NEVI

Clinical Presentation
- common mole: well circumscribed, round, uniformly pigmented macules/papules <1.5 cm
- average number of moles per person: 18-40
- 3 stages of evolution: junctional NMN, compound NMN, and dermal NMN

Table 5. Evolution of Acquired Nevomelanocytic Nevi

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of Onset</th>
<th>Clinical Presentation</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junctional</td>
<td>Childhood</td>
<td>Flat, regularly bordered, uniformly tan-dark brown, sharply demarcated macule</td>
<td>Melanocytes at dermal-epidermal junction above basement membrane</td>
</tr>
<tr>
<td></td>
<td>Majority progress to compound nevus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Any age</td>
<td>Dorsed, regularly bordered, smooth, round, tan-dark brown papule Face, trunk, extremities, scalp NOT found on palms or soles</td>
<td>Melanocytes at dermal-epidermal junction; migration into dermis</td>
</tr>
<tr>
<td>Dermal</td>
<td>Adults</td>
<td>Soft, dome-shaped, skin-coloured to tan/brown papules or nodules Sites: face, neck</td>
<td>Melanocytes exclusively in dermis</td>
</tr>
</tbody>
</table>

DDx of Hyperpigmented Macules
- Purpura (e.g. solar, ASA, anti-coagulants, steroids, hemosiderin stain)
- Post-inflammatory
- Melasma
- Melanoma
- Fixed drug eruption

Other Nevi
- Halo nevus: often a typical appearing nevus surrounded by a ring of depigmentation; not rare in children; uncommonly associated with vitiligo; no treatment required unless irregular colour or borders
- Blue nevus: round to oval macule/papule with homogenous blue to blue-black colour; often appears in childhood and late adolescence; no treatment required unless atypical features are noted
Management
- new or changing pigmented lesions should be evaluated for typical features which could indicate a melanoma
- excisional biopsy should be considered if the lesion demonstrates asymmetry, varied colours, irregular borders, pruritus or persistent bleeding

OTHER ACQUIRED PIGMENTED LESIONS

Table 6. Comparison of Other Acquired Pigmented Lesions

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Differential Diagnosis</th>
<th>Clinical Course and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical Nevus (Dysplastic Nevus)</td>
<td>Variegated macule/papule with irregular distinct melanocytes in the basal layer Risk factors: family history</td>
<td>Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus Often with region of adjacent nests</td>
<td>&gt;5 atypical nevi increases risk for melanoma Numerous dysplastic nevi may be part of familial atypical mole and melanoma syndrome</td>
<td>Follow with baseline photographs for changes Excisional biopsy if lesion changing or highly atypical</td>
</tr>
<tr>
<td>Ephelides (Freckles)</td>
<td>Small (&lt;5 mm) well-demarcated light brown macules Sites: sun-exposed skin</td>
<td>Increased melanin within basal layer keratinocytes secondary to sun exposure</td>
<td>Skin phototypes I-II most commonly</td>
<td>Junctional nevi Juvenile lentigines Multiply and darken with sun exposure, fade in winter No treatment required Skin and sun avoidance may prevent the appearance of new freckles</td>
</tr>
<tr>
<td>Solar Lentigo (Liver Spot)</td>
<td>Well-demarcated brown/black macules Sites: sun-exposed skin</td>
<td>Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure</td>
<td>Most common in Caucasians &gt;40 yr Skin phototypes I-III most commonly</td>
<td>Lentigo maligna, seborrheic keratosis, pigmented actinic keratosis Laser therapy, shave excisions, cryotherapy</td>
</tr>
<tr>
<td>Becker’s Nevus</td>
<td>Hairy, light brown macule/patch with a papular verrucous surface Sites: trunk and shoulders onset in teen years</td>
<td>Pigmented hamartoma with increased melanin in basal cells</td>
<td>M:F</td>
<td>Hairy congenital melanocytic nevus Hair growth follows onset of pigmentation Cosmetic management (usually too large to remove)</td>
</tr>
<tr>
<td>Melasma</td>
<td>Dark, usually symmetrical, skin discoloration on sun-exposed areas of face (forehead, upper lip, cheeks, chin)</td>
<td>Increase in number and activity of melanocytes Associated with estrogen and progesterone</td>
<td>F&gt;M Common in pregnancy and women taking OCP or HRT Risk factors: sun exposure, dark skin tone Can occur with mild endocrine disturbances, antiepileptic medications and other photosensitizing drugs</td>
<td>Post-inflammatory hyperpigmentation Often fades over several months after stopping hormone treatment or delivering baby Treatment: hydroquinone, azelaic acid, retinoic acid, topical steroid, combination creams, destructive modalities (chemical peels, laser treatment), camouflage make-up, sunscreen, sun avoidance</td>
</tr>
</tbody>
</table>

Vascular Lesions

Table 7. Vascular Tumours Compared to Vascular Malformations

<table>
<thead>
<tr>
<th>Vascular Tumours</th>
<th>Vascular Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Endothelial hyperplasia Congenital malformation with normal endothelial turnover</td>
</tr>
<tr>
<td>Presence at Birth</td>
<td>Usually postnatal 100% at birth (not always obvious)</td>
</tr>
<tr>
<td>M:F</td>
<td>1:3-5 1:1</td>
</tr>
<tr>
<td>Natural History</td>
<td>Phases Proliferating Involuting Involuted Proportionate growth (can expand)</td>
</tr>
</tbody>
</table>

HEMANGIOMAS

Clinical Presentation
- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a “bag of worms” when palpated

Pathophysiology
- benign vascular tumour
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

A spider angioma will blanch when the tip of a paperclip is applied to the centre of the lesion
Table 8. Vascular Tumours

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Clinical Course</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma of Infancy</td>
<td>Hot, firm red to blue plaques or tumours</td>
<td>Benign vascular proliferation of endothelial lining</td>
<td>Appears shortly after birth; rarely may be congenital</td>
<td>Appears shortly after birth, increases in size over months, then regresses. 50% of lesions resolve spontaneously by 5 yr. 10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis. Consider treatment if not gone by school age; topical timolol, propranolol; systemic corticosteroids; laser treatment; surgery.</td>
</tr>
<tr>
<td>Spider Angioma (Campbell Telangiectasia)</td>
<td>Central red arteriole with slender branches, blanchable</td>
<td>Can be associated with hyperestrogenic state (e.g. in hepatocellular disease, pregnancy, OCP) but often is not</td>
<td>Any age</td>
<td>Increase in number over time. Reassurance. Electrodesiccation or laser surgery if patient wishes.</td>
</tr>
<tr>
<td>Cherry Angioma (Campbell De Morgan Spot)</td>
<td>Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm</td>
<td>Benign vascular neoplasm</td>
<td>&gt;30 yr old</td>
<td>Lesions do not fade in time. Lesions bleed infrequently. Usually no treatment needed. Laser or electocautery for small lesions. Excision of large lesions if necessary.</td>
</tr>
<tr>
<td>Pyogenic Granuloma</td>
<td>Bright red, dome-shaped sessile or pedunculated friable nodule Sites: fingers, lips, mouth, trunk, toes</td>
<td>Rapidly developing hemangioma Proliferation of capillaries with erosion of epidermis and neutrophilia</td>
<td>&lt;30 yr old</td>
<td>Lesion grows rapidly over weeks to months, then stabilizes. Lesion may persist indefinitely if untreated. Surgical excision with histologic examination. Electrocautery; laser; cryotherapy.</td>
</tr>
</tbody>
</table>

VASCULAR MALFORMATIONS

Table 9. Vascular Malformations

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevus Flammeus (Port-wine stain)</td>
<td>Red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline. Most common site: nape of neck. Never spontaneously regress but grows in proportion to the child.</td>
<td>Congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution).</td>
<td>Laser or make-up.</td>
</tr>
<tr>
<td>Nevus Simplex (salmon patch)</td>
<td>Pink-red irregular patches Midline macule on glabella known as “Angel Kiss”; on nuchal region known as “Stork Bites”. Present in 1/3 of newborns. Majority regress spontaneously.</td>
<td>Congenital dilation of dermal capillaries.</td>
<td>No treatment required.</td>
</tr>
</tbody>
</table>

Lipoma

Clinical Presentation
- single or multiple non-tender subcutaneous tumours that are soft and mobile
- occurs most frequently on the trunk, and extremities but can be anywhere on the body

Pathophysiology
- adipocytes enclosed in a fibrous capsule

Epidemiology
- often solitary or few in number, if multiple can be associated with rare syndromes

Differential Diagnosis
- angiolipoma, liposarcoma

Investigations
- biopsy only if atypical features (painful, rapid growth, firm)

Management
- reassurance
- excision or liposuction only if desired for cosmetic purposes
Acneiform Eruptions

Acne Vulgaris/Common Acne

Clinical Presentation
A common inflammatory pilosebaceous disease categorized with respect to severity
- Type I: comedonal, sparse, no scarring
- Type II: comedonal, papular, moderate ± little scarring
- Type III: comedonal, papular, and pustular, with scarring
- Type IV: nodulocystic acne, risk of severe scarring
- Sites of predilection: face, neck, upper chest, and back

Pathophysiology
- Hyperkeratinization at the follicular ostia (opening) blocks the secretion of sebum leading to the formation of microcomedones
- Androgens promote excess sebum production
- Propionibacterium acnes metabolize sebum to free fatty acids and produces pro-inflammatory mediators

Epidemiology
- Age of onset in puberty (10-17 yr in females, 14-19 yr in males)
- In prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital adrenal hyperplasia)
- Incidence decreases in adulthood
- Genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

Differential Diagnosis
- Folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

Table 10. Management of Acne

<table>
<thead>
<tr>
<th>Compound/Drug Class</th>
<th>Product Names</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MILD ACNE: Topical Therapies OTC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoyl peroxide (BPO)</td>
<td>Solugel, Benzac, Desquam, Fostex</td>
<td>Helps prevent P. acnes resistance, is a bactericidal agent (targets P. acnes) and is comedolytic</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Akurza® Cream, DermaZone</td>
<td>Used when patients cannot tolerate a topical retinoid due to skin irritation</td>
</tr>
<tr>
<td><strong>MILD ACNE: Prescription Topical Therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrobials</strong></td>
<td>Clindamycin (Dalacin T), Erythromycin</td>
<td>High rate of resistance when used as monotherapy</td>
</tr>
<tr>
<td><strong>Retinoids</strong></td>
<td>Vitamin A Acid (Tretinoin, Stieva-A, Retin A) Adapalene (Differin)</td>
<td>Backbone of topical acne therapy All regimens should include a retinoid unless patient cannot tolerate</td>
</tr>
<tr>
<td><strong>Combination products</strong></td>
<td>Clindoxyloxy (Clindamycin and BPO) Benzaclin (Clindamycin and BPO) Tactuo (Adapalene and BPO) Biacna (Clindamycin and Tretinoin) Benzamycin (BPO and Erythromycin)</td>
<td>Allows for greater adherence and efficacy Combines different mechanisms of action to increase efficacy and maximize tolerability</td>
</tr>
<tr>
<td><strong>MODERATE ACNE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline/Minocycline/Doxycycline</td>
<td>Sumycin/Minocin/Vibramycin</td>
<td>Use caution with regard to drug interactions: do not use with isotretinoin Sun sensitivity Antibiotics require 3 mo of use before assessing efficacy</td>
</tr>
<tr>
<td>Cyproterone acetate-ethinyl estradiol</td>
<td>Diane-35®</td>
<td>After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances are fully weighing the risk/benefit ratio with physician guidance</td>
</tr>
<tr>
<td>Spironolactone (source ADA)</td>
<td>Aldactone</td>
<td>May cause hyperkalemia at higher doses Black box warning for breast cancer</td>
</tr>
<tr>
<td><strong>SEVERE ACNE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Accutane®, Clarus®, Epinus®</td>
<td>See Table 27 for full side effect profile Most adverse effects are temporary and will resolve when the drug is discontinued Baseline lipid profile (risk of hypertriglyceridemia), LFTs and β-hCG before treatment May transiently exacerbate acne before patient sees improvement Refractory cases may require multiple courses of isotretinoin</td>
</tr>
</tbody>
</table>

Acne Exacerbating Factors
- Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danaol
- Topical agents: steroids, tars, ointments, oily cosmetics
- Mechanical pressure or occlusion, such as leaning face on hands
- Emotional stress

Acne Myths Debunked
- Eating greasy food and chocolate does not cause or worsen acne
- Blackheads (comedones) are black because of oxidized fatty acids, not dirt
- Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator

Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo)

A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone

Intralesional injections
Intralesional corticosteroids injections are effective in the treatment of individual acne nodules

Isotretinoin and Pregnancy
- Use of Isotretinoin during pregnancy is associated with spontaneous abortion and major birth defects such as facial dysmorphism and cognitive impairment
- Pregnancy should be ruled out before starting isotretinoin
- Patients should use 2 forms of contraception while on isotretinoin

Treatment of Acne Scars
- Tretinoin creams
- Vincoc acid
- Chemical peels for superficial scars
- Injectable fillers (collagen, hyaluronic acid) for pitted scars
- Fraxel laser
- CO₂ laser resurfacing
Perioral Dermatitis

**Clinical Presentation**
- discrete erythematous micropapules that often become confluent, forming inflammatory plaques on perioral, perinasal, and periorbital skin
- commonly symmetrical, rim of sparing around vermillion border of lips

**Epidemiology**
- 15-40 yr old, occasionally in younger children
- predominantly females

**Differential Diagnosis**
- contact dermatitis, rosacea, acne vulgaris

**Management**
- avoid all topical steroids
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid
- systemic: tetracycline family antibiotic (utilized for its anti-inflammatory properties)
- occasional use of a non-steroidal anti-inflammatory cream (i.e. tacrolimus or pimecrolimus)

Rosacea

**Clinical Presentation**
- dome-shaped inflammatory papules ± pustules
- flushing, non-transient erythema, and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks, and chin; rarely on scalp, neck, and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, caffeine, spices
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration and lymphedema in the skin can develop
- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: blepharoconjunctivitis, keratitis, iritis

**Pathophysiology**
- unknown

**Epidemiology**
- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 yr old; F>M

**Differential Diagnosis**
- acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis

**Management**
- trigger avoidance and daily sunscreen use for long-term management
- avoid topical corticosteroids
- telangiectasia: treated by physical ablation; electrical hyfrecators, vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; parring, electrosurgery, cryotherapy, laser therapy (CO₂, argon, Nd:YAG)

**Guidelines for the Diagnosis of Rosacea**

- Presence of one or more of the following primary features:
  - Flushing (transient erythema)
  - Nontransient erythema
  - Papules and pustules
  - Telangiectasia
- May include one or more of the following secondary features:
  - Burning or stinging
  - Dry appearance
  - Edema
  - Phymatous changes
  - Ocular manifestations
  - Peripheral location

**Table 11. Specific Rosacea Treatments**

<table>
<thead>
<tr>
<th>1st Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tetracyclines</td>
<td>Topical clindamycin</td>
<td>Oral retinoids</td>
</tr>
<tr>
<td>Topical metronidazole</td>
<td>Topical erythromycin 2% solution</td>
<td></td>
</tr>
<tr>
<td>Oral erythromycin (250-500 mg PO bid)</td>
<td>Topical benzoyl peroxide</td>
<td></td>
</tr>
<tr>
<td>Topical azelaic acid</td>
<td>Oral metronidazole</td>
<td></td>
</tr>
<tr>
<td>Topical Ivermectin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dermatitis (Eczema)

**Definition**
- inflammation of the skin

**Clinical Presentation**
- poorly demarcated erythematous patches or plaques
- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting, excoriations
- chronic dermatitis: lichenification, xerosis, fissuring

**Asteatotic Dermatitis**

**Clinical Presentation**
- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (i.e. "winter itch") but starts in the fall
- shins predominate, looks like a "dried river bed"

**Management**
- skin rehydration with moisturizing routine ± corticosteroid creams

**Atopic Dermatitis**

**Clinical Presentation**
- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution depends on age
- inflammation, lichenification excoriations are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with: keratosis pilaris (hyperkeratosis of hair follicles, "chicken skin"), xerosis, occupational hand dryness

**Epidemiology**
- frequently affects infants, children, and young adults
- 10-20% of children in developed countries under the age of 5 are affected
- associated with personal or family history of atopy (asthma, hay fever), anaphylaxis, eosinophilia
- polygenic inheritance: one parent >60% chance for child; two parents >80% chance for child
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

**Pathophysiology**
- a T-cell driven inflammatory process with epidermal barrier dysfunction

**Investigations**
- clinical diagnosis
- consider: skin biopsy, patch testing if allergic contact dermatitis is suspected

**Management**
- goal: reduce signs and symptoms, prevent or reduce recurrences/flares
- better outcome (e.g. less flare-ups, modified course of disease) if diagnosis made early
- avoid triggers of AD
- non-pharmacologic therapy
  - moisturizers
    - apply liberally and reapply at least twice a day with goal of minimizing xerosis
    - include in treatment of mild to severe disease as well as in maintenance therapy
  - bathing practices
    - bathe in plain warm water for a short period of time once daily followed by lightly but not completely drying the skin with a towel; immediately apply topical agents or moisturizers after this
  - use fragrance-free hypoallergenic non-soap cleansers
- pharmacologic therapy
  - topical corticosteroids
    - effective in reducing acute and chronic symptoms as well as prevention of flares
    - choice of steroid potency depends on age, body site, short vs. long-term use
    - apply 1 adult fingertip unit (0.5 g) to an area the size of 2 adult palms bid for acute flares
    - local side effects: skin atrophy, purpura, telangiectasia, striae, hypertrichosis, and acneiform eruption are all very rarely seen

**Triggers for Atopic Dermatitis**
- Irritants (detergents, solvents, clothing, water hardness)
- Contact allergens
- Environmental aeroallergens (e.g. dust mites)
- Inappropriate bathing habits (e.g. long hot showers)
- Sweating
- Microbes (e.g. S. aureus)
- Stress

Figure 4. Atopic dermatitis distribution
The typical distribution of atopic dermatitis in infants <6 mo (top), children >18 mo (middle) and adults (bottom)
- topical calcineurin inhibitors
  - tacrolimus 0.03%, 0.1% (Protopic®) and pimecrolimus 1% (Elidel®)
  - use as steroid-sparing agents in the long-term
  - advantages over long-term corticosteroid use: sustained effect in controlling pruritus; no skin atrophy; safe for the face and neck
  - apply 2x/d for acute flares, and 2-3x/wk to recurrent sites to prevent relapses
  - local side effects: stinging, burning, allergic contact dermatitis
  - U.S. black box warning of malignancy risk: rare cases of skin cancer and lymphoma reported; no causal relationship established

Complications
- infections
  - treatment of infections
    - topical mupirocin or fusidic acid (Canada only, not available in US)
    - oral antibiotics (e.g. cloxacillin, cephalaxin) for widespread S. aureus infections

Contact Dermatitis
- cutaneous inflammation caused by an external agent(s)

Table 12. Contact Dermatitis

<table>
<thead>
<tr>
<th>Mechanism of Reaction</th>
<th>Toxic injury to skin; non-immune mechanism</th>
<th>Cell-mediated delayed (Type IV) hypersensitivity reaction (see Rheumatology, RH2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Reaction</td>
<td>Erythema, dryness, fine scale, burning</td>
<td>Erythema with a papulovesicular eruption, swelling, pruritus</td>
</tr>
<tr>
<td></td>
<td>Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Majority; will occur in anyone given sufficient concentration of irritants</td>
<td>Minority; patient acquires susceptibility to allergen that persists indefinitely</td>
</tr>
<tr>
<td>Distribution</td>
<td>Hands are the most common site</td>
<td>Areas exposed to allergen</td>
</tr>
<tr>
<td>Examples</td>
<td>Soaps, weak alkali, detergents, organic solvents, alcohol, oil</td>
<td>Many allergens are irritants, so may coincide with irritant dermatitis</td>
</tr>
<tr>
<td>Management</td>
<td>Avoidance of irritants</td>
<td>Patch testing to determine specific allergen</td>
</tr>
<tr>
<td></td>
<td>Wet compresses with Burrow’s solution</td>
<td>Avoid allergen and its cross-reactants</td>
</tr>
<tr>
<td></td>
<td>Barrier moisturizers</td>
<td>Wet compresses soaked in Burrow’s solution (drying agent)</td>
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<tr>
<td></td>
<td>Topical/oral steroids</td>
<td>Topical Steroids BID prn</td>
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<tr>
<td></td>
<td></td>
<td>Systemic steroids prn if extensive</td>
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</tbody>
</table>
**Dyshidrotic Dermatitis**

**Clinical Presentation**
- "tapioca pudding" papulovesicular dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infections common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

**Pathophysiology**
- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate flares

**Management**
- topical: high potency corticosteroid with plastic cling wrap occlusion to increase penetration
- intralesional triamcinolone injection
- systemic
  - prednisone in severe cases
  - antibiotics for secondary S. aureus infection

**Nummular Dermatitis**

**Clinical Presentation**
- nummular (coin-shaped), pruritic, dry, scaly, erythematous plaques
- often associated with atopic and dyshidrotic dermatitis
- secondary infection common

**Pathophysiology**
- little is known, but it is often accompanied by xerosis, which results from a dysfunction of the epidermal lipid barrier; this in turn can allow permeation of environmental agents, which can induce an allergic or irritant response

**Management**
- moisturization
- mid to high potency corticosteroid ointment bid

**Seborrheic Dermatitis**

**Clinical Presentation**
- greasy, erythematous, yellow, scaling, minimally elevated papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: "cradle cap"
- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus and underlying erythema
- sites: scalp, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

**Pathophysiology**
- possible etiologic association with Malassezia spp. (yeast)

**Epidemiology**
- common in infants and adolescents
- increased incidence and severity in immunocompromised patients
- in adults, can cause dandruff ( pityriasis sicca)

**Management**
- face: ketoconazole (Nizoral®) cream daily or bid + mild steroid cream daily or bid
- scalp: salicylic acid in olive oil or Derma-Smoother FS® lotion (peanut oil, mineral oil, fluocinolone acetonide 0.01%) to remove dense scales, 2% ketoconazole shampoo (Nizoral®), ciclopirox (Stiepro®) shampoo, selenium sulfide (e.g. Selsun®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)
Stasis Dermatitis

Clinical Presentation
- erythematous, scaly, pruritic plaques in lower legs, particularly the medial ankle
- brown hemosiderin deposition, woody fibrosis, atrophy blanche, and lipodermatosclerosis in late stages
  usually bilateral, accompanied by swelling, oozing, crusting, may have accompanying varicosities

Pathophysiology
- chronic venous insufficiency leads to venous stasis
- surrounding soft tissue inflammation and fibrosis results

Investigations
- Doppler and colour-coded Duplex sonography if suspicious for DVT
- swab for bacterial culture if there is crusting

Management
- compression stockings
- rest and elevate legs (above the level of the heart)
- moisturizer to treat xerosis
- mid-high potency topical corticosteroids to control inflammation

Complications
- ulceration (common at medial malleolus), secondary bacterial infections

Lichen Simplex Chronicus

Clinical Presentation
- well-defined plaque(s) of lichenified skin with increased skin markings ± excoriations
- common sites: neck, scalp, lower extremities, urogenital area
- often seen in patients with atopy

Pathophysiology
- skin hyperexcitable to itch, continued rubbing/scratching of skin results
- eventually lichenification occurs

Investigations
- if patient has generalized pruritus, rule out systemic cause: CBC with differential count, transaminases, bilirubin, renal and thyroid function tests, TSH, glucose, SPEP
- CXR if lymphoma suspected

Management
- antipruritics (e.g. antihistamines, topical or intralesional glucocorticoids, Unna boot)

Papulosquamous Diseases

Lichen Planus

Clinical Presentation
- acute or chronic inflammation of mucous membranes or skin, especially on flexural surfaces
- morphology: pruritic, well-demarcated, violaceous, polygonal, flat-topped papules
- common sites: wrists, ankles, mucous membranes in 60% (mouth, vulva, glans), nails, scalp
- distribution: symmetrical and bilateral
- Wickham's striae: reticulate white-grey lines over surface; pathognomonic but may not be present
- mucous membrane lesions: lacy, whitish reticular network, milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging; dystrophic; pterygium formation
- scalp: scarring alopecia with perifollicular hyperkeratosis
- spontaneously resolves but may last for weeks, months or years (mouth and skin lesions)
- rarely associated with hepatitis C
- Köbner phenomenon

Pathophysiology
- autoimmune, antigen unknown
- lymphocyte activation leads to keratinocyte apoptosis

Epidemiology
- 1%
- 30-60 yr old, F>M
Investigations
- consider a skin biopsy
- hepatitis C serology if patient has risk factors

Management
- topical or intralesional corticosteroids
- short courses of oral prednisone (rarely)
- phototherapy or oral retinoids or systemic immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine) for extensive or recalcitrant cases

Pityriasis Rosea

Clinical Presentation
- acute, self-limiting eruption characterized by red, oval plaques/patches with central scale that does not extend to edge of lesion
- long axis of lesions follows skin tension lines (i.e. Langer's Lines) parallel to ribs producing "Christmas tree" pattern on back
- varied degree of pruritus
- most start with a “herald” patch which precedes other lesions by 1-2 wk
- common sites: trunk, proximal aspects of arms and legs

Etiology
- suspected HHV-7 or HHV-6 reactivation

Investigations
- none required

Management
- none required; clears spontaneously in 6-12 wk
- symptomatic: topical glucocorticoids if pruritic, cool compresses, emollients

Psoriasis

Classification
1. plaque psoriasis
2. guttate psoriasis
3. erythrodermic psoriasis
4. pustular psoriasis
5. inverse psoriasis

Pathophysiology
- not fully understood, genetic and immunologic factors
- shortened keratinocyte cell cycle leads to Th1 and Th17-mediated inflammatory response

Epidemiology
- 1.5-2%, M=F
- all ages: peaks of onset: 20-30 and 50-60
- polygenic inheritance: 8% with 1 affected parent, 41% with both parents affected
- risk factors: smoking, obesity, alcohol, drugs, infections

Differential Diagnosis
- AD, mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea, nummular dermatitis, lichen planus

Investigations
- biopsy (if atypical presentation, rarely needed)

1. PLAQUE PSORIASIS

Clinical Presentation
- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- often worse in winter (lack of sun and humidity)
- Auspitz sign: bleeds from minute points when scale is removed
- common sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

Topical Treatments for Chronic Plaque Psoriasis
Cochrane Database Syst Rev 2013;(1):CD005028
Purpose: To compare the effectiveness, tolerability and safety of topical treatments for chronic plaque psoriasis, and to compare vitamin D analogues with other topical treatments.
Methods: Systematic review of RCTs comparing active topical treatments against placebo or against vitamin D analogues (used alone or in combination) in people with chronic plaque psoriasis. Primary outcome was investigator assessed of overall global improvement, total severity scores, psoriasis area and severity index, and patient assessment of overall global improvement.
Results: 48 trials were included in total, with 26 trials focused on scalp psoriasis and 2 trials on sites of psoriasis, facial psoriasis or both. Most vitamin D analogues were significantly more effective than placebo for topical use on the body. Most corticosteroids were significantly more effective than placebo, with potent corticosteroids having similar benefits to very potent corticosteroids. Topical treatments with vitamin D analogues and corticosteroids performed at least as well as vitamin D analogues, and they are associated with a lower incidence of local adverse events. Combined treatment with vitamin D and corticosteroids, and tacrolimus performed significantly better than placebo. Combined treatment with vitamin D and corticosteroids performed significantly better than vitamin D alone or corticosteroids alone for body and scalp psoriasis. Vitamin D generally performed better than placebo, but findings compared to dithranol were mixed. Vitamin D was significantly less effective than both potent and very potent corticosteroids for scalp psoriasis. Potent corticosteroids were less likely than vitamin D to cause local adverse events (i.e., burning, irritation). Combined treatment with vitamin D and corticosteroids was tolerant as well as potent corticosteroids, and significantly better than vitamin D alone for body and scalp use.
Conclusion: Corticosteroids perform at least equally if not superior to vitamin D analogues and are associated with fewer local adverse events. The risk of skin dermal atrophy with long-term use of corticosteroids for people with chronic plaque psoriasis remains unclear.
Management
- Principles of management depend on severity of disease, as defined by BSA affected or less commonly Psoriasis Area and Severity Index (PASI)
- Mild (<3% BSA)
  - Topical steroids, topical vitamin D3 analogues, or a combination of the two are first line
  - Topical retinoid ± topical steroid combination, anthralin, and tar are also effective but tend to be less tolerated than first line therapies
  - Emollients
  - Phototherapy or systemic treatment may be necessary if the lesions are scattered or if it involves sites that are difficult to treat such as palms, soles, scalp, genitals
- Moderate (3-10% BSA) to severe (>10% BSA)
  - Goal of treatment is to attain symptom control that is adequate from patient’s perspective
  - Phototherapy if accessible
  - Systemic or biological therapy based on patient’s treatment history and comorbidities
  - Topical steroid ± topical vitamin D3 analogue as adjunct therapy

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<thead>
<tr>
<th>Table 13. Topical Treatment of Psoriasis</th>
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<tbody>
<tr>
<td>Treatment</td>
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<tr>
<td>Emollients</td>
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<tr>
<td>Salicyclic acid 1-12%</td>
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<tr>
<td>Tar (LCD: liquor carbonis detergens)</td>
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<tr>
<td>Topical Corticosteroids</td>
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<tr>
<td>Vitamin D3 analogues: Calcipotriene / calcipotrol (Dovonex®, Siliks®)</td>
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<tr>
<td>1,25-dihydroxyvitamin D3 to inhibit keratinocyte proliferation</td>
</tr>
<tr>
<td>Betamethasone + calcipotriene (Dovobet®)</td>
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<tr>
<td>Tazarotene (Tazorac®) (gel/cream)</td>
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<tr>
<th>Table 14. Systemic Treatment of Psoriasis</th>
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<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Acitretin</td>
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<tr>
<td>Cyclosorin</td>
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<tr>
<td>Methotrexate</td>
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<tr>
<td>Apremilast (Otezla®)</td>
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<td>PUVA</td>
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<td>UVB and “Narrow band” UVB (311-312 nm)</td>
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<tr>
<th>Table 15. Biologics Approved in Canada</th>
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<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Etanercept (Enbrel®)*</td>
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<tr>
<td>Adalimumab (Humira®)*</td>
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<tr>
<td>Infliximab (Remicade®)*</td>
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<tr>
<td>Ustekinumab (Stelara®)</td>
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<tr>
<td>Secukinumab (Cosentyx®)</td>
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<tr>
<td>Ixekizumab (Taltz®)</td>
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</tbody>
</table>

*Can also be used to treat psoriatic arthritis

- Biologics under study for treatment of psoriasis: brodalumab, risankizumab, tildrakizumab, guselkumab
2. GUTTATE PSORIASIS (“DROP-LIKE”)

Clinical Presentation
- discrete, scattered salmon-pink small scaling papules
- sites: diffuse, usually on trunk and legs, sparing palms and soles
- often antecedent streptococcal pharyngitis

Management
- UVB phototherapy, sunlight, lubricants, topical steroids
- penicillin V or erythromycin if Group A β hemolytic Streptococcus on throat culture

3. ERYTHRODERMIC PSORIASIS

Clinical Presentation
- generalized erythema (> 90% of body surface area) with fine desquamative scale on surface
- associated signs and symptoms: arthralgia, pruritus, dehydration, electrolyte imbalance
- aggravating factors: lithium, β-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

Management
- IV fluids, monitor fluids and electrolytes, may require hospitalization
- treat underlying aggravating condition, sun avoidance
- cyclosporine, acitretin, methotrexate, UV, biologics

4. PUSTULAR PSORIASIS

Clinical Presentation
- sudden onset of erythematous macules and papules which evolve rapidly into pustules, can be painful
- may be generalized or localized
- patient usually has a history of psoriasis; may occur with sudden withdrawal from steroid therapy

Management
- methotrexate, cyclosporine, acitretin, UV, biologics

5. INVERSE PSORIASIS

Clinical Presentation
- erythematous plaques on flexural surfaces such as axillae, inframammary folds, gluteal fold, inguinal folds
- lesions may be macerated

Management
- low potency topical corticosteroids
- topical vitamin D derivatives such as calcipotriene or calcitriol
- topical calcineurin inhibitors such as tacrolimus or pimecrolimus

6. PSORIATIC ARTHRITIS

- 20-30% of patients with psoriasis can also be suffering from psoriatic arthritis
- psoriatic patients with nail or scalp involvement are at a higher risk for developing psoriatic arthritis
- see Rheumatology, RH23

Vesiculobullous Diseases

Bullous Pemphigoid

Clinical Presentation
- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- can present as urticarial plaques without bullae
- common sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth in 33%

Pathophysiology
- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leads to subepidermal bullae

Epidemiology
- mean age of onset: 60-80 yr old, F=M
**Investigations**
- Immunofluorescence shows linear deposition of IgG and C3 along the basement membrane
- Anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

**Prognosis**
- Heals without scarring, usually chronic
- Rarely fatal

**Management**
- Prednisone 0.5-1 mg/kg/day until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclosporine, mycophenolate mofetil)
- Topical potent steroids (clobetasol) may be as effective as systemic steroids in limited disease
- Tetracycline ± nicotinamide is effective for some cases
- Immunosuppressants such as azathioprine, mycophenolate mofetil, cyclosporine
- IVlg and plasmapheresis for refractory cases

---

**Pemphigus Vulgaris**

**Clinical Presentation**
- Autoimmune blistering disease characterized by flaccid, non-pruritic intraepidermal bullae/vesicles on an erythematous or normal skin base
- May present with erosions and secondary bacterial infection
- Sites: mouth (90%), scalp, face, chest, axilla, groin, umbilicus
- Nikolsky's sign: epidermal detachment with shear stress
- Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

**Pathophysiology**
- IgG against epidermal desmoglein-1 and -3 lead to loss of intercellular adhesion in the epidermis

**Epidemiology**
- 40-60 yr old, M=F, higher prevalence in Jewish, Mediterranean, Asian populations
- Paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine

**Investigations**
- Immunofluorescence: shows IgG and C3 deposition intraepidermally
- Circulating serum anti-desmoglein IgG antibodies

**Prognosis**
- Lesions heal with hyperpigmentation but do not scar
- May be fatal unless treated with immunosuppressive agents

**Management**
- Prednisone 1-2 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclophosphamide, cyclosporine, IVlg, mycophenolate mofetil, rituximab)

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**Dermatitis Herpetiformis**

**Clinical Presentation**
- Grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging, excoriations
- Lesions grouped, bilaterally symmetrical
- Common sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

**Pathophysiology**
- Transglutaminase IgA deposits in the skin alone or in immune complexes leading to eosinophil and neutrophil infiltration
- 90% have HLA B8, DR3, DQWZ
- 90-100% associated with an often subclinical gluten-sensitive enteropathy (i.e. celiac disease)
- 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

**Epidemiology**
- 20-60 yr old, M:F = 2:1

**Investigations**
- Biopsy
- Immunofluorescence shows IgA deposits in perilesional skin

**Management**
- Dapsone (sulfapyridine if contraindicated or poorly tolerated)
- Gluten free diet for life – this can reduce risk of lymphoma
Porphyria Cutanea Tarda

**Clinical Presentation**
- skin fragility followed by formation of tense vesicles/bullae and erosions on photoexposed skin
- gradual healing to scars, milia
- periorbital violaceous discoloration, diffuse hypermelanosis, facial hypertrichosis
- common sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

**Pathophysiology**
- uroporphyrinogen decarboxylase deficiency leads to excess heme precursors
- can be associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

**Epidemiology**
- 30-40 yr old, M>F

**Investigations**
- urine + 5% HCl shows orange-red fluorescence under Woods lamp (UV rays)
- 24 h urine for uroporphyrins (elevated)
- stool contains elevated coproporphyrins
- immunofluorescence shows IgE at dermal-epidermal junctions

**Management**
- discontinue aggravating substances (alcohol, estrogen therapy)
- phlebotomy to decrease body iron load
- low dose hydroxychloroquine

Drug Eruptions

**Exanthematous**

**EXANTHEMATIC DRUG REACTION**

**Clinical Presentation**
- morphology: erythematous macules and papules ± scale
- spread: symmetrical, trunk to extremities
- time course: 7-14 d after drug initiation, fades 7-14 d after withdrawal

**Epidemiology**
- most common cutaneous drug reaction; increased in presence of infections
- common causative agents: penicillin, sulfonamides, phenytoin

**Management**
- weigh risks and benefits of drug discontinuation
- antihistamines, emollients, topical steroids

**DRUG INDUCED HYPERSENSITIVITY SYNDROME (DIHS) / DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)**

**Clinical Presentation**
- morphology: morbilliform rash involving face, trunk, arms; can have facial edema
- systemic features: fever, malaise, cervical lymphadenopathy, internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonia, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- spread: starts with face or periorbitally and spreads caudally; no mucosal involvement
- time course: onset 1-6 weeks after first exposure to drug; persists weeks after withdrawal of drug

**Epidemiology**
- rare: incidence varies considerably depending on drug
- common causative agents: anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, lamotrigine), sulfonamides, and allopurinol
- 10% mortality if severe, undiagnosed, and untreated

**Management**
- discontinue offending drug ± prednisone 0.5mg/kg per day, consider cyclosporine in severe cases
- may progress to generalized exfoliative dermatitis/erythroderma if drug is not discontinued
Urticarial

DRUG INDUCED URTICARIA AND ANGIOEDEMA

Clinical Presentation
- morphology: wheals lasting >24 h unlike non drug induced urticaria, angioedema (face and mucous membranes)
  - systemic features: may be associated with systemic anaphylaxis (bronchospasm, laryngeal edema, shock)
  - time course: hours to days after exposure depending on the mechanism

Epidemiology
- second most common cutaneous drug reaction
- common causative agents: penicillins, ACEI, analgesics/anti-inflammatories radiographic contrast media

Management
- discontinue offending drug, treatment with antihistamines, steroids, epinephrine if anaphylactic

SERUM SICKNESS-LIKE REACTION

Clinical Presentation
- morphology: symmetrical cutaneous eruption (usually urticarial)
- systemic features: malaise, low grade fever, arthralgia, lymphadenopathy
- time course: appears 1-3 wk after drug initiation, resolve 2-3 wk after withdrawal

Epidemiology
- more prevalent in kids 0.02-0.2%
- common causative agents: cefaclor in kids; bupropion in adults

Management
- discontinue offending drug ± topical/oral corticosteroids

Pustular

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)

Clinical Presentation
- morphology: erythematous edema and sterile pustules prominent in intertriginous areas
- systemic features: high fever, leukocytosis with neutrophilia
- spread: starts in face and intertriginous areas and spread to trunk and extremities
- time course: appears 1 wk after drug initiation, resolve 2 wk after withdrawal

Epidemiology
- rare: 1-5/million
- common causative agents: aminopenicillins, cephalosporins, clindamycin, calcium channel blockers

Management
- discontinue offending drug and systemic corticosteroids

Bullous

STEVEN JOHNSON SYNDROME (SJS)/TOXIC EPIDERMAL NECROLYSIS (TEN)

Clinical Presentation
- morphology: prodromal rash (morbilliform/targetoid lesions ± purpura, or diffuse erythema), confluence of flaccid blisters, positive Nikolsky sign (epidermal detachment with shear stress), full thickness epidermal loss; dusky tender skin, bullae, desquamation/skin sloughing, atypical targets
- classification: BSA with epidermal detachment: <10% in SJS, 10-30% in SJS/TEN overlap, and >30% in TEN
- spread: face and extremities; may generalize; scalp, palms, soles relatively spared; erosion of mucous membranes (lips, oral mucosa, conjunctiva, GU mucosa)
- systemic features: fever (higher in TEN), cytopenias, renal tubular necrosis/AKI, tracheal erosion, infection, contractures, corneal scarring, phimosis, vaginal synechiae
- time course: appears 1-3 wk after drug initiation; progression <4 d; epidermal regrowth in 3 wk
- can have constitutional symptoms: malaise, fever, hypotension, tachycardia

Epidemiology
- SJS: 1.2-6/million; TEN: 0.4-1.2/million
- risk factors: SLE, HIV/AIDS, HLA-B1502 (associated with carbamazepine), HLA-B5801 (associated with allopurinol)
- common causative agents: drugs (allopurinol, anti-epileptics, sulfonamides, NSAIDs, cephalosporins) responsible in 50% of SJS and 80% of TEN; viral or mycoplasma infections
- prognosis: 5% mortality in SJS, 30% in TEN due to fluid loss and infection

SCORTEN Score for TEN Prognosis

One point for each of: age ≥40, malignancy, body surface area detached ≥10%, tachycardia >120 bpm, serum urea >10 mmol/L, serum glucose >14 mmol/L serum bicarbonate <20 mmol/L

Used to determine appropriate clinical setting: score 0-1 can be treated in non-specialized wards; score ≥2 should be transferred to intensive care or burn unit

Score at admission is predictive of survival: 94% for 0-1, 87% for 2, 53% for 3, 25% for 4, and 17% for ≥5
**Differential Diagnosis**
- scarlet fever, phototoxic eruption, GVHD, SSSS, exfoliative dermatitis, AGEP, paraneoplastic pemphigus

**Management**
- discontinue offending drug
- admit to intermediate/intensive care/burn unit
- supportive care: IV fluids, electrolyte replacement, nutritional support, pain control, wound care, sterile handling, monitor for and treat infection
- IV Ig or cyclosporine or etanercept

**FIXED DRUG ERUPTION**

**Clinical Presentation**
- morphology: sharply demarcated erythematous oval patches on the skin or mucous membranes
- spread: commonly face, mucosa, genitalia, acral; recurs in same location upon subsequent exposure to the drug (fixed location)

**Epidemiology**
- common causative agents: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein

**Management**
- discontinue offending drug ± prednisone 1mg/kg/d x 2 wk for generalized lesions ± potent topical corticosteroids for non-eroded lesions or antimicrobial ointment for eroded lesions

**PHOTOSENSITIVITY REACTION**

**Clinical Presentation**
- phototoxic reaction: “exaggerated sunburn” (erythema, edema, vesicles, bullae) confined to sun-exposed areas
- photoallergic reaction: pruritic eczematous eruption with papules, vesicles, scaling, and crusting that may spread to areas not exposed to light

**Pathophysiology**
- phototoxic reaction: direct tissue injury
- photoallergic reaction: type IV delayed hypersensitivity

**Epidemiology**
- common causative agents: chlorpromazine, doxycycline, thiazide diuretics, procainamide

**Management**
- sun protection ± topical/oral corticosteroids

**Heritable Disorders**

**Ichthyosis Vulgaris**

**Clinical Presentation**
- xerosis with fine scaling as well as large adherent scales (“fish-scales”)
- affects arms, legs, palms, soles, back, forehead, and cheeks; spares flexural creases
- improves in summer, with humidity, and as the child grows into adulthood

**Pathophysiology**
- genetic deficiency in filaggrin protein leads to abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

**Epidemiology**
- 1:300 incidence
- autosomal dominant inheritance
- associated with AD and keratosis pilaris

**Investigations**
- electron microscopy keratohyalin granules

**Management**
- immersion in bath and oils followed by an emollient cream, humectant cream, or creams/oil containing urea or α or β-hydroxy acids
- intermittent systemic retinoids for severe cases
Neurofibromatosis (Type I; von Recklinghausen’s Disease)

Clinical Presentation
- diagnostic criteria includes 2 or more of the following
  1. more than 5 café-au-lait patches >1.5 cm in an adult or more than 5 café-au-lait macules >0.5 cm in a child <5 yr
  2. axillary or inguinal freckling
  3. iris hamartomas (Lisch nodules)
  4. optic gliomas
  5. neurofibromas
  6. distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)
  7. first degree relative with neurofibromatosis type 1
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see Pediatrics, P79)

Pathophysiology
- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence of neurofibromin (a tumour suppressor gene)

Epidemiology
- incidence 1:3,000

Investigations
- Wood’s lamp examination to detect café-au-lait macules in patients with pale skin

Management
- refer to orthopedics, ophthalmology, plastics, and psychology for relevant management
- follow-up annually for brain tumours such as astrocytoma
- excise suspicious or painful lesions
- see Pediatrics, P79

Vitiligo

Clinical Presentation
- primary pigmented disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply margined white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

Pathophysiology
- acquired autoimmune destruction of melanocytes

Epidemiology
- 1% incidence, polygenic
- 30% with positive family history

Investigations
- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison’s disease, Type I DM
- Wood’s lamp to detect lesions: illuminates UV light onto skin to detect amelanosis (porcelain white discolouration)

Management
- sun avoidance and protection
- topical calcineurin inhibitor (e.g. tacrolimus, pimecrolimus) or topical corticosteroids
- PUVA or Narrow band UVB
- make-up
- “bleaching” normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation

Interventions for Vitiligo
Cochrane Database Syst Rev. 2015;2:CD003263
Purpose: To assess the effects of existing interventions used in the management of vitiligo.
Study: Systematic review of RCTs assessing the effects of vitiligo treatments (topical treatments, light therapies, oral treatments, surgical methods).
Primary outcomes were quality of life and >75% repigmentation adverse effects.
Results: Ninety-six RCTs with 4,512 participants were deemed eligible, of which only 25 reported on the primary outcomes and were finally included. Repigmentation was better with combination therapy (calcipotriol plus pсорalen with UVA light (PUVA) than PUVA alone, hydrocortisone-17-butyrate plus excimer laser vs. excimer laser alone; oral minipulse of prednisolone (OMP) plus narrowband UVB (NB-UVB) vs. OMP alone; aclarromine with PUVA vs. PUVA alone; 8-methoxypsoralen (8-MOP) plus sunlight versus psoralen). A non-significant increase in proportion of participants with >75% re-pigmentation was noted in favour of NB-UVB compared to PUVA. Compared to PUVA, the NB-UVB group reported lower incidences of nausea and erythema, but not itching.
Conclusions: Some studies support existing therapies for vitiligo management, but follow-up is needed to assess permanence of re-pigmentation and higher quality RCTs need to be conducted.
**Bacterial Infections**

**EPIDERMIS**

**IMPETIGO**

**Clinical Presentation**
- acute purulent infection which appears vesicular; progresses to golden yellow “honey-crusted” lesions surrounded by erythema
- can present with bullae
- common sites: face, arms, legs, and buttocks

**Etiology**
- GAS, *S. aureus*, or both

**Epidemiology**
- preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

**Differential Diagnosis**
- infected eczema, HSV, VZV

**Investigations**
- Gram stain and culture of lesion fluid or biopsy

**Management**
- remove crusts, use saline compresses, and topical antiseptic soaks bid
- topical antibacterials such as 2% mupirocin or fusidic acid (Canada only) tid; continue for 7-10 d after resolution
- systemic antibiotics such as cloxacillin or cephalaxin for 7-10 d

---

**Location Matters!**

- **Impetigo** → just below stratum corneum
- **Erysipelas** → epidermis and upper dermis only
- **Cellulitis** → primarily lower dermis and subcutis (primarily not raised, and demarcation less distinct than erysipelas)
- **Necrotizing fasciitis** → deep fascia and muscle

---

**Figure 7. Layers of skin affected by bacterial infections**
DERMIS

**Table 16. Comparison of Erysipelas and Cellulitis**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Etiology</th>
<th>Complications</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erysipelas</strong></td>
<td>Involves upper dermis</td>
<td>GAS</td>
<td>Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy</td>
<td>DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, phlebitis reaction, stasis dermatitis, panniculitis, vasculitis</td>
<td>Clinical diagnosis: rarely do skin/blood culture If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology</td>
</tr>
<tr>
<td></td>
<td>Confluent, erythematous, sharp raised edge, warm plaque, well demarcated Very painful (“St. Anthony’s fire”)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sites: face and legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic symptoms: fever, chills, headache, weakness (if present, sign of more serious infection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cellulitis</strong></td>
<td>Involves lower dermis/subcutaneous fat Unilateral erythematous flat lesion, often with vesicles poorly demarcated, not uniformly aised Tende</td>
<td>GAS, S. aureus (large sized wounds), H. influenzae (periorbital), Pasteurella multocida (dog/cat bite)</td>
<td>Uncommon</td>
<td>Same as erysipelas</td>
<td>Same as erysipelas 1st line: clindamycin or cefazolin/cephalexin 2nd line: erythromycin or clindamycin Children: cefuroxime If DM (foot infections): TMP/SMX and metronidazole</td>
</tr>
<tr>
<td></td>
<td>Sites: commonly on legs Systemic symptoms (uncommon): fever, leukocytosis, lymphadenopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COMMON HAIR FOLLICLE INFECTIONS**

**Table 17. Comparison of Superficial Folliculitis, Furuncles, and Carbuncles**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Etiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superficial Folliculitis</strong></td>
<td>Superficial infection of the hair follicle (versus pseudofolliculitis: inflammation of follicle due to friction, irritation, or occlusion) Acute lesion consists of a dome-shaped pustule at the mouth of hair follicle Pustule ruptures to form a small crust Sites: primarily scalp, shoulders, anterior chest, upper back, other hair-bearing areas</td>
<td>Normal non-pathogenic bacteria (Staphylococcus – most common; Pseudomonas – hot tub) Phytosporum</td>
</tr>
<tr>
<td><strong>Furuncles (Boils)</strong></td>
<td>Red, hot, tender, inflammatory nodules with central yellowish point, which forms over summit and ruptures Involves subcutaneous tissue that arises from a hair follicle Sites: hair-bearing skin (thigh, neck, face, axillae, perineum buttocks)</td>
<td>S. aureus</td>
</tr>
<tr>
<td><strong>Carbuncles</strong></td>
<td>Deep-seated abscess formed by multiple coalescing furuncles Usually in areas of thicker skin Occasionally ulcerates Lesions drain through multiple openings to the surface Systemic symptoms may be associated</td>
<td>S. aureus</td>
</tr>
</tbody>
</table>

**Dermatophytoses**

**Clinical Presentation**
- infection of skin, hair, and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

**Pathophysiology**
- digestion of keratin by dermatophytes results in scaly skin, broken hairs, crumbling nails/onycholysis

**Etiology**
*Trichophyton, Microsporum, Epidermophyton* species (*Pityrosporum* is a superficial yeast and not a dermatophyte)

**Investigations**
- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia

**Management**
- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type): clotrimazole, or terbinafine or ciclopirox olamine cream applied bid
- oral therapy is indicated for onychomycosis or tinea capitis: terbinafine (Lamisil® – liver toxicity, CYP2D6 inhibitor) or itraconazole (Sporanox® – CYP3A4 inhibitor, liver toxicity)
Table 18. Different Manifestations of Dermatophyte Infection

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea Capitis</td>
<td>Round, scaly patches of alopecia, possibly with broken off hairs; pruritic</td>
<td>Alopecia areata, psoriasis, seborrheic dermatitis, trichotillomania</td>
<td>Wood’s light examination of hair: green fluorescence only for Microsporum infection Culture of scales/hair shaft Microscopic examination of KOH preparation of scales or hair shafts</td>
</tr>
<tr>
<td>Tinea Corporis</td>
<td>Pruritic, scaly, round/oval plaque with active erythematous margin, and central clearing Site: trunk, limbs, face</td>
<td>Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis</td>
<td>Microscopic examinations of KOH prep of scales shows hyphae Culture of scales</td>
</tr>
<tr>
<td>Tinea Cruris</td>
<td>Scaly patch/plaque with a well-defined, curved border and central clearing Pruritic, erythematous, dry/macerated Site: medial thigh</td>
<td>Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td>Tinea Pedis</td>
<td>Pruritic scaling and/or maceration of the web spaces, and powdery scaling of soles Acute infection: inte digital (especially 4th web space) red/white scales, vesicles, bullae, often with maceration Secondary bacterial infection may occur Chronic: non-pruritic, pink, scaling keratosis on soles and sides of feet May present as flare-up of chronic tinea pedis Predisposing factors: heat, humidity, occlusive footwear</td>
<td>AG, contact dermatitis, dyshidrotic dermatitis, erythrasma, intertrigo, inverse psoriasis</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td>Tinea Manuum</td>
<td>Primary fungal infection of the hand is rare; usually associated with tinea pedis Acute: blisters at edge of red areas on hands Chronic: single dry scaly patch</td>
<td>AG, contact dermatitis, granuloma annulare, psoriasis</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td>Tinea Unguim</td>
<td>Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris Toenail infections usually precede fingertip infections T. rubrum (80% of all toenail infections)</td>
<td>Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophies, bacterial infections</td>
<td>Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae Culture of subungual scraping or nail clippings on Sabouraud’s agar PAS stain of nail clipping by nail clippings on Sabouraud’s agar Microscopic examination of KOH prep of scales shows hyphae</td>
</tr>
</tbody>
</table>

Parasitic Infections

SCABIES

Clinical Presentation
- characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- primary lesion: superficial linear burrows; inflammatory papules and nodules in the axilla and groin
- secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- common sites: axillae, groin, buttocks, hands/feet (especially web spaces), sparing of head and neck (except in infants)

Pathophysiology
- scabies mite remains alive 2-3 d on clothing/sheets
- incubation of 1 mo, then pruritus begins
- re-infection followed by hypersensitivity in 24 h

Etiology
- Sarcoptes scabiei (a mite)
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

Differential Diagnosis
- atopic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)
Infections

**Investigations**
- microscopic examination of root and content of burrow and mineral oil mount for mite, eggs, feces
- skin biopsy may sometimes show scabies mite

**Management**
- bath, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment 7 d after first treatment)
- change underwear and linens; wash twice with detergent in hot water cycle then machine dry
- treat family and close contacts
- pruritus may persist for 2-3 wk after effective treatment due to prolonged hypersensitivity reaction
- mid potency topical steroids and antihistamines for symptom management

**LICE (PEDICULOSIS)**

**Clinical Presentation**
- intensely pruritic red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs; red, excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs; excoriations
- body lice: nits and lice in seams of clothing; excoriations and secondary infection mainly on shoulders, belt-line and buttocks

**Etiology**
- *Phthirus pubis* (pubic), *Pediculus humanus capitis* (scalp), *Pediculus humanus humanus* (body): attaches to body hair and feeds
- can transmit infectious agents such as *Bartonella quintana* and *Rickettsia prowazekii*

**Differential Diagnosis**
- bacterial infection of scalp, seborrheic dermatitis

**Diagnosis**
- lice visible on inspection of affected area or clothing seams

**Management**
- permethrin 1% (Nix® cream rinse) (ovicidal) or permethrin 1% (RC & Cor®, Kwella-P® shampoo)
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 d after first treatment
- shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle then machine dry

**BED BUGS (HEMIPTERA)**

**Clinical Presentation**
- burning wheals, turning to firm papules, often in groups of three – “breakfast, lunch and dinner” – in areas with easy access (face, neck, arms, legs, hands)

**Etiology**
- caused by *Cimex lectularius*, a small insect that feeds mainly at night (hide in crevices in walls and furniture during the day)

**Differential Diagnosis**
- dermatitis herpetiformis, drug eruptions, ecthyma, other insect bites, scabies

**Investigations**
- none required, but lesional biopsy can confirm insect bite reaction

**Management**
- professional fumigation
- topical steroids and oral H1-antagonists for symptomatic relief
- definitive treatment is removal of clutter in home and application of insecticides to walls and furniture
Viral Infections

HERPES SIMPLEX

Clinical Presentation
- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- primary
  - children and young adults
  - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - followed by antibody formation and latency of virus in dorsal nerve root ganglion
- secondary
  - recurrent form seen in adults; much more common than primary
  - prodrome: tingling, pruritus, pain
  - triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- complications: dendritic corneal ulcer, EM, herpes simplex encephalitis (infants at risk), HSV infection on AD causing Kaposi’s varicelliform eruption (eczema herpeticum)
- two biologically and immunologically different subtypes: HSV-1 and HSV-2
  - HSV-1
    - typically "cold sores" (grouped vesicles at the mucocutaneous junction which quickly burst)
    - recurrent on face, lips and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)
  - HSV-2
    - usually sexually transmitted; incubation 2-20 d
    - gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
    - vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
    - urethritis: watery discharge in males
    - recurrent on vulva, vagina, penis for 5-7 d
    - differential diagnosis of genital ulcers: Candida balanitis, chancroid, syphilitic chancres

Investigations
- Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
- viral culture, electron microscopy, and direct fluorescence antibody test of specimen taken from the base of a relatively new lesion
- serologic testing for antibody for current or past infection if necessary

Management
- HSV-1
  - treat during prodrome to prevent vesicle formation
  - topical antiviral (Zovirax®/Xerese®) cream, apply 5-6x/d x 4-7 d for facial/genital lesions
  - oral antivirals (e.g. acyclovir, famciclovir, valacyclovir) are far more effective and have an easier dosing schedule than topicals
- HSV-2
  - rupture vesicle with sterile needle if you wish to culture it
  - wet dressing with aluminum subacetate solution, Burrow’s compression, or betadine solution
  - 1st episode: acyclovir 200 mg PO 5x/d x 10 d
  - maintenance: acyclovir 400 mg PO bid
  - famciclovir and valacyclovir may be substituted and have better enteric absorption and less frequent dosing
  - in case of herpes genitalis, look for and treat any other sexually-transmitted infections STIs
  - for active lesions in pregnancy, see Obstetrics, OB29

HERPES ZOSTER (SHINGLES)

Clinical Presentation
- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last days to weeks
- pain can be pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Hutchinson’s sign: shingles on the tip of the nose signifies ocular involvement. Shingles in this area involves the nasociliary branch of the ophthalmic branch of the trigeminal nerve (V1)
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV

Etiology
- caused by reactivation of VZV
- risk factors: immunosuppression, old age, occasionally associated with hematologic malignancy
Differential Diagnosis
- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)

Investigations
- none required, but can do Tzanck test, direct fluorescence antibody test, or viral culture to rule out HSV

Management
- compress with normal saline, Burow’s, or betadine solution
- analgesics (NSAIDs, amitriptyline)
- famciclovir, valacyclovir, or acyclovir for 7 d; must initiate within 72 h to be of benefit
- gabapentin 300-600 mg PO tid for post-herpetic neuralgia

MOLLUSCUM CONTAGIOSUM

Clinical Presentation
- discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus (Molluscum contagiosum virus)
- common sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

Etiology
- virus is spread via direct contact, auto-inoculation, sexual contact
- common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)
- virus is self-limited and can take 1-2 yr to resolve

Investigations
- none required, however can biopsy to confirm diagnosis

Management
- topical cantharidin (a vesicant)
- cryotherapy
- curettage
- topical retinoids
- Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

WARTS (VERRUCA VULGARIS) (HUMAN PAPILLOMAVIRUS INFECTIONS)

Table 19. Different Manifestations of HPV Infection

<table>
<thead>
<tr>
<th>Verruca Vulgaris (Common Warts)</th>
<th>Definition and Clinical Features</th>
<th>Differential Diagnosis</th>
<th>Distribution</th>
<th>HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkeratotic, elevated discrete epithelial growths with papillated surface caused by HPV</td>
<td>Molluscum contagiosum, seborrheic keratosis</td>
<td>Located at trauma sites: fingers, hands, knees of children and teens</td>
<td>At least 80 types are known</td>
<td></td>
</tr>
</tbody>
</table>

| Verruca Planaris (Plantar Warts) and Verruca Palmaris (Palmar Warts) | Hyperkeratotic, shiny, sharply margined growths Paring of surface reveals red-brown specks (capillaries), interruption of epidermal ridges | May need to scrape (“pare”) lesions to differentiate wart from callus and corn | Located at pressure sites: metatarsal heads, heels, toes | Commonly HPV 1, 2, 4, 10 |

| Verruca Planae (Flat Warts) | Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration Common in children | Syringoma, seborrheic keratosis, molluscum contagiosum, lichen planus | Sites: face, dorsa of hands, shins, knees | Commonly HPV 3, 10 |

| Condyloma Acuminata (Genital Warts) | Skin-coloured pinhead papules to soft cauliflower like masses in clusters Often occurs in young adults, infants, children Can be asymptomatic, lasting months to years Highly contagious, transmitted sexually and non-sexually (e.g. Keboen phenomenon via scratching, shaving), and can spread without clinically apparent lesions Investigations: acetowhitrning (subclinical lesions seen with 5% acetic acid x 5 min and hand lens) Complications: fairy-ring warts (satellite warts at periphery of treated area of original warts) | Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), molluscum contagiosum | Sites: genitalia and perianal areas | Commonly HPV 6 and 11 HPV 16, 18, 31, 33 cause cervical dysplasia, SCC and invasive cancer |
Treatment for Warts
- **first line therapies**
  - salicylic acid preparations (patches, solutions, creams ointments), cryotherapy, topical cantharone
- **second line therapies**
  - topical imiquimod, topical 5-fluorouracil, topical tretinoin, podophyllotoxin
- **third line therapies**
  - curettage, cautery, surgery for non plantar warts, CO2 laser, oral cimetidine (particularly children), intraslesional bleomycin (plantar warts), trichloroacetic acid, diphencyprone
  - other viruses associated with skin changes, such as measles, roseola, fifth disease, etc.
  - see Pediatrics, Pediatric Exanthems, P50

**Yeast Infections**

**CANDIDIASIS**

**Etiology**
- many species of Candida (70-80% of infections are from Candida albicans)
- opportunistic infection in those with predisposing factors (e.g. trauma, malnutrition, immunodeficiency)

**Candidal Paronychia**
- clinical presentation: painful red swellings of periungual skin
- management: topical agents not as effective; oral antifungals recommended

**Candidal Intertrigo**
- clinical presentation
  - macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
  - peripheral “satellite” pustules
  - starts as non-infectious maceration from heat, moisture, and friction
- predisposing factors: obesity, DM, systemic antibiotics, immunosuppression, malignancy
- management: keep area dry, terbinafine, ciclopirox olamine, ketoconazole/clotrimazole cream bid until rash clears

**PITYRIASIS (TINEA) VERSICOLOR**

**Clinical Presentation**
- asymptomatic superficial fungal infection with brown/white scaling macules
- affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
- common sites: upper chest and back

**Pathophysiology**
- microbe produces azelaic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
- affinity for sebaceous glands; require fatty acids to survive

**Etiology**
- Pityrosporum ovale (Malassezia furfur)
- also associated with folliculitis and seborrheic dermatitis
- predisposing factors: summer, tropical climates, excessive sweating, Cushing's syndrome, prolonged corticosteroid use

**Investigations**
- clinical diagnosis but can perform microscopic examination, KOH prep of scales for hyphae and spores

**Management**
- ketoconazole shampoo or cream daily
- topical terbinafine or ciclopirox olamine bid
- systemic fluconazole or itraconazole for 7 d if extensive

**Sexually Transmitted Infections**

**SYPHILIS**

**Clinical Presentation**
- characterized initially by a painless ulcer (chancre)
- following inoculation, systemic infection with secondary and tertiary stages

**Etiology**
- Treponema pallidum
- transmitted sexually, congenitally, or rarely by transfusion
Table 20. Stages of Syphilis

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Syphilis</strong></td>
<td>CANNOT be based on clinical presentation alone</td>
<td>Penicillin G, 2.4 million units IM, single dose</td>
</tr>
<tr>
<td>Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate</td>
<td>VDRL negative – repeat weekly for 1 mo</td>
<td></td>
</tr>
<tr>
<td>Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-8 wk; chancre may also develop on lips or anus</td>
<td>Fluorescent treponemal antibody-syphilis (FTA-ABS) test has greater sensitivity and may detect disease earlier in course</td>
<td></td>
</tr>
<tr>
<td>Regional non-tender lymphadenopathy appears &lt; 1 wk after onset of chancre</td>
<td>Dark field examination – spirochete in chancre fluid or lymph node aspirate</td>
<td></td>
</tr>
<tr>
<td>DDx: chancroid (painful), HSV (multiple lesions)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Syphilis**

Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre)

Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia

Lesions heal in 1-5 wk and may recur for 1 yr

3 types of lesions:
1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus)
2. Condyloma lata: wart-like moist papules around genital/perianal region
3. Mucous patches: macerated patches mainly found in oral mucosa

VDRL positive

FTA-ABS +ve; –ve after 1 yr following appearance of chancre

Dark field +ve in all secondary

As for primary syphilis

**Tertiary Syphilis**

Extremely rare

3-7 yr after secondary

Main skin lesion: ‘Gumma’ – a granulomatous nontender nodule

As in primary syphilis, VDRL can be falsely negative

Treatment: penicillin G, 2.4 million units IM weekly x 3 wk

GONOCOCCEMIA

**Clinical Presentation**
- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- common sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis, and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

**Etiology**
- *Neisseria gonorrhoeae*

**Investigations**
- requires high index of clinical suspicion plays because tests are often negative
- bacterial culture of blood, joint fluid, and skin lesions
- joint fluid cell count and Gram stain

**Management**
- notify Public Health authorities
- screen for other STIs
- cefixime 400 mg PO (drug of choice) or ceftriaxone 1 g IM

HSV
- see Viral Infections, D29

HPV
- see Viral Infections, D30
Pre-Malignant Skin Conditions

Actinic Keratosis (Solar Keratosis)

Clinical Presentation
- ill-defined, scaly, erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

Pathophysiology
- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of AK to SCC (~1/1,000), but higher likelihood if AK is persistent
- UV-induced p53 gene mutation
- risk factors: increased age, light skin/eyes/hair, immunosuppression, syndromes such as albinism or xeroderma pigmentosum
- risk factors for malignancy: immunosuppression, history of skin cancer, persistence of the AK

Epidemiology
- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III, rare in darker skin as melanin is protective

Differential Diagnosis
- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

Investigations
- biopsy lesions that are refractory to treatment

Management
- destructive: cryotherapy, electrodesiccation, and curettage
- topical pharmacotherapy (mechanism: destruction of rapidly growing cells or immune system modulation)
  - topical 5-Fluorouracil cream (for 2-4 wk), Imiquimod 5% (2 times per wk for 16 wk), Imiquimod 3.75% (daily for 2 wk then none for 2 wk then daily for 2 wk) Ingenol Mebutate gel 0.015% (daily for 3 d on the head and neck), Ingenol mebutate 0.05% gel (daily for 2 d on the body)
- photodynamic therapy
- excision

Types of AK
- Erythematous: typical AK lesion
- Hypertrophic: thicker, rough papule/plaque
- Cutaneous horn: firm hyperkeratotic outgrowth
- Actinic cheilitis: confluent AKs on the lip
- Pigmented: flat, tan-brown, scaly plaque
- Spreading pigmented
- Proliferative
- Conjunctival: pinguecula, pterygium

Leukoplakia

Clinical Presentation
- a morphologic term describing homogenous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

Pathophysiology
- precancerous or premalignant condition
- oral form is strongly associated with tobacco use and alcohol consumption

Epidemiology
- 1-5% prevalence in adult population after 30 yr of age; peak at age 50
- M>F, fair-skinned
- most common oral mucosal premalignant lesion

Differential Diagnosis
- lichen planus, oral hairy leukoplakia

Investigations
- biopsy is mandatory because it is premalignant

Management
- low risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, follow-up
- moderate/dysplastic lesions: excision, cryotherapy
Malignant Skin Tumours

Non-Melanoma Skin Cancers

BASAL CELL CARCINOMA

Subtypes
- noduloulcerative (typical)
  - skin-coloured papule/nodule with rolled, translucent ("pearly") telangiectatic border, and depressed/eroded/ulcerated centre
- pigmented variant
  - flecks of pigment in translucent lesion with surface telangiectasia
  - may mimic malignant melanoma
- superficial variant
  - flat, tan to red-brown plaque, often with scaly, pearly border and fine telangiectasia at margin
  - least aggressive subtype
- sclerosing (morpheaform) variant
  - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders, indurated

Pathophysiology
- malignant proliferation of basal keratinocytes of the epidermis
  - low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
  - usually due to UVB light exposure, therefore >80% on face
  - may also occur in previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin syndrome)

Epidemiology
- most common malignancy in humans
- 75% of all malignant skin tumours >40 yr, increased prevalence in the elderly
- M>F , skin phototypes I and II, chronic cumulative sun exposure, ionizing radiation, immunosuppression, arsenic exposure

Differential Diagnosis
- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular malignant melanoma, SCC

Management
- imiquimod 5% cream (Aldara®) or cryotherapy is indicated for superficial BCCs on the trunk
- fluorouracil and photodynamic therapy can also be used for superficial BCC
- shave excision + electrodessication and curettage for most types of BCCs, not including morpheaform
- Mohs surgery: microscopically controlled, minimally invasive, stepwise excision for lesions on the face or in areas that are difficult to reconstruct
- radiotherapy used in advanced cases of BCC where surgical intervention is not an option
- vismodegib is approved for metastatic BCC
- life-long follow-up every 6 mo-1 yr
  - 95% cure rate if lesion <2 cm in diameter or if treated early

SQUAMOUS CELL CARCINOMA

Clinical Presentation
- indurated, pink/red/skin-coloured papule/plaque/nodule with surface scale/crust ± ulceration
- more rapid enlargement than BCC
- exophytic (grows outward), may present as a cutaneous horn
- sites: face, ears, scalp, forearms, dorsum of hands

Pathophysiology
- malignant neoplasm of keratinocytes (primarily vertical growth)
  - predisposing factors include: UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar, and nitrogen mustards), HPV 16, 18, immunosuppression
- may occur in previous scar (SCC more commonly than BCC)

Epidemiology
- second most common type of cutaneous neoplasm
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- in organ transplant recipients SCC is most common cutaneous malignancy, with increased mortality as compared to non immunocompromised population

Differential Diagnosis
- benign: nummular eczema, psoriasis, irritated seborrheic keratosis
- malignant: keratoacanthoma, Bowen’s disease, BCC
Management
• surgical excision with primary closure, skin flaps or grafting
• Mohs surgery
• lifelong follow-up (more aggressive treatment than BCC)

Prognosis
• good prognostic factors: early treatment, negative margins, and small size of lesion
• SCCs that arise from AK metastasize less frequently (~1%) than other SCCs arising de novo in old
  burns (2-5% of cases)
• overall control is 75% over 5 yr, 5-10% metastasize
• metastasis rates are higher if diameter >2 cm, depth >4 mm, recurrent, involvement of bone/muscle/
  nerve, location on scalp/ears/nose/lips, immunosuppressed, caused by arsenic ingestion, or tumour
  arose from scar/chronic ulcer/burn/genital tract/sinus tract

BOWEN’S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

Clinical Presentation
• sharply demarcated erythematous patch/thin plaque with scale and/or crusting
• often 1-3 cm in diameter and found on the skin and mucous membranes
• evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

Management
• same as for BCC
• biopsy required for diagnosis
• topical 5-fluorouracil (Efudex®) or imiquimod (Aldara®) used if extensive and as a tool to identify
  margins of poorly defined tumours
• cryosurgery
• shave excision with electrodesiccation and curettage

KERATOACANTHOMA

Clinical Presentation
• rapidly growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled
  crater, resembling an erupting volcano
• may spontaneously regress within a year, leaving a scar
• sites: sun-exposed skin

Pathophysiology
• epithelial neoplasm with atypical keratinocytes in epidermis
• low grade variant of SCC

Etiology
• HPV, UV radiation, chemical carcinogens (tar, mineral oil)

Epidemiology
• >50 yr, rare <20 yr

Differential Diagnosis
• treat as SCC until proven otherwise
• hypertrophic solar keratosis, verruca vulgaris

Management
• surgical excision or saucerization (shave biopsy) followed by electrodesiccation of the base, treated
  similarly to SCC

Malignant Melanoma

Clinical Presentation
• malignant characteristics of a mole: “ABCDE” mnemonic
• sites: skin, mucous membranes, eyes, CNS

Clinical Subtypes of Malignant Melanoma
• lentigo maligna
  • malignant melanoma in situ (normal and malignant melanocytes confined to the epidermis)
  • 2-6 cm, tan brown/black uniformly flat macule or patch with irregular borders
  • lesion grows radially and produces complex colours
  • often seen in the elderly
  • 10% evolve to lentigo maligna melanoma

Does this Patient have a Mole or Melanoma?

ABCD checklist
Asymmetry
Border (irregular and/or indistinct)
Colour (varied)
Diameter (increasing or >6 mm)
Enlargement, elevation, evolution (i.e. change in colour, size, or shape)

Sensitivity 92% (CI 82-98%)
Specificity 100% (CI 84-100%)

JAMA 1998;279:696-701
• **lentigo maligna melanoma** (15% of all melanomas)
  - malignant melanocytes invading into the dermis
  - associated with pre-existing solar lentigo, not pre-existing nevi
  - flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  - with time, colour changes from uniform brown to dark brown with black and blue
  - found on all skin surfaces, especially those often exposed to sun, such as the face and hands

• **superficial spreading melanoma** (60-70% of all melanomas)
  - atypical melanocytes initially spread laterally in epidermis then invade the dermis
  - irregular, indurated, enlarging plaques with red/white/blue discoloration, focal papules or nodules
  - ulcerate and bleed with growth

• **nodular melanoma** (30% of all melanomas)
  - atypical melanocytes that initially grow vertically with little lateral spread
  - uniformly ulcerated, blue black, and sharply delineated plaque or nodule
  - rapidly fatal
  - may be pink or have no colour at all, this is called an amelanotic melanoma
  - “EFG” elevated, firm, growing

• **acral lentiginous melanoma** (5% of all melanomas)
  - ill-defined dark brown, blue-black macule
  - palmar, plantar, subungual skin
  - melanomas on mucous membranes have poor prognosis

**Pathophysiology**
- malignant neoplasm of pigment-forming cells (melanocytes and nevus cells)

**Epidemiology**
- incidence: 1/75 (Canada) 1/50 (US)
- risk factors: numerous moles, fair skin, red hair, personal/family history, 1 large congenital nevus (>20 cm), familial dysplastic nevus syndrome, any dysplastic nevi, immunosuppression, > 50 common nevi, and sun exposure with sunburns, tanning beds
- most common sites: back (M), calves (F)
- worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

**Differential Diagnosis**
- benign: nevi, solar lentigo, seborrheic keratosis
- malignant: pigmented BCC

**Management**
- excisional biopsy preferable, otherwise incisional biopsy
- remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
- beware of lesions that regress – tumour is usually deeper than anticipated
- high dose IFN for stage II (regional), chemotherapy (cis-platinum, BCG) and high dose IFN for stage III (distant) disease
- newer chemotherapeutic, gene therapies, and vaccines starting to be used in metastatic melanoma
- radiotherapy may be used as adjunctive treatment

**Table 21. American Joint Committee on Cancer Staging System Based on Breslow’s Thickness of Invasion**

<table>
<thead>
<tr>
<th>Tumour Depth</th>
<th>Stage</th>
<th>Approximate 5 Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 &lt;1.0 mm</td>
<td>Stage I T1a – T2a</td>
<td>5-yr survival 90%</td>
</tr>
<tr>
<td>T2 1.01-2.0 mm</td>
<td>Stage II T2b – T4b</td>
<td>5-yr survival 70%</td>
</tr>
<tr>
<td>T3 2.01-4.0 mm</td>
<td>Stage III any nodes</td>
<td>5-yr survival 45%</td>
</tr>
<tr>
<td>T4 &gt;4.0 mm</td>
<td>Stage IV any mets</td>
<td>5-yr survival 10%</td>
</tr>
</tbody>
</table>

a = no ulceration; b = ulceration

**Other Cutaneous Cancers**

**CUTANEOUS T-CELL LYMPHOMA**

**Clinical Presentation**
- **Mycosis fungoides** (limited superficial type)
  - characterized by erythematous patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy telangiectasia, hyperpigmentation, hypopigmentation)
  - common sites include: trunk, buttocks, proximal limbs
  - mildly symptomatic, usually excellent prognosis for early disease

- **Sézary syndrome** (widespread systemic type)
  - rare variant characterized by erythroderma, lymphadenopathy, WBC >20 x 10^9/L with Sézary cells
  - associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
  - often fatal
Pathophysiology
• clonal proliferation of skin-homing CD4 T-cells

Epidemiology
• >50 yr old, M:F 2:1

Differential Diagnosis
• tinea corporis, nummular dermatitis, psoriasis DLE, Bowen’s disease

Investigations
• skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
• blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is Sézary)
• imaging (for systemic involvement)

Management
• Mycosis fungoides
  • depends on stage of disease
  • topical steroids and/or PUVA, narrow band UVB (NBUVB, 311-313nm)
• Sézary syndrome
  • oral retinoids and IFN
  • extra-corporeal photopheresis
  • may need radiotherapy for total skin electron beam radiation
  • may maintain on UV therapy
  • other chemotherapy agents

Diseases of Hair Density

Hair Growth
• hair grows in a cyclic pattern that is defined in 3 stages (most scalp hairs are in anagen phase)
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
• total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
• growth of the hair follicles is also based on the hormonal response to testosterone and DHT; this response is genetically controlled

Non-Scarring (Non-Cicatricial) Alopecia

ANDROGENETIC ALOPECIA

Clinical Presentation
• male- or female-pattern alopecia
• males: fronto-temporal areas progressing to vertex, entire scalp may be bald
• females: widening of central part, "Christmas tree" pattern

Pathophysiology
• action of testosterone on hair follicles

Epidemiology
• males: early 20s-30s
• females: 40s-50s

Management
• minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
• males: spironolactone (anti-androgenic effects), cyproterone acetate (Diane-35°)
• males: finasteride (Propecia®) (5-a-reductase inhibitor) 1 mg/d
• hair transplant

PHYSICAL
• trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
• traumatic (e.g. tight "corn-row" braiding of hair, wearing tight pony tails, tight tying of turbans)

DDx of Non-Scarring (Non-Cicatricial) Alopecia
• Autoimmune
  • Alopecia areata
• Endocrine
  • Hypothyroidism
  • Androgens
• Micronutrient deficiencies
  • Iron
  • Zinc
• Toxins
  • Heavy metals
  • Anticoagulants
  • Chemotherapy
  • Vitamin A
• Trauma to the hair follicle
  • Trichotillomania
• ‘Corn-row’ braiding
• Other
  • Syphilis
  • Severe illness
  • Childbirth
TELOGEN EFFLUVIUM

Clinical Presentation
- uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle

Pathophysiology
- variety of precipitating factors
- hair loss typically occurs 2-4 mo after exposure to precipitant
- regrowth occurs within a few months but may not be complete

ANAGEN EFFLUVIUM

Clinical Presentation
- hair loss due to insult to hair follicle impairing its mitotic activity (growth stage)

Pathophysiology
- precipitated by chemotherapeutic agents (most common), other meds (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron arsenic)
- dose-dependent effect
- hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
- reversible effect; follicles resume normal mitotic activity few weeks after agent stopped

ALOPECIA AREATA

Clinical Presentation
- autoimmune disorder characterized by patches of complete hair loss often localized to scalp but can affect eyebrows, beard, eyelashes, etc.
- may be associated with dystrophic nail changes – fine stippling, pitting
- “exclamation mark” pattern (hairs frayed and have tapered shafts, i.e. looks like "!")
- may be associated with pernicious anemia, vitiligo, thyroid disease, Addison’s disease
- spontaneous regrowth may occur within months of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress

Management
- generally unsatisfactory
- intralesional triamcinolone acetonide (corticosteroids) can be used for isolated patches
- UV or PUVA therapy
- immunomodulatory (diphenycyprone)

Scarring (Cicatricial) Alopecia

Clinical Presentation
- irreversible loss of hair follicles with fibrosis

Etiology
- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (HZV)
- inflammatory
  - lichen planus (lichen planopilaris)
  - DLE (note that SLE can cause a alopecia unrelated to DLE lesions which are non-scarring)
  - morphea: “coup de sabre” with involvement of centre of scalp
- central centrifugal cicatricial alopecia (CCCA): seen in up to 40% of black women, starting at central scalp; one of most commonly diagnosed scarring alopecias, may be associated with hair care practices in this population

Investigations
- biopsy from active border

Management
- infections: treat underlying infection
- inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials
## Table 22 Nail Changes in Systemic and Dermatological Conditions

<table>
<thead>
<tr>
<th>Nail Abnormality</th>
<th>Definition/Etiology</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAIL PLATE CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clubbing</td>
<td>Proximal nail plate has greater than 180° angle to nail fold, watch-glass nails, bulbous digits</td>
<td>Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.</td>
</tr>
<tr>
<td>Koilonychia</td>
<td>Spoon shaped nails</td>
<td>Iron deficiency, malnutrition, DM</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>Separation of nail plate from nail bed</td>
<td>Psoriasis, dermatophytes, thyroid disease</td>
</tr>
<tr>
<td>Onychogryphosis</td>
<td>Hypertrophy of the nail plate producing a curved, claw-like deformity</td>
<td>Poor circulation, chronic inflammation, tinea</td>
</tr>
<tr>
<td>Onychohemia</td>
<td>Subungual hematoma</td>
<td>Trauma to nail bed</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>Fungal infection of nail (e.g. dermatophyte yeast, mould)</td>
<td>HIV, DM, peripheral arterial disease</td>
</tr>
<tr>
<td>Onychocryptosis</td>
<td>Ingrown toenail often hallux with congenital malalignment, painful inflammation, granulation tissue</td>
<td>Tight fitting shoes, excessive nail clipping</td>
</tr>
<tr>
<td><strong>SURFACE CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-shaped nicking</td>
<td>Distal margin has v shaped loss of the nail plate</td>
<td>Darier’s disease (keratosis follicularis)</td>
</tr>
<tr>
<td>Pterygium inversus unguium</td>
<td>Distal nail plate does not separate from underlying nail bed</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Pitting</td>
<td>Punctate depressions that migrate distally with growth</td>
<td>Psoriasis (random pattern), alopecia areata (geometric grid shaped arrangement), eczema</td>
</tr>
<tr>
<td>Transverse ridging</td>
<td>Transverse depressions often more in central portion of nail plate</td>
<td>Serious acute illness slows nail growth (when present in all nails = Beau’s lines), eczema, chronic paronychia, trauma</td>
</tr>
<tr>
<td>Transverse white lines</td>
<td>Bands of white discoloration</td>
<td>Poisons, hypoalbuminemia (Muehrcke’s lines)</td>
</tr>
<tr>
<td><strong>COLOUR CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow</td>
<td></td>
<td>Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis tobacco use</td>
</tr>
<tr>
<td>Green</td>
<td></td>
<td>Pseudomonas</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>Melanoma, hematoma</td>
</tr>
<tr>
<td>Brown</td>
<td></td>
<td>Nicotine use, psoriasis, poisons, longitudinal melanonychia (ethnic)</td>
</tr>
<tr>
<td>Splinter hemorrhages</td>
<td>Extrasavation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows</td>
<td>Trauma, bacterial endocarditis, blood dyscrasias, psoriasis</td>
</tr>
<tr>
<td>Oil spots</td>
<td>Brown-yellow discoloration</td>
<td>Psoriasis</td>
</tr>
<tr>
<td><strong>NAIL FOLD CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpetic whitlow</td>
<td>HSV infection of distal phalanx</td>
<td>HSV infection</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Local inflammation of the nail fold around the nail bed</td>
<td>Acute: painful infection Chronic: constant wetting (e.g. dishwashing, thumbsucking)</td>
</tr>
<tr>
<td>Nail fold telangiectasias</td>
<td>Cuticular hemorrhages, roughness, capillary changes</td>
<td>Scleroderma, SLE, dermatomyositis</td>
</tr>
</tbody>
</table>
## Table 23. Skin Manifestations of Internal Conditions

<table>
<thead>
<tr>
<th>Disease</th>
<th>Related Dermatoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUTOIMMUNE DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Painful aphthous ulcers in oral cavity ± genital mucous membranes, erythema nodosum, acniform papules</td>
</tr>
<tr>
<td>Buerger’s disease</td>
<td>Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital obstructions</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Periorbital and extensor violaceous erythema, heliotropic rash with edema, Gottron’s papules (violaceous flat-topped papules with atrophy), periangual erythema, telangiectasia, calcinosis cutis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Subcutaneous nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livedo reticularis, ulceration</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>Palpable purpura in cold-exposed areas, Raynaud’s, cold urticaria, acral hemorrhagic necrosis, bleeding and plaques of pregnancy</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Petechiae, urticaria, erythema nodosum, rheumatoid nodules, evanescent rash</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Raynaud’s nonpitting edema, waxy/shiny/tense atrophic skin (or morphea), ulcers, cutaneous calcification, periangual telangiectasia, acrosclerosis, salt-and-pepper pigmentation</td>
</tr>
<tr>
<td>SLE</td>
<td>Malar erythema, discoid rash (erythematous papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy diffuse alopecia, mucosal ulcers, photosensitivity</td>
</tr>
<tr>
<td>Cohn’s disease/UC</td>
<td>Pyoderma gangrenosum, erythema nodosum, Sweet’s syndrome</td>
</tr>
<tr>
<td><strong>ENDOCRINE DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Generalized hyperpigmentation or limited to skin folds, buccal mucosa, and scars</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Infections (e.g., boils, carbuncles, Candidiasis, S. aureus, dermatophytoses, tinea pedis and cruris, infectious eczematous dermatitis), pruritus, eruptive xanthomas, necrobiotic lipoidic diabeticorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretilial myxedema, acropachy, onycholysis</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows</td>
</tr>
<tr>
<td><strong>HIV-RELATED</strong></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Viral (e.g., HSV, HIV, HP, CMV, molluscum contagiosum, oral hairy leukoplaikia), bacterial (impetigo, acneiform folliculitis, dental caries, cellulitis, bacillary epitheloid angiomatosis, syphilis), fungal (candidiasis, histoplasmosis, cryptococcus, blastomycosis)</td>
</tr>
<tr>
<td>Inflammatory dermatoses</td>
<td>Seborrhea, psoriasis, pityriasis rosea, vasculitis</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Kaposi’s sarcoma, lymphoma, BCC, SCC, MM</td>
</tr>
<tr>
<td><strong>MALIGNANCY</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Peutz-Jeghers; pigmented macules on lips/oral mucosa</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Paget’s disease; eroding scaling plaques of perineum</td>
</tr>
<tr>
<td>Cervix/anus/rectum</td>
<td>Paget’s disease, eczematous and crusting lesions of the skin of the nipple and usually areola of the breast</td>
</tr>
<tr>
<td><strong>Carcinoma</strong></td>
<td>Palmoplantar keratoderma: thickened skin of palms/soles</td>
</tr>
<tr>
<td>Breast</td>
<td>Sipple’s syndrome: multiple mucosal neuromas</td>
</tr>
<tr>
<td>GI</td>
<td>Dermatomyositis: heliotrope erythema of eyelids and violaceous plaques over knuckles</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Lymphoma/leukemia: telangiectasia on pinna, bulbar conjunctiva</td>
</tr>
<tr>
<td>Breast/ovary</td>
<td>Ataxia Telangiectasia: telangiectasia on pinna, bulbar conjunctiva</td>
</tr>
<tr>
<td><strong>Hodgkin’s</strong></td>
<td>Ichthyosis: generalized scaling especially on extremities, Sweet’s syndrome</td>
</tr>
<tr>
<td><strong>Acute leukemia</strong></td>
<td>Bloom’s syndrome: butterfly erythema on face, associated with short stature</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Amyloidosis: large, smooth tongue with waxy papules on eyelids, nasolabial folds and lips, as well as facial petechiae</td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry’s nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Pruritus, pigmentation, half and half nails, perforating dermatosis, calciphylaxis</td>
</tr>
<tr>
<td>Pruritic urticarial papules and plaques of pregnancy</td>
<td>Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms and lower back</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Palpable purpura in cold-exposed areas, Raynaud’s, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection</td>
</tr>
</tbody>
</table>
Pediatric Exanthems

Miscellaneous Lesions

Angioedema and Urticaria

Angioedema
- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
  - onset in childhood; 80% have positive family history
  - recurrent attacks; 25% die from laryngeal edema
  - triggers minor trauma, emotional upset, temperature changes
- types of acquired angioedema
  - acute allergic angioedema (allergens include food, drugs, contrast media, insect venom, latex)
  - non-allergic drug reaction (drugs include ACEI)
  - acquired C1 inhibitor deficiency
- treatment
  - prophylaxis with danazol or stanozolol for hereditary angioedema
  - epinephrine pen to temporize until patient reaches hospital in acute attack

Urticaria
- also known as “hives”
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 h
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen

Table 24. Classification of Urticaria

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Urticaria</td>
<td>Drugs: especially ASA, NSAIDs, Foods: nuts, shellfish, eggs, fruit, Idiopathic (vast majority) Infection Insect stings (bees, wasps, hornets) Perforative absorption: cosmetics, work exposures Stress Systemic diseases: SLE, endocrinopathy, neoplasm</td>
</tr>
<tr>
<td>&gt;2/3 of cases</td>
<td>Attacks last &lt;6 wk Individual lesions last &lt;24 h</td>
</tr>
<tr>
<td>Chronic Urticaria</td>
<td>IgE-dependent: trigger associated Idiopathic (90% of chronic urticaria patients) Aeroallergens Drugs (antibiotics, hormones, local anesthetics) Foods and additives Insect stings Parasitic infections Physical contact (animal saliva, plant resins, latex, metals, lotions, soap) Direct mast cell release Opiates, muscle relaxants, radio-contrast agents Complement-mediated Serum sickness, transfusion reactions Infections, viral/bacterial (&gt;80% of urticaria in pediatric patients) Urticarial vasculitis Arachidonic acid metabolism ASA, NSAIDs Physical Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholinergic (hot shower, exercise), solar, pressure (shoulder strap, buttocks), agenesis (exposure to water) adrenergic (stress), heat Other Mastocytosis, urticaria pigmentosa</td>
</tr>
<tr>
<td>&lt;1/3 of cases</td>
<td>Attacks last &gt;6 wk Individual lesions last &lt;24 h</td>
</tr>
</tbody>
</table>

Approach to Urticaria
- Thorough Hx and P/E
- Acute: no immediate investigations needed; consider referral for allergy testing
- Chronic: further investigations required: CBC and differential, urinalysis, ESR, TSH, LFTs to help identify underlying cause
- Vasculitic: biopsy of lesion and referral to dermatology

Wheat
- Typically erythematous flat-topped, palpable lesions varying in size with circumscribed dermal edema
- Individual lesion lasts <24 h
- Associated with mast cell release of histamine
- May be pruritic

Mastocytosis (Urticaria Pigmentosa)
- Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Darier’s sign), due to mast cell degranulation; this occurs within minutes
### Erythema Nodosum

**Clinical Presentation**
- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on extensor lower legs (typically shins), knees, arms
- associated with arthralgia, fever, malaise

**Etiology**
- 40% are idiopathic
- drugs: sulfonamides, OCPs (also pregnancy), analgesics, trans retinoic acid
- infections: GAS, TB, histoplasmosis, Yersinia
- inflammation: sarcoidosis, Crohn's > UC
- malignancy: acute leukemia, Hodgkin's lymphoma

**Epidemiology**
- 15-30 yr old, F:M = 3:1
- lesions last for days and spontaneously resolve in 6 wk

**Investigations**
- chest x-ray (to rule out chest infection and sarcoidosis)
- throat culture, ASO titre, PPD skin test

**Management**
- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids
- treat underlying cause

---

### Pruritus

**Clinical Presentation**
- a sensation provoking a desire to scratch, with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

**Etiology**
- dermatologic – generalized
  - asthenic dermatitis ("winter itch" due to dry skin)
  - pruritus of senescent skin (may not have dry skin, any time of year)
  - infestations: scabies, lice
  - drug eruptions: ASA, antidepressants, opiates
  - psychogenic states
- dermatologic – local
  - atopc and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin's lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, Fe deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumours), non-Hodgkin's lymphoma
  - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis

**Investigations**
- blood work: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture and serology for parasites

**Management**
- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- topical corticosteroid and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria
- phototherapy with UVB or PUVA
- doxepin, amitriptyline
- immunosuppressive agents if severe: steroids and steroid-sparing

---

**DDx of Erythema Nodosum**

- NODOSUMM
- NO cause (idiopathic) in 40%
- Drugs (sulfonamides, OCP, etc.)
- Other infections (GAS+)
- Sarcoidosis
- UC and Crohn's
- Malignancy (leukemia, Hodgkin's lymphoma)
- Many Infections

**DDx of Pruritus**

- SCRATCHED
- Scabies
- Cholestasis
- Renal
- Autoimmune
- Tumours
- Crazies (psychiatric)
- Endocrine (polycythemia, lymphoma)
- Drugs, Dry skin

Consider biopsy of any nonhealing wound to rule out cancer.
Wounds and Ulcers

• see Plastic Surgery, PL8, PL16

Sunburn
• erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
• chronic UVA and UVB exposure leads to photoageing, immunosuppression, photocarcinogenesis
• prevention: avoid peak UVR (10 am–4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
• clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

Sunscreens and Preventative Therapy

Sunburn
• erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
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• prevention: avoid peak UVR (10 am–4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
• clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

Sunscreens
• under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen
• topical chemical: absorbs UV light
  • requires application at least 15-30 min prior to exposure, should be reapplied every 2 h (more often if sweating, swimming)
  • UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
  • UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
• topical physical: reflects and scatters UV light
  • titanium dioxide, zinc oxide, kaolin, talc, ferric chloride, and melanin
  • all are effective against the UVA and UVB spectrum
  • less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
• some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

Management
• sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, topical corticosteroids)
• antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin

Topical Steroids

Table 25. Potency Ranking of Topical Steroids

<table>
<thead>
<tr>
<th>Relative Potency</th>
<th>Relative Strength</th>
<th>Generic Names</th>
<th>Trade Names</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>x1</td>
<td>hydrocortisone – 2.5% (1% available over-the-counter)</td>
<td>Emo Cort®</td>
<td>Intertiginous areas, children, face, thin skin</td>
</tr>
<tr>
<td>Moderate</td>
<td>x3</td>
<td>hydrocortisone 17-valerate – 0.2% desonide mometasone furate</td>
<td>Westcort®</td>
<td>Arm, leg, trunk</td>
</tr>
<tr>
<td>Potent</td>
<td>x6</td>
<td>betamethasone – 0.1% 17-valerate – 0.1% amcinonide</td>
<td>Betnovate®</td>
<td>Celestoderm – V® Cicleson®</td>
</tr>
<tr>
<td>Very Potent</td>
<td>x9</td>
<td>betamethasone dipropionate – 0.05% fluorocinonide – 0.05% halcinonide</td>
<td>Diprosone®</td>
<td>Lides, Topsyngel® Lyderm® Halog®</td>
</tr>
<tr>
<td>Extremely Potent</td>
<td>x12</td>
<td>clobetasol propionate – 0.05% (most potent) betamethasone dipropionate ointment halobetasol propionate – 0.05%</td>
<td>Dermovate®</td>
<td>Diprolene® Ultravate®</td>
</tr>
</tbody>
</table>

SPF = burn time with cream/burn time without cream

UV Radiation

UVA (320-400 nm): Aging
• Penetrates skin more effectively than UVB or UVC
• Responsible for tanning, burning, wrinkling, photodamage and premature skin aging
• Penetrates clouds, glass and is reflected off water, snow and cement

UVB (290-320 nm): Burning
• Absorbed by the outer dermis
• Is mainly responsible for burning and premature skin aging
• Primarily responsible for BCC, SCC
• Does not penetrate glass and is substantially absorbed by ozone

UVC (200-290 nm)
• Is filtered by ozone layer

Body Site:
Relative Percutaneous Absorption
Forearm 1.0
Plantar foot 0.14
Palm 0.83
Back 1.7
Scalp 3.7
Forehead 6.0
Cheeks 13.0
Scrotum 42.0

Surface Area
30 g covers full adult body once. Children have a greater surface area/volume ratio and there are consequently greater side effects

Side Effects of Topical Steroids
• Local: atrophy, perioral dermatitis, steroid acne, rosacea, contact dermatitis, tachyphylaxis (tolerance), telangiectasia, striae, hypertrichosis, hypopigmentation
• Systemic: suppression of HPA axis
## Table 26. Common Topical Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol (Devonex®)</td>
<td>0.005% cream, ointment, scalp solution, apply bid For maintenance therapy apply OD</td>
<td>Psoriasis</td>
<td>Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk &gt;14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)</td>
</tr>
<tr>
<td>Imiquimod (Aldara®)</td>
<td>5% cream applied 3x/wk Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water Max duration 16 wks</td>
<td>Genital warts Cutaneous warts AK Superficial BCC</td>
<td>Avoid natural/artificial UV exposure Local skin and application site reactions Erythema, ulceration, edema, flu-like symptoms Works best for warts on mucosal surfaces May induce inflammation and erosion</td>
</tr>
<tr>
<td>Permethrin (Kwellada® P Lotion and Nix® Dermal Cream)</td>
<td>1% or 5% cream, applied once overnight to all skin areas from neck down, repeated one week later</td>
<td>Scabies (Kwellada P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)</td>
<td>Do not use in children &lt; 2 yr Hypersensitivity to drug, or known sensitivity to chrysanthemums Local reactions only (resolve rapidly); including burning, pruritus Low toxicity, excellent results Consider second application after 7 d</td>
</tr>
<tr>
<td>Pimecrolimus (Eidel®)</td>
<td>1% cream bid Use for as long as lesions persist and discontinue upon resolution of symptoms</td>
<td>AD (mild to moderate)</td>
<td>Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive</td>
</tr>
<tr>
<td>Tacrolimus Topical (Protopic®)</td>
<td>0.03% (children) or 0.1% (adults) ointment bid Continue for duration of disease PLUS 1 wk after clearing</td>
<td>AD (mild to moderate)</td>
<td>Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive</td>
</tr>
</tbody>
</table>

## Table 27. Common Oral Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin (Soriatane®)</td>
<td>25-50 mg PO OD; maximum 75 mg/d</td>
<td>Severe psoriasis Other disorders of hyperkeratization (ichthyosis, Darier’s disease)</td>
<td>Monitoring strategies Monitor lipids, LF Ts at baseline and q1-2wk until stable Contraindications Women of childbearing potential unless strict contraceptive requirements are met</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Famiclovir (Famvir®) 250 mg PO tid x 7-10 d (for 1st episode of genital herpes) 125 mg PO bid x 5 d (for recurrent genital herpes)</td>
<td>Chickenpox Herpes zoster Genital herpes Acute and prophylactic to reduce transmission in infected patients Herpes labialis</td>
<td>Side effects Headache, nausea, diarrhea, abdominal pain Reduce dose if impaired renal function</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir (Valtrex®) 1000 mg PO bid x 7-10 d (for 1st episode of genital herpes) 500 mg PO bid x 5 d (for recurrent genital herpes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (Neoral®)</td>
<td>2.5-4 mg/kg/d PO divided bid Max 4 mg/kg/d After 4 wk may increase by 0.5 mg/kg q2wks Concomitant dose of magnesium may protect the kidneys</td>
<td>Psoriasis May also be effective in: Lichen planus EM Recalcitrant urticaria Recalcitrant AD</td>
<td>Monitoring strategies Blood pressure, renal function Contraindications Abnormal renal function, uncontrolled hypertension, malignancy (except NMSC), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug Long-term effects preclude use of cyclosporine for &gt;2 yr; discontinue earlier if possible May consider rotating therapy with other drugs to minimize adverse effects of each drug</td>
</tr>
<tr>
<td>Dapsone</td>
<td>50-100-150 mg PO OD tapering to 25-50 mg PO OD to as low as 50 mg 2x/wk</td>
<td>Dermatitis herpetiformis, neutrophilic dermatoses</td>
<td>Monitoring strategies Obtain GSPD levels before initiating; in the initial two wk obtain methemoglobin levels and follow the blood counts carefully for the first few months Side effects Neutropathy Hemolysis (Vitamin C and E supplementation can help prevent this) Drug interactions Substrate of CYP2C8 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major) Often a dramatic response within hours</td>
</tr>
</tbody>
</table>
### Table 27. Common Oral Therapies (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxycycline</strong></td>
<td>50 mg PO bid</td>
<td>Acne vulgaris, Rosacea, Bullous pemphigoid</td>
<td>Contraindications: Pregnancy, hepatic impairment, drug hypersensitivity. Taking acitretin, isotretinoin, or penicillin antibiotic. Oral typhoid vaccine.</td>
</tr>
<tr>
<td><strong>Isotretinoin</strong></td>
<td>0.5-1 mg/kg/d given OD to achieve a total dose of 120 mg/kg (20-24 wk)</td>
<td>Severe nodular and/or inflammatory acne, Acne conglobata, Recalcitrant acne, Widespread comedonal acne</td>
<td>Monitoring strategies: Baseline lipid profile and LFTs before treatment, β-hCG. Contraindications: Teratogenic – in sexually active females, 2 forms of reliable contraception necessary. Generally regarded as unsafe in lactation. Side effects: Decreased night vision, decreased tolerance to contact lenses, dry mucous membranes. May transiently exacerbate acne, dry skin. Depression, myalgia. Drug interactions: Caution if used at the same time as tetracycline family antibiotics – both may cause pseudotumour cerebri. Discontinue vitamin A supplements.</td>
</tr>
<tr>
<td><strong>Itraconazole</strong></td>
<td>100-400 mg PO OD, depending on infection</td>
<td>Onychomycosis, Tinea corporis, cruris, versicolor, Toenails: 200 mg PO bid x 7 d once per month, repeated 2x</td>
<td>Monitoring strategies: Baseline renal, liver, and hematological studies. Contraindications: CHF. Side effects: Serious hepatotoxicity. Drug Interactions: Inhibits CYP3A4. Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs).</td>
</tr>
<tr>
<td><strong>Ivermectin</strong></td>
<td>200-250 µg/kg PO qweekly x 2</td>
<td>Onchocerciasis (USA only) Not licensed for use in Canada. Also effective for: scabies</td>
<td>No significant serious side effects. Efficacious.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>10-25 mg qwk, PO, IM, or IV. Max: 30 mg/vk. To minimize side effects, administer with folic acid supplementation: 1-5 mg OD</td>
<td>Psoriasis, AD, Lymphomatoid papulosis. May also be effective in: cutaneous sarcoidosis.</td>
<td>Monitoring strategies: Baseline renal, liver, and hematological studies. Contraindications: Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug. Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy. May be combined with cyclosporine to allow lower doses of both drugs.</td>
</tr>
<tr>
<td><strong>OCPs</strong></td>
<td>1 pill PO once daily</td>
<td>Hormonal acne (chin, jawline). Acne associated with polycystic ovarian syndrome or other endocrine abnormalities.</td>
<td>All combined OCPs are helpful in acne but those listed on the left have undergone RCTs. Contraindications: Smoking, HTN, migraines with aura, pregnancy. Routine gynecological health maintenance should be up to date.</td>
</tr>
<tr>
<td><strong>Spironolactone</strong></td>
<td>50-100 mg PO OD alone or with OCPs</td>
<td>Hormonal acne (chin, jawline). Acne with endocrine abnormality.</td>
<td>Contraindications: Pregnancy. Side effects: Menstrual irregularities at higher doses if not on OCPs. Breast tenderness, mild diuresis common. Risk of hyperkalemia – counsel patients to reduce intake of potassium rich foods such as bananas.</td>
</tr>
<tr>
<td><strong>Terbinafine</strong></td>
<td>250 mg PO OD x 2 wk. Fingernails x 6 wk. Toenails x 12 wk. Confirm diagnosis prior to treatment</td>
<td>Onychomycosis, Tinea corporis, cruris, pedis, versicolor, capitis.</td>
<td>Contraindications: Pregnancy, chronic or active liver disease. Drug interactions: Potent inhibitor of CYP2D6; use with caution when also taking β-blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics. Drug concentrates rapidly in skin, hair, and nails at levels associated with fungicidal activity.</td>
</tr>
<tr>
<td><strong>Tetracycline</strong></td>
<td>250-500 mg PO bid to tid; Taken 1 h before or 2 h after a meal</td>
<td>Acne vulgaris, Rosacea, Bullous pemphigoid.</td>
<td>Contraindications: Severe renal or hepatic dysfunction.</td>
</tr>
</tbody>
</table>
References


DeStefano RC, Kemp SH. Allergic reactions to drugs and biologic agents. JAMA 1999;279:1895-1906.


Raymous JC, Stevens-Johnson syndrome and toxic epidermal necrolysis are severe variants of the same disease which differs from erythema multiforme. J Dermatol 1997;24:726-729.


Vindal JD, Grichnik J M. The rational clinical examination. Does this patient have a mole or a melanoma? JAMA 1999;279:696-701.


<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronyms</td>
<td>2</td>
</tr>
<tr>
<td>Patient Assessment/Management</td>
<td>2</td>
</tr>
<tr>
<td>1. Rapid Primary Survey</td>
<td></td>
</tr>
<tr>
<td>2. Resuscitation</td>
<td></td>
</tr>
<tr>
<td>3. Secondary Survey</td>
<td></td>
</tr>
<tr>
<td>Ethical Considerations</td>
<td></td>
</tr>
<tr>
<td>Traumatology</td>
<td>7</td>
</tr>
<tr>
<td>Considerations for Traumatic Injury</td>
<td></td>
</tr>
<tr>
<td>Head Trauma</td>
<td></td>
</tr>
<tr>
<td>Mild Traumatic Brain Injury</td>
<td></td>
</tr>
<tr>
<td>Spine and Spinal Cord Trauma</td>
<td></td>
</tr>
<tr>
<td>Chest Trauma</td>
<td></td>
</tr>
<tr>
<td>Abdominal Trauma</td>
<td></td>
</tr>
<tr>
<td>Genitourinary Tract Injuries</td>
<td></td>
</tr>
<tr>
<td>Orthopedic Injuries</td>
<td></td>
</tr>
<tr>
<td>Wound Management</td>
<td></td>
</tr>
<tr>
<td>Approach to Common ED Presentations</td>
<td>18</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td>Acute Pelvic Pain</td>
<td></td>
</tr>
<tr>
<td>Altered Level of Consciousness</td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Joint and Back Pain</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Shortness of Breath</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>Sexual Assault</td>
<td></td>
</tr>
<tr>
<td>Medical Emergencies</td>
<td>28</td>
</tr>
<tr>
<td>Anaphylaxis and Allergic Reactions</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Cardiac Dysrhythmias</td>
<td></td>
</tr>
<tr>
<td>Acute Exacerbation of COPD (AECOPD)</td>
<td></td>
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<tr>
<td>Acute Decompensated Heart Failure (ADHF)</td>
<td></td>
</tr>
<tr>
<td>Venous Thromboembolism (VTE)</td>
<td></td>
</tr>
<tr>
<td>Diabetic Emergencies</td>
<td></td>
</tr>
<tr>
<td>Electrolyte Disturbances</td>
<td></td>
</tr>
<tr>
<td>Hypertensive Emergencies</td>
<td></td>
</tr>
<tr>
<td>Acute Coronary Syndrome (ACS)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Stroke and TIA</td>
<td></td>
</tr>
<tr>
<td>Otolaryngological Presentations and Emergencies</td>
<td>39</td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
</tr>
<tr>
<td>Gynecologic/Urologic Emergencies</td>
<td>40</td>
</tr>
<tr>
<td>Vaginal Bleeding</td>
<td></td>
</tr>
<tr>
<td>Pregnant Patient in the ED</td>
<td></td>
</tr>
<tr>
<td>Nephrolithiasis (Renal Colic)</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic Emergencies</td>
<td>42</td>
</tr>
<tr>
<td>Dermatologic Emergencies</td>
<td>43</td>
</tr>
<tr>
<td>Environmental Injuries</td>
<td>45</td>
</tr>
<tr>
<td>Heat Exhaustion and Heat Stroke</td>
<td></td>
</tr>
<tr>
<td>Hypothermia and Cold Injuries</td>
<td></td>
</tr>
<tr>
<td>Burns</td>
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</tr>
<tr>
<td>Inhalation Injury</td>
<td></td>
</tr>
<tr>
<td>Bites</td>
<td></td>
</tr>
<tr>
<td>Near Drowning</td>
<td></td>
</tr>
<tr>
<td>Toxicology</td>
<td>49</td>
</tr>
<tr>
<td>“ABCD: EFG” of Toxicology</td>
<td></td>
</tr>
<tr>
<td>D1 – Universal Antidotes</td>
<td></td>
</tr>
<tr>
<td>D2 – Draw Bloods</td>
<td></td>
</tr>
<tr>
<td>D3 – Decontamination and Enhanced Elimination</td>
<td></td>
</tr>
<tr>
<td>E – Expose and Examine the Patient</td>
<td></td>
</tr>
<tr>
<td>F – Full Vitals, ECG Monitor, Foley, X-Rays</td>
<td></td>
</tr>
<tr>
<td>G – Give Specific Antidotes and Treatments</td>
<td></td>
</tr>
<tr>
<td>Alcohol Related Emergencies</td>
<td></td>
</tr>
<tr>
<td>Approach to the Overdose Patient</td>
<td></td>
</tr>
<tr>
<td>Disposition from the Emergency Department</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Emergencies</td>
<td>56</td>
</tr>
<tr>
<td>Approach to Common Psychiatric Presentations</td>
<td></td>
</tr>
<tr>
<td>Acute Psychosis</td>
<td></td>
</tr>
<tr>
<td>Suicidal Patient</td>
<td></td>
</tr>
<tr>
<td>Common Pediatric ED Presentations</td>
<td>57</td>
</tr>
<tr>
<td>Modified Glasgow Coma Score</td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td></td>
</tr>
<tr>
<td>Febrile Infant and Febrile Seizures</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td>Common Infections</td>
<td></td>
</tr>
<tr>
<td>Child Abuse and Neglect</td>
<td></td>
</tr>
<tr>
<td>Common Medications</td>
<td>60</td>
</tr>
<tr>
<td>References</td>
<td>62</td>
</tr>
</tbody>
</table>
### Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>abd minal aortic aneurysm</td>
</tr>
<tr>
<td>ABC</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>ACS</td>
<td>acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AED</td>
<td>automatic external defibrillator</td>
</tr>
<tr>
<td>AEI</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>AG</td>
<td>anoxia/acidosis</td>
</tr>
<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AVN</td>
<td>avascular necrosis</td>
</tr>
<tr>
<td>AVPU</td>
<td>alert, voice, pain, unresponsive</td>
</tr>
<tr>
<td>AVXR</td>
<td>abdominal X-ray</td>
</tr>
<tr>
<td>Bi-PAP</td>
<td>bilevel positive airway pressure</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CAS</td>
<td>Child's Aid Society</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CVA</td>
<td>costovertebral angle</td>
</tr>
<tr>
<td>CXR</td>
<td>chest X-ray</td>
</tr>
<tr>
<td>D&amp;C</td>
<td>dilatation and curettage</td>
</tr>
<tr>
<td>DGI</td>
<td>disseminated gonococcal infection</td>
</tr>
<tr>
<td>DIC</td>
<td>disseminated intravascular coagulation</td>
</tr>
<tr>
<td>DKA</td>
<td>diabetic ketoacidosis</td>
</tr>
<tr>
<td>DRE</td>
<td>digital rectal exam</td>
</tr>
<tr>
<td>DT</td>
<td>delirium tremens</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>ED</td>
<td>emergency department</td>
</tr>
<tr>
<td>EM</td>
<td>erythema multiforme</td>
</tr>
<tr>
<td>ETT</td>
<td>endotracheal tube</td>
</tr>
<tr>
<td>FAST</td>
<td>focused abdominal sonogram for trauma</td>
</tr>
<tr>
<td>FFP</td>
<td>fresh frozen plasma</td>
</tr>
<tr>
<td>GERD</td>
<td>gastroesophageal reflux disease</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>HI</td>
<td>head injury</td>
</tr>
<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>IBS</td>
<td>irritable bowel syndrome</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>ICS</td>
<td>intercostal space</td>
</tr>
<tr>
<td>JVP</td>
<td>jugular venous pressure</td>
</tr>
<tr>
<td>LBBB</td>
<td>left bundle branch block</td>
</tr>
<tr>
<td>LOC</td>
<td>level of consciousness</td>
</tr>
<tr>
<td>LP</td>
<td>lumbar puncture</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MDI</td>
<td>metered dose inhaler</td>
</tr>
<tr>
<td>MVC</td>
<td>motor vehicle collision</td>
</tr>
<tr>
<td>NG</td>
<td>nasogastric</td>
</tr>
<tr>
<td>NS</td>
<td>normal saline</td>
</tr>
<tr>
<td>N/V</td>
<td>nausea and vomiting</td>
</tr>
<tr>
<td>OD</td>
<td>oral daily</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>PID</td>
<td>pelvic inflammatory disease</td>
</tr>
<tr>
<td>PNS</td>
<td>parasympathetic nervous system</td>
</tr>
<tr>
<td>POG</td>
<td>plasma osmolar gap</td>
</tr>
<tr>
<td>pRBC</td>
<td>packed red blood cells</td>
</tr>
<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
</tr>
<tr>
<td>RPS</td>
<td>rapid sequence induction</td>
</tr>
<tr>
<td>RSI</td>
<td>rapid sequence induction</td>
</tr>
<tr>
<td>TAC</td>
<td>tricuspid anterynergic</td>
</tr>
<tr>
<td>TAC</td>
<td>venous thromboembolism</td>
</tr>
</tbody>
</table>

### Patient Assessment/Management

#### 1. Rapid Primary Survey

- Airway maintenance with C-spine control
- Breathing and ventilation
- Circulation (pulses, hemorrhage control)
- Disability (neurological status)
- Exposure (complete) and Environment (temperature control)
  - continually reassessed during secondary survey
  - changes in hemodynamic and/or neurological status necessitates a return to the primary survey beginning with airway assessment
- IMPORTANT: Always watch for signs of shock while doing primary survey
- address ng the “ABCs” is the hallmark of the emergency department
  - in the setting of cardiac arrest, the approach changes to “CABs”: chest compressions, airway, and breathing

##### A. AIRWAY

- first priority is to secure airway
- assume a cervical injury in every trauma patient and immobilize with collar
- assess ability to breathe and speak
- can change rapidly, therefore reassess frequently
- assess for facial fractures/edema/burns (impending airway collapse)

**Airway Management**

- anatomic optimization to allow for oxygenation and ventilation

1. Basic Airway Management

- protect the C-spine
- head-tilt (if C-spine injury not suspected) or jaw thrust to open the airway
- sweep and suction to clear mouth of foreign material

2. Temporizing Measures

- nasopharyngeal airway (if gag reflex present i.e. conscious)
- orotracheal airway (if gag reflex absent i.e. unconscious)
- “rescue” airway devices (e.g. laryngeal mask airway, Combitube®)
- transtracheal jet ventilation through cricothyroid membrane (last resort)

3. Definitive Airway Management

- ETT intubation with in-line stabilization of C-spine
  - orotracheal ± RSI preferred
  - nasotracheal may be tolerated in conscious patient
  - relatively contraindicated with basilar skull fracture
  - does not provide 100% protection against aspiration
- surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
- cricothyroidotomy

**Contraindications to Intubation**

- supraglottic/glottic pathology that would preclude successful intubation
**Breathing**

- **Look**
  - mental status (anxiety, agitation, decreased LOC), colour, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring
- **Listen**
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping
- **Feel**
  - tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

**Breathing Assessment**

- objective measures of respiratory function: rate, oximetry, ABG, A-a gradient

**Management of Breathing**

- nasal prongs → simple face mask → non-rebreather mask → CPAP/BiPAP (in order of increasing FiO₂)
- Bag-Valve mask and CPAP to supplement inadequate ventilation

**Circulation**

**Definition of Shock**

- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities)

**Causes of Shock**

- Septic, spinal/neurogenic
- Hemorrhagic
- Obstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
- Cardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)
- Endocrine (e.g. Addison’s, myxedema, coma)
- Drugs

**Table 1. Major Types of Shock**

<table>
<thead>
<tr>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Distributive (vasodilation)</th>
<th>Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage (external and internal)</td>
<td>Myocardial ischemia</td>
<td>Septic</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Severe burns</td>
<td>Dysrhythmias</td>
<td>Anaphylactic</td>
<td>Tension pneumothorax</td>
</tr>
<tr>
<td>High output fistulas</td>
<td>CHF</td>
<td>Neurogenic (spinal cord injury)</td>
<td>PE</td>
</tr>
<tr>
<td>Dehydration (diarrhea, DKA)</td>
<td>Cardiomyopathies</td>
<td>Aortic stenosis</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Cardiac valve problems</td>
<td></td>
<td>Constrictive pericarditis</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Evaluation**

- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities, and reduced central venous pressure
- late: hypotension and altered mental status, reduced urine output

**Table 2. Estimation of Degree of Hemorrhagic Shock**

<table>
<thead>
<tr>
<th>Class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Loss</td>
<td>&lt;750 cc</td>
<td>750-1,500 cc</td>
<td>1,500-2,000 cc</td>
<td>&gt;2,000 cc</td>
</tr>
<tr>
<td>% of Blood Volume</td>
<td>&lt;15%</td>
<td>15-30%</td>
<td>30-40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>&gt;120</td>
<td>&gt;140</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>20</td>
<td>30</td>
<td>35</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Capillary Refill</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Urinary Output</td>
<td>30 cc/h</td>
<td>20 cc/h</td>
<td>10 cc/h</td>
<td>None</td>
</tr>
<tr>
<td>Fluid Replacement</td>
<td>Crystalloid</td>
<td>Crystalloid</td>
<td>Crystalloid + blood</td>
<td>Crystalloid + blood</td>
</tr>
</tbody>
</table>

**Figure 1. Approach to endotracheal intubation in an injured patient**

BREATHING

- Look
  - mental status (anxiety, agitation, decreased LOC), colour, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring
- Listen
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping
- Feel
  - tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

**Breathing Assessment**

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C. CIRCULATION

**Definition of Shock**

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**Causes of Shock**

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- Hemorrhagic
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- Cardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)
- Endocrine (e.g. Addison’s, myxedema, coma)
- Drugs

**Estimated Systolic Blood Pressure Based on Position of Most Distal Palpable Pulse**

<table>
<thead>
<tr>
<th>sBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial</td>
</tr>
<tr>
<td>Femoral</td>
</tr>
<tr>
<td>Carotid</td>
</tr>
</tbody>
</table>

*Note: clearing the C spine requires radiologic and clinical assessment*
Management of Hemorrhagic Shock

- clear airway and breathing either first or simultaneously
- apply direct pressure on external wounds while elevating ex remities. Do not remove impaled objects in the emergency room setting as they may tamponade bleeds
- start TWO LARGE BORE (14-16G) IVs in the brachial/cephalic vein of each arm
- run 1-2 L bolus of IV Normal Saline/Ringer’s Lactate (warmed, if possible)
- if continual bleeding or no response to crystalloids, consider PRBC transfusion, ideally crossmatched. If crossmatched blood is unavailable, consider O- for women of childbearing age and O+ for men. Use FFP, platelets or tranexamic acid in early bleeding
- consider common sites of internal bleeding (abdomen, chest, pelvis, long bones) where surgical intervention may be necessary

D. DISABILITY

- assess LOC using GCS
- pupils
  - assess equality, size, symmetry, reactivity to light
  - inequality/sluggish suggests local eye problem or lateralizing CNS lesion
  - relative afferent pupillary defect (swinging light test) – optic nerve damage
  - extraocular movements and nystagmus
  - fundoscopy (papilledema, hemorrhages)
  - reactive pupils + decreased LOC: metabolic or structural cause
  - non-reactive pupils + decreased LOC: structural cause (especially if asymmetric)

Glasgow Coma Scale

- for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- most useful if repeated; change in GCS with time is more relevant than the absolute number
- less meaningful for metabolic coma
- patient with deteriorating GCS needs immediate attention
- prognosis based on best post-resuscitation GCS
- reported as a 3 part score: Eyes + Verbal + Motor = Total
- if patient intubated, GCS score reported out of 10 + T (T = tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eyes Open</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously</td>
<td>4 Answers questions appropriately</td>
<td>5 Obey commands</td>
</tr>
<tr>
<td>To voice</td>
<td>3 Confused, disoriented</td>
<td>4 Localizes to pain</td>
</tr>
<tr>
<td>To pain</td>
<td>2 Inappropriate words</td>
<td>3 Withdraws from pain</td>
</tr>
<tr>
<td>No response</td>
<td>1 Incomprehensible sounds</td>
<td>2 Decorticate (flexion)</td>
</tr>
<tr>
<td></td>
<td>No verbal response</td>
<td>1 Decerebrate (extension)</td>
</tr>
</tbody>
</table>

3:1 Rule
Since only 30% of infused isotonic crystalloids remains in intravascular space, you must give 3x estimated blood loss

Fluid Resuscitation

- Give bolus until HR decreases, urine output increases, and patient stabilizes
- Maintenance: 4:2:1 rule
  - 0-10 kg: 4 cc/kg/h
  - 10-20 kg: 2 cc/kg/h
  - Remaining weight: 1 cc/kg/h
- Replace ongoing losses and deficits (assume 10% of body weight)

E. EXPOSURE/ENVIRONMENT

- expose patient completely and assess entire body for injury; log roll to examine back
- DRE
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

2. Resuscitation

- done concurrently with primary survey
- attend to ABCs
- manage life-threatening problems as they are identified
- vital signs q5-15 min
- ECG, BP, and O2 monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type
### Table 4. 2010 AHA CPR Guidelines

<table>
<thead>
<tr>
<th>Step/Action</th>
<th>Adult: &gt;8 yr</th>
<th>Child: 1-8 yr</th>
<th>Infant: &lt;1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>Head tilt-chin lift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breaths</td>
<td>2 breaths at 1 s/breath – stop once see chest rise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign-Body Airway Obstruction</td>
<td>Abdominal thrust</td>
<td>Back slaps and chest thrusts</td>
<td></td>
</tr>
</tbody>
</table>

#### Compressions

- **Compression landmarks**
  - In the centre of the chest, between nipples
  - Just below nipple line
- **Compression method:** push hard and fast, and allow for complete recoil
  - 2 hands: heel of 1 hand with second hand on top
  - 2 hands: heel of 1 hand with second on top, or 1 hand: heel of 1 hand only
  - 2 fingers, or thumbs
- **Compression depth**
  - 2-2.4 inches
  - About ½ to ½ the depth of the chest
- **Compression rate**
  - 100-120/min with complete chest wall recoil between compressions
- **Compression-ventilation ratio**
  - 30 compressions to 2 ventilations
- **Compression-only CPR**
  - Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only

#### Defibrillation

- Immediate defibrillation for all rescuers responding to a sudden witnessed collapse
- Compressions (5 cycles/2 min) before AED is considered if unwitnessed arrest
- Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available

### 3. Secondary Survey

- done after primary survey once patient is hemodynamically and neurologically stabilized
- identifies major injuries or areas of concern
- full physical exam and x-rays (C-spine, chest, and pelvis – required in blunt trauma, consider T-spine and L-spine if indicated)

**HISTORY**

- "SAMPLE": Signs and symptoms, Allergies, Medications, Past medical history, Last meal, Events related to injury

---

![Figure 2: Four areas of a FAST](https://via.placeholder.com/150)
PHYSICAL EXAM

Head and Neck
• palpation of facial bones, scalp

Chest
• inspect for: 1. midline trachea and 2. flail segment: ≥2 rib fractures in ≥2 places; if present look for associated hemothorax, pneumothorax, and contusions
• auscultate lung fields
• palpate for subcutaneous emphysema

Abdomen
• assess for peritonitis, abdominal distention, and evidence of intra-abdominal bleeding
• DRE for GI bleed, high riding prostate, and anal tone

Musculoskeletal
• examine all extremities for swelling, deformity, contusions, tenderness, ROM
• check for pulses (using Doppler probe) and sensation in all injured limbs
• log roll and palpate thoracic and lumbar spines
• palpate iliac crests and pubic symphysis and assess pelvic stability (lateral, AP, vertical)

Neurological
• GCS
• full cranial nerve exam
• alterations of rate and rhythm of breathing are signs of structural or metabolic abnormalities with progressive deterioration in breathing indicating a failing CNS
• assess spinal cord integrity
• conscious patient: assess distal sensation and motor function
• unconscious patient: response to painful or noxious stimulus applied to extremities

INITIAL IMAGING
• non-contrast CT head/face/C-spine (rule out fractures and bleeds)
• chest x-ray
• FAST (see Figure 2) or CT abdomen/pelvis (if stable)
• pelvis x-ray

Ethical Considerations

Consent to Treatment: Adults
• see Ethical, Legal, and Organizational Medicine, ELOM7
• Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury AND obtaining consent is either: a) not possible, OR b) would increase risk to the patient
  • assumes that most people would want to be saved in an emergency
  • any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
  • exceptions to the Emergency Rule – treatment cannot be initiated if
    • a competent patient has previously refused the same or similar treatment and there is no evidence to suggest the patient’s wishes have changed
    • an advanced directive is available (e.g. do not resuscitate order)
  • NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
  • if in doubt, initiate treatment
  • care can be withdrawn if necessary at a later time or if wishes are clarified by family

Consent to Treatment: Children
• treat immediately if patient is at imminent risk
• parents/guardians have the right to make treatment decisions
• if parents refuse treatment that is life-saving or will potentially alter the child’s quality of life, CAS must be contacted – consent of CAS is needed to treat

Other Issues of Consent
• need consent for HIV testing, as well as for administration of blood products
• however, if delay in substitute consent for blood transfusions puts patient at risk, transfusions can be given

Duty to Report
• law may vary depending on province and/or state
• examples: gunshot wounds, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others
Traumatology

- **epidemiology**
  - leading cause of death in patients <45 yr
  - 4th highest cause of death in North America
  - causes more deaths in children/adolescents than all diseases combined

- **trimodal distribution of death**
  - minutes: death usually at the scene from lethal injuries
  - early: death within 4-6 h – “golden hour” (decreased mortality with trauma care)
  - days-weeks: death from multiple organ dysfunction, sepsis, etc

- **injuries fall into two categories**
  - blunt (most common): MVC, pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  - penetrating (increasing in incidence): gunshot wound, stabbing, impalement

Considerations for Traumatic Injury

- important to know the mechanism of injury to anticipate traumatic injuries
- always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- always inquire about HI, loss of consciousness, amnesia, vomiting, headache, and seizure activity

<table>
<thead>
<tr>
<th>Table 5. Mechanisms and Considerations of Traumatic Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Injury</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>MVC</td>
</tr>
<tr>
<td>Pedestrian-Automobile Impact</td>
</tr>
<tr>
<td>Falls</td>
</tr>
</tbody>
</table>

Head Trauma

- see Neurosurgery, NS30
- 60% of MVC-related deaths are due to HI

Specific Injuries

- fractures
  - Dx: non-contrast head CT and physical exam
  - A. skull fractures
    - vault fractures
      - linear, non-depressed
        - most common
        - typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
    - depressed
      - open (associated overlying scalp laceration and torn dura, skull fracture disrupting paranasal sinuses or middle ear) vs. closed
    - basal skull fractures
      - typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
      - clinical diagnosis superior as poorly visualized on CT
  - B. facial fractures (see Plastic Surgery, PL31)
    - neuronal injury
    - beware of open fracture or sinus fractures (risk of infection)
    - severe facial fractures may pose risk to airway from profuse bleeding

Signs of Basal Skull Fracture

- Battle’s sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF rhinorrhea/otorrhea

Cardiac Box: sternal notch, nipples, and xiphoid process; injuries inside this area should increase suspicion of cardiac injury

High Risk Injuries

- MVC at high speed, resulting in ejection from vehicle
- Motorcycle collisions
- Vehicle vs. pedestrian crashes
- Fall from height >12 ft (3.6 m)

Vehicle vs. Pedestrian Crash

In adults look for triad of injuries (Waddle’s triad)

- Tibia-fibula or femur fracture
- Truncal injury
- Craniofacial injury

Always completely expose and count the number of wounds
scalp laceration
- can be a source of significant bleeding
- achieve hemostasis, inspect and palpate for skull bone defects ± CT head (rule-out skull fracture)

neuronal injury
A. diffuse
- mild TBI = concussion
- transient alteration in mental status that may involve loss of consciousness
- hallmarks of concussion: confusion and amnesia, which may occur immediately after the trauma or minutes later
- loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h
- diffuse axonal injury
  - mild: coma 6-24 h, possibly lasting deficit
  - moderate: coma >24 h, little or no signs of brainstem dysfunction
  - severe: coma >24 h, frequent signs of brainstem dysfunction
B. focal injuries
- contusions
- intracranial hemorrhage (epidural, subdural, intracerebral)

ASSESSMENT OF BRAIN INJURY

History
- pre-hospital status
- mechanism of injury

Physical Exam
- assume C-spine injury until ruled out
- vital signs
  - shock (not likely due to isolated brain injury, except in infants)
  - Cushing’s response to increasing ICP (bradycardia, HTN, irregular respiration)
- severity of injury determined by
  1. LOC
    - GCS ≤8 intubate, any change in score of 3 or more = serious injury
    - mild TBI = 13-15, moderate = 9-12, severe = 3-8
  2. pupils: size anisocoria >1 mm (in patient with altered LOC), response to light
  3. lateralizing signs (motor/sensory)
    - may become subtler with increasing severity of injury
- reassess frequently

Investigations
- labs: CBC, electrolytes, PT/PTT or INR/PTT, glucose, toxicology screen
- CT scan head and neck (non-contrast) to exclude intracranial hemorrhage/hematoma
- C-spine imaging

Management
- goal in ED: reduce secondary injury by avoiding hypoxia, ischemia, decreased CPP, seizure
- general
  - ABCs
  - ensure oxygen delivery to brain through intubation and prevent hypercarbia
  - maintain BP (sBP >90)
  - treat other injuries
- early neurosurgical consultation for acute and subsequent patient management
- seizure treatment/prophylaxis
  - benzodiazepines, phenytoin, phenobarbital
  - steroids are of no proven value
- treat suspected raised ICP, consider if HI with signs of increased ICP:
  - intubate
  - calm (sedate) if risk for high airway pressures or agitation
  - paralyze if agitated
  - hyperventilate (100% O₂) to a pCO₂ of 30-35 mmHg
  - elevate head of bed to 20°
  - adequate BP to ensure good cerebral perfusion
  - diurese with mannitol 1g/kg infused rapidly (contraindicated in shock/renal failure)

Disposition
- neurosurgical ICU admission for severe HI
- in hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
- for minor HI not requiring admission, provide 24 h HI protocol to competent caregiver, follow-up with neurology as even seemingly minor HI may cause lasting deficits

Warning Signs of Severe Head Injury
- GCS <8
- Deteriorating GCS
- Unequal pupils
- Lateralizing signs

N.B. Altered LOC is a hallmark of brain injury

Canadian CT Head Rule
Lancet 2001;357:1391-96
CT Head is only required for patients with minor HI with any one of the following
High Risk (for neurological intervention)
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, “raccoon” eyes, CSF otorrhea/rhinorrhea, Battle’s sign)
- Vomiting ≥2 episodes
- Age ≥65 yr
Medium Risk (for brain injury on CT)
- Amnesia before impact >30 min (i.e. cannot recall events just before impact)
- Dangerous mechanism (pedestrian struck by MVC, occupant ejected from motor vehicle, fall from height >3 ft or five stairs)

Minor HI is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

NB: Canadian CT Head Rule does not apply for non-trauma cases, for GCS<13, age <16, for patients on Coumadin® and/or having a bleeding disorder, or having an obvious open skull fracture.
**Mild Traumatic Brain Injury**

**Epidemiology**
- TBI results in 1.7 million deaths, hospitalizations, and ED visits each year (US)
- 75% are estimated to be mild TBI; remainder are moderate or severe (see *Neurosurgery*, NS30)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

**Clinical Features**
- somatic: headache, sleep disturbance, N/V, blurred vision
- cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
- emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils

**Etiology**
- falls, MVC, struck by an object, assault, sports

**Investigations**
- neurological exam
- concussion recognition tool (see thinkfirst.ca)
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

**Treatment**
- close observation and follow-up; for patients at risk of intracranial complications, give appropriate discharge instructions to patient and family; watch for changes to clinical features above, and if change, return to ED
- hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
- early rehabilitation to maximize outcomes
- pharmacological management of pain, depression, headache
- follow Return to Play guidelines

**Prognosis**
- most recover with minimal treatment
- athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life-threatening cerebral edema or permanent impairment

**Spine and Spinal Cord Trauma**
- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck, or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (see Figure 1)
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

**History**
- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

**Physical Exam**
- ABCs
- abdominal: ecchymosis, tenderness
- neurological: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; log roll, then palpate T-spine and L-spine, assess rectal tone
  - when palpating, assess for tenderness, muscle spasm, bony deformities, step-off, and spinous process malalignment
  - extremities: check capillary refill, suspect thoracolumbar injury with calcaneal fractures

**Investigations**
- bloodwork: CBC, electrolytes Cr, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - full C-spine x-ray series for trauma (AP, lateral, odontoid)
  - thoracolumbar x-rays
  - AP and lateral views
• indications
  • C-spine injury
  • unconscious patients (with appropriate mechanism of injury)
  • neurological symptoms or findings
  • deformities that are palpable when patient is log rolled
  • back pain
  • bilateral calcaneal fractures (due to fall from height)
  – concurrent burst fractures of the lumbar or thoracic spine in 10% (T11-L2)
  • consider CT (for subtle bony injuries), MRI (for soft tissue injuries) if appropriate

**Approach to clearing the C-spine**

**Suspected C-Spine Injury**

**History:** midline neck pain, numbness or paresthesia, presence of distracting pain, head injury, intoxication, loss of consciousness or past history of spinal mobility disorder

**Physical exam:** posterior neck spasm, tenderness or crepitus; any neurologic deficit or autonomic dysfunction, altered mental state

1. Plain x-rays, 3 views
   - Normal films
   - Abnormal films
   1. Flexion/extension films
   2. MRI
   - Normal neurological exam
   - Abnormal neurological exam
   - C-spine cleared

2. CT scan if
   - C-spine cleared
   - Neck pain
   1. Normal films
   2. Abnormal films
   - C-spine cleared
   - MRI

**Management of Cord Injury**

- immobilize
- evaluate ABCs
- treat neurogenic shock (maintain sBP >100 mmHg)
- insert NG and Foley catheter
- high dose steroids: methylprednisolone 30 mg/kg bolus, then 5.4 mg/kg/h drip, start within 6-8 h of injury (controversial and recently has less support)
- complete imaging of spine and consult spine service if available
- continually reassess high cord injuries as edema can travel up cord
- if cervical cord lesion, watch for respiratory insufficiency
  - low cervical transsection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact but loss of innervation of intercostals and other accessory muscles of breathing)
  - high cervical cord injury (above C4) may require intubation and ventilation
- treatment: warm blanket, Trendelenburg position (occasionally), volume infusion, consider vasopressors

**Approach to C-Spine X-Rays**

- 3-view C-spine series is the screening modality of choice
  1. lateral C1-T1 ± swimmer’s view
  2. odontoid view (open mouth or oblique submental view)
- examine the dens for fractures
  - if unable to rule out fracture, repeat view or consider CT or plain film tomography
- examine lateral aspects of C1 and spacing relative to C2

---

**The Canadian C-Spine Rule**

*JAMA* 2001;286:1841-48

For Alert (GCS Score = 15) and Stable Trauma Patients where C-Spine Injury is a Concern

1. Any high-risk factor that mandates radiography?
   - Age <65 yr
   - Dangerous mechanism
   - Paralysis in extremities
   - No
   - Radiography

2. Any low-risk factor that allows safe assessment of ROM?
   - Simple rear-end MVC
   - Sitting postion in ED
   - Ambulatory at any time
   - Delayed onset of neck pain
   - Absence of midline C-spine tenderness
   - No
   - No radiography

3. Able to actively rotate neck?
   - >45º left and right
   - Yes
   - No radiography

*Dangerous Mechanism:
  • Fall from ≥1 meter/5 stairs
  • Axial load to head (e.g. diving)
  • MVC >60 km/h, rollover, ejection
  • Motorized recreational vehicles
  • Bicycle collision

Simple rear-end MVC excludes:
- Pushed into oncoming traffic
- Hit by bus/long truck
- Robber
- Hit by high-speed vehicle
- Delayed: not immediate onset of neck pain

---

**Lines of contour on a lateral C-spine x-ray**

© Kim Auchinachie

1. Anterior vertebral line
2. Posterior vertebral line (anterior margin of spinal canal)
3. Posterior border of facets
4. Laminar fusion line (posterior margin of spinal canal)
5. Posterior spinous line (along tips of spinous processes)

Prevertebral soft tissue swelling is only 49% sensitive for injury
3. AP view

- alignment of spinous processes in the midline
- spacing of spinous processes should be equal
- check vertebral bodies and facet dislocations

Table 6. Interpretation of Lateral View: The ABCS

<table>
<thead>
<tr>
<th>A</th>
<th>Adequacy and Alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must see C1 to C7-T1 junction; if not, downward traction of shoulders, swimmer’s view, bilateral supine obliques, or CT scan needed</td>
<td></td>
</tr>
<tr>
<td>Lines of contour in children &lt; 8 yr of age, can see physiologic subluxation of C2 on C3, and C3 on C4, but the spino-laminal line is maintained</td>
<td></td>
</tr>
<tr>
<td>Fanning of spinous processes suggests posterior ligamentous disruption</td>
<td></td>
</tr>
<tr>
<td>Widening of facet joints</td>
<td></td>
</tr>
<tr>
<td>Line extending inferiorly from clivus should transect odontoid</td>
<td></td>
</tr>
<tr>
<td>Atlanto-axial articulation, widening of predental space (normal: &lt; 3 mm in adults, &lt; 5 mm in children) indicates injury of C1 or C2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Bones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, width, and shape of each vertebral body</td>
<td></td>
</tr>
<tr>
<td>Pedicles, facets, and laminae should appear as one – doubling suggests rotation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>Cartilage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S</th>
<th>Soft Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widening of retropharyngeal (normal: &lt; 7 mm at C1-4, may be wide in children &lt; 2 yr on expiration) or retrotracheal spaces (normal: &lt; 22 mm at C6-T1, &lt; 14 mm in children &lt; 5 yr)</td>
<td></td>
</tr>
</tbody>
</table>

Sequelaes of C-Spine Fractures

- see Neurosurgery, NS34
- acute phase of SCI
  - spinal shock: absence of all voluntary and reflex activity below level of injury
  - decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
  - neurogenic shock: loss of vasomotor tone, SNS tone
  - watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
  - occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
  - provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
- chronic phase of SCI
  - autonomic dysreflexia: in patients with an SCI at level T6 or above
  - signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
  - common triggers:
    - GU causes: bladder distention, urinary tract infection, and kidney stones
    - GI causes: fecal impaction or bowel distension
  - treatment: monitoring and controlling BP, prior to addressing causative issue

Chest Trauma

- two types: those found and managed in 1° survey and those found and managed in 2° survey

Table 7. Life-Threatening Chest Injuries Found in 1° Survey

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway Obstruction</td>
<td>Anxiety, stridor, hoarseness, altered mental status, Apnea, cyanosis</td>
<td>Do not wait for ABG to intubate</td>
</tr>
<tr>
<td>Tension Pneumothorax</td>
<td>Respiratory distress, tachycardia, distended neck veins, cyanosis, asymmetry of chest wall motion</td>
<td>Non-radiographic diagnosis</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>One-way valve causing accumulation of air in pleural space</td>
<td>Percussion hyperresonance, Unilateral absence of breath sounds</td>
</tr>
</tbody>
</table>
Penetrating Neck Trauma
- includes all penetrating trauma to the three zones of the neck
- management: injuries deep to platysma require further evaluation by angiography, contrast CT, or surgery
- do not explore penetrating neck wounds except in the OR
Airway Injuries
• always maintain a high index of suspicion
• larynx
  - history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma
  - triad: hoarseness, subcutaneous emphysema, palpable fracture
  - other symptoms: hemoptysis, dyspnea, dysphonia
  - investigations: CXR, CT scan, arteriography (if penetrating)
  - management
    - airway: manage early because of edema
    - C-spine may also be injured, consider mechanism of injury
    - surgical: tracheotomy vs. repair
• trachea/bronchus
  - frequently missed
  - history: deceleration, penetration, increased intra-thoracic pressure, complaints of dyspnea, hemoptysis
  - examination: subcutaneous air, Hamman's sign (crunching sound synchronous with heart beat)
  - CXR: mediastinal air, persistent pneumothorax or persistent air leak after chest tube inserted for pneumothorax
  - management: surgical repair if >1/3 circumference

Abdominal Trauma
• two mechanisms
  - blunt: usually causes solid organ injury (spleen = most common, liver = 2nd)
  - penetrating: usually causes hollow organ injury or liver injury (most common)

BLUNT TRAUMA
• results in two types of hemorrhage: intra-abdominal and retroperitoneal
• adopt high clinical suspicion of bleeding in multi-system trauma

History
• mechanism of injury, SAMPLE history

Physical Exam
• often unreliable in multi-system trauma, wide spectrum of presentations
  - slow blood loss not immediately apparent
  - tachycardia, tachypnea, oliguria, febrile, hypotension
  - other injuries may mask symptoms
  - serial examinations are required
• abdomen
  - inspect: contusions, abrasions, seat-belt sign, distention
  - auscultate: bruises, bowel sounds
  - palpate: tenderness, rebound tenderness, rigidity, guarding
  - DRE: rectal tone, blood, bone fragments, prostate location
  - placement of NG, Foley catheter should be considered part of the abdominal exam
  - other systems to assess: cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

Investigations
• labs: CBC, electrolytes, coagulation, cross and type, glucose, Cr, CK, lipase, amylase, liver enzymes, ABG, blood EtOH, β-hCG, U/A, toxicology screen

Table 9. Imaging in Abdominal Trauma
<table>
<thead>
<tr>
<th>Imaging</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td>Chest (looking for free air under diaphragm, diaphragmatic hernia, air-flu d levels), pelvis, cervical, thoracic, lumbar spines</td>
<td>Soft tissue not well visualized</td>
</tr>
<tr>
<td>CT Scan</td>
<td>Most specific test</td>
<td>Radiation exposure 20x more than x-ray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cannot use if hemodynamic instability</td>
</tr>
<tr>
<td>Diagnostic Peritoneal</td>
<td>Most sensitive test Tests for intra-peritoneal bleed</td>
<td>Cannot test for retroperitoneal bleed or diaphragmatic rupture</td>
</tr>
<tr>
<td>Lavage (rarely used)</td>
<td></td>
<td>Cannot distinguish lethal from trivial bleed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results can take up to 1 h</td>
</tr>
<tr>
<td>Ultrasound: FAST</td>
<td>Identities presence/absence of free fluid in peritoneal cavity</td>
<td>NOT used to identify specific organ injuries If patient has ascites, FAST will be falsely positive</td>
</tr>
<tr>
<td></td>
<td>RAPID exam: less than 5 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can also examine pericardium and pleural cavities</td>
<td></td>
</tr>
</tbody>
</table>

If Penetrating Neck Trauma Present, DON'T:
• clamp structures (can damage nerves)
• probe
• insert NG tube (leads to bleeding)
• remove weapon/impaled object

Criteria for Positive Lavage
• ≥10 cc gross blood
• bile, bacteria, foreign material
• RBC count >100,000 x 10^6/L
• WBC >500 x 10^3/L
• Amylase >175 IU

Seatbelt Injuries May Cause
• Retroperitoneal duodenal trauma
• Intraperitoneal bowel transection
• Mesenteric injury
• L spine injury

Indications for Foley and NG Tube in Abdominal Trauma
Foley catheter: unconscious or patient with multiple injuries who cannot void spontaneously or is unconscious NG tube: used to decompress the stomach and proximal small bowel. Contraindicated if suspected facial or basal skull fractures

Figure 6. Zones of the neck in trauma
imaging must be done if:
- equivocal abdominal examination, altered sensorium, or distracting injuries (e.g. head trauma, spinal cord injury resulting in abdominal anesthesia)
- unexplained shock/hypotension
- patients have multiple traumas and must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
- fractures of lower ribs, pelvis, spine
- positive FAST

Management
- general: ABCs, fluid resuscitation, and stabilization
- surgical: watchful waiting vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion of injury: admit and observe for 24 h

**Penetrating Trauma**
- high risk of gastrointestinal perforation and sepsis
- history: size of blade, calibre/distance from gun, route of entry
- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  - thoracoabdominal region (may cause pneumothorax)
  - back or flanks (muscles too thick)

Management
- general: ABCs, fluid resuscitation, and stabilization
- gunshot wounds always require laparotomy

**Genitourinary Tract Injuries**
- see Urology, U32

Etiology
- blunt trauma: often associated with pelvic fractures
  - upper tract
    - renal
      - contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
      - parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
    - ureter: rare, at uretero-pelvic junction
  - lower tract
    - bladder
      - extraperitoneal rupture of bladder from pelvic fracture fragments
      - intraperitoneal rupture of bladder from trauma and full bladder
    - urethra
      - posterior urethral injuries: MVCs, falls, pelvic fractures
      - anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
  - external genitalia
  - penetrating trauma
    - damage to: kidney, bladder, ureter (rare), external genitalia
  - acceleration/deceleration injury
    - renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
  - iatrogenic
    - ureter and urethra (from instrumentation)

History
- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension

Physical Exam
- abdominal pain, flank pain, CVA tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen
- urethral injury: perineal ecchymosis, scrotal hematoma, blood at penile meatus, high riding prostate, pelvic fractures

Laparotomy is Mandatory if Penetrating Trauma and:
- shock
- peritonitis
- evisceration
- free air in abdomen
- blood in NG tube, Foley catheter, or on DRE

“Rule of Thirds” for Stab Wounds
- 1/3 do not penetrate peritoneal cavity
- 1/3 penetrate but are harmless
- 1/3 cause injury requiring surgery

Gross hematuria suggests bladder injury
Investigations
• urethra: retrograde urethrography
• bladder: U/A, CT scan, urethrogram ± retrograde cystoscopy ± cystogram (distended bladder + post-void)
• ureter: retrograde ureterogram
• renal: CT scan (best, if hemodynamically stable), intravenous pyelogram

Management
• urology consult
• renal
  • minor injuries: conservative management
    • bedrest, hydration, analgesia, antibiotics
  • major injuries: admit
    • conservative management with frequent reassessments, serial U/A ± re-imaging
    • surgical repair (exploration, nephrectomy): hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis
• ureter
  • ureteroureterostomy
• bladder
  • extraperitoneal
    • minor rupture: Foley drainage x 10-14 d
    • major rupture: surgical repair
  • intraperitoneal
    • drain abdomen and surgical repair
• urethra
  • anterior: conservative, if cannot void, Foley or suprapubic cystostomy and antibiotics
  • posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair

Orthopedic Injuries
• see Orthopedics (see Shoulder OR10, Knee OR31, Wrist OR20, Ankle OR37)

Goals of ED Treatment
• diagnose potentially life/limb threatening injuries
• reduce and immobilize fractures (cast/splint) as appropriate
• provide adequate pain relief
• arrange proper follow-up if necessary

History
• use SAMPLE, mechanism of injury may be very important

Physical Exam
• look (inspection): “SEADS” swelling, erythema, atrophy, deformity, and skin changes (e.g. bruises)
• feel (palpation): all joints/bones for local tenderness, swelling, warmth, crepitus, joint effusions, and subtle deformity
• move: joints affected plus those above and below injury – active ROM preferred to passive
• neurovascular status: distal to injury (before and after reduction)

LIFE- AND LIMB-THREATENING INJURIES

Table 10. Life- and Limb-Threatening Orthopedic Injuries

<table>
<thead>
<tr>
<th>Life-Threatening Injuries (usually blood loss)</th>
<th>Limb-Threatening Injuries (usually interruption of blood supply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major pelvic fractures</td>
<td>Fracture/dislocation of ankle (talar AVN)</td>
</tr>
<tr>
<td>Traumatic amputations</td>
<td>Crush injuries</td>
</tr>
<tr>
<td>Massive long bone injuries and associated fat emboli syndrome</td>
<td>Compartment syndrome</td>
</tr>
<tr>
<td>Vascular injury proximal to knee/elbow</td>
<td>Open fractures</td>
</tr>
<tr>
<td></td>
<td>Dislocations of knee/hip</td>
</tr>
<tr>
<td></td>
<td>Fractures above knee/elbow</td>
</tr>
</tbody>
</table>

Open Fractures
• communication between fracture site and external surface of skin – increased risk of osteomyelitis
• remove gross debris, irrigate cover with sterile dressing – formal irrigation and debridement often done in the OR
• control bleeding with pressure (no clamping)
• splint
• antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
• standard of care is to secure definitive surgical management within 6 h, time to surgery may vary from case-to-case
Vascular Injuries
- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

Compartment Syndrome
- when the intracompartmental pressure within an anatomical area (e.g. forearm or lower leg) exceeds the capillary perfusion pressure, eventually leading to muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - tense compartment
  - look for “the 6 Ps” (note radial pulse pressure is 120/80 mmHg while capillary perfusion pressure is 30 mmHg, seeing any of the 6ps indicates advanced compartment syndrome, therefore do not wait for these signs to diagnose and treat)
- requires prompt decompression: remove constrictive casts, dressing; emergent fasciotomy may be needed

UPPER EXTREMITY INJURIES
- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
  - reduce (traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with orthopedics
  - with forceful injury, look for fracture
- Colles’ fracture
  - distal radius fracture with dorsal displacement from “Fall on Outstretched Hand” (FOOSH)
  - AP film: shortening, radial deviation, radial displacement
  - lateral film: dorsal displacement, volar angulation
  - reduce, immobilize with splint, out-patient follow-up with orthopedics or immediate orthopedic referral if complicated fracture
  - if involvement of articular surface, emergent orthopedic referral
- scaphoid fracture
  - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
  - negative x-ray: thumb spica splint, repeat x-ray in 1 wk ± CT scan/bone scan
  - positive x-ray: thumb spica splint x 6-8 wk, repeat x-ray in 2 wk
  - risk of AVN of scaphoid if not immobilized
  - outpatient orthopedics follow-up

LOWER EXTREMITY INJURIES
- ankle and foot fractures
  - see Ottawa Ankle and Foot Rules
- knee injuries
  - see Ottawa Knee Rules
  - avulsion of the base of 5th metatarsal
  - occurs with inversion injury
  - supportive tensor or below knee walking cast for 3 wk
- calcaneal fracture
  - associated with fall from height
  - associated injuries may involve ankles, knees, hips, pelvis, lumbar spine

A knee x-ray examination is required only for acute injury patients with one or more of:
- Age 55 yr or older
- Tenderness at head of fibula
- Isolated tenderness of patella
- Inability to flex to 90°
- Inability to bear weight both immediately and in the ED (four steps)

Figure 7. Colles’ fracture

Figure 8. Carpal bones

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Figure 9. Ottawa knee rules
Adapted from: Stiell IG, et al. JAMA 1997;278:2075-2079
Wound Management

Goals of ED Treatment
• identify injuries and stop any active bleeding – direct pressure
• manage pain
• wound examination and exploration (history and physical)
• cleansing ± antibiotic and tetanus prophylaxis
• closure and dressing

Tetanus Prophylaxis
• both tetanus toxoid (Td) and immunoglobulin (TIG) are afe in pregnancy

Table 11 Guidelines for Tetanus Prophylaxis for Wounds

<table>
<thead>
<tr>
<th>Vaccination History</th>
<th>Clean, Minor Wounds</th>
<th>All Other Wounds*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown or fewer than 3 doses</td>
<td>Tdap or Td⁰</td>
<td>TIG</td>
</tr>
<tr>
<td>3 or more doses</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite

Tdap is preferred to Td for adults who have never received Tdap. Single antigen tetanus toxoid (TT) is no longer available in the United States

Yes, if more than ten years since the last tetanus toxoid-containing vaccine dose

Yes, if more than five years since the last tetanus toxoid-containing vaccine dose


Bruises
• non-palpable = ecchymosis
• palpable collection (not swelling) = hematoma following blunt trauma
• assess for coagulopathy (e.g. liver disease), anticoagulant use

Abrasions
• partial to full thickness break in skin
• management
• clean thoroughly with brush to prevent foreign body impregnation ± local anesthetic antisepptic ointment (Polysporin* or Vaseline*) for 7 d for facial and complex abrasions
• tetanus prophylaxis

Lacerations
• see Plastic Surgery, PL8
• consider every structure deep to a laceration injured until proven otherwise
• in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury

An ankle radiographic series is required only if there is any pain in malleolar zone and any of these findings:
1. Bony tenderness at A or
2. Bony tenderness at B or
3. Inability to bear weight both immediately and in ED

A radiographic series is required only if there is any pain in midfoot zone and any of these findings:
1. Bony tenderness at C or
2. Bony tenderness at D or
3. Inability to bear weight both immediately and in ED

Suture Use and Duration

<table>
<thead>
<tr>
<th>Suture to:</th>
<th>Close with Nylon or Other Non-absorbable Suture</th>
<th>Approx. Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>6-0</td>
<td>5</td>
</tr>
<tr>
<td>Not Joint</td>
<td>4-0</td>
<td>7</td>
</tr>
<tr>
<td>Joint</td>
<td>3-0</td>
<td>10</td>
</tr>
<tr>
<td>Scalp</td>
<td>4-0</td>
<td>7</td>
</tr>
</tbody>
</table>

Mucous Membrane absorbable (vicryl)/N/A

N.B. Patients on steroid therapy may need sutures for longer periods of time
• physical exam
  • think about underlying anatomy
  • examine tendon function actively against resistance and neurovascular status distally
  • clean and explore under local anesthetic; look for partial tendon injuries
  • x-ray or U/S wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radioopaque), or if suspect intra-articular involvement
• management
  • disinfect skin/use sterile techniques
  • irrigate copiously with normal saline
  • analgesia ± anesthetics
    • 7 mg/kg with epinephrine
    • 5 mg/kg without epinephrine
  • in children, topical anesthetics such as LET (lidocaine, epinephrine, and tetracaine), and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
  • secure hemostasis
  • evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
  • ± prophylactic antibiotics (consider for animal/human bites, intra-oral lesion, or puncture wounds to the foot)
  • suture unless: delayed presentation (>6-8 h), puncture wound, mammalian bite, crush injury, or retained foreign body
  • take into account patient and wound factors when considering suturing
  • advise patient when to have sutures removed
  • cellulitis and necrotizing fasciitis (see Plastic Surgery, PL15)

Approach to Common ED Presentations

Abdominal Pain

Table 12. Selected Differential Diagnosis of Abdominal Pain

<table>
<thead>
<tr>
<th>Emergent</th>
<th>Usually Less Emergent</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Perforated viscus, bowel obstruction, ischemic bowel, appendicitis, strangulated hernia, IBD flare, esophageal rupture, peptic ulcer disease</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Hepatic/splenic injury, pancreatitis, cholangitis spontaneous bacterial peritonitis</td>
</tr>
<tr>
<td>Genital</td>
<td>Female: Ovarian torsion, PID, ectopic pregnancy Male: Testicular torsion</td>
</tr>
<tr>
<td>Urinary</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>CVS</td>
<td>MI, aortic dissection AAA</td>
</tr>
<tr>
<td>Respiriology</td>
<td>PE, empyema</td>
</tr>
<tr>
<td>Metabolic</td>
<td>DKA, sickle cell crisis, toxin, Addisonian crisis</td>
</tr>
<tr>
<td>Other</td>
<td>Significant trauma, acute angle closure glaucoma</td>
</tr>
</tbody>
</table>

• differential can be focused anatomically by location of pain: RUQ, LUQ, RLQ, LLQ, epigastric, periumbilical, diffuse

History
• pain: OPQRST
• review symptoms from GU, gynecological, GI, respiratory, and CV systems
• abdominal trauma/surgeries, most recent colonoscopy

Physical Exam
• vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and cardiac exams as indicated by history

Investigations
• ABCs, do not delay management and consultation if patient unstable
• labs: CBC, electrolytes, glucose, BUN/Cr, U/A ± liver enzymes, LFTs, lipase, β-hCG, ECG, troponins, ± VBG/lactate
• AXR: look for calcifications, free air, gas pattern, air fluid levels
• CXR upright: look for pneumoperitoneum (free air under diaphragm), lung disease
• U/S: biliary tract, ectopic pregnancy, AAA, free fluid
• CT: trauma, AAA, pancreatitis, nephro-/ureolithiasis appendicitis, and diverticulitis

Early wound irrigation and debridement are the most important factors in decreasing infection risk

Alternatives to Sutures
• Tissue glue
• Steristrips®
• Staples

Be vigilant: very young, elderly, alcoholics, immunosuppressed patients often present atypically
Old age, pregnancy (T3), and chronic corticosteroid use can blunt peritoneal findings, so have an increased level of suspicion for an intra-abdominal process in these individuals

Unstable patients should not be sent for imaging

If elevated AST and ALT
Think hepatocellular injury
AST > ALT: alcohol-related
ALT > AST: viral, drug, toxin

If elevated ALP and GGT
Think biliary tree obstruction
**Management**
- NPO, IV, NG tube, analgesics, consider antibiotics and anti-emetics
- growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: general surgery, vascular surgery, gynecology, etc

**Disposition**
- admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develops

---

**Acute Pelvic Pain**

**Etiology**
- gynecological
  - ovaries: ruptured ovarian cysts (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass)
  - fallopian tubes: salpingitis, tubal abscess, hydrosalpinx
  - uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in a pregnant patient (degeneration), PID, endometriosis
  - other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), endometriosis and dysmenorrhea, sexual or physical abuse non-gynecological (see causes of lower abdominal pain above)

**History and Physical Exam**
- pain: OPQRST
- associated symptoms: vaginal bleeding, discharge, dyspareunia, bowel and/or bladder symptoms
- pregnancy and sexual history
- vitals
- gynecological exam: assess for cervical motion tenderness/"chandelier sign" (suggests PID)
- abdominal exam

**Investigations**
- β-hCG for all women of childbearing age
- CBC and differential, electrolytes, glucose, Cr, BUN, G&S, PTT/INR
- urinalysis to rule out urologic causes
- vaginal and cervical swabs for C&S during physical exam
- pelvic and abdominal U/S: evaluate adnexa, thickness of endometrium, pregnancy, free fluid or masses in the pelvis
- Doppler flow studies for ovarian torsion

**Management**
- general: analgesia, determine if admission and consults are needed
- specific:
  - ovarian cysts
    - unruptured or ruptured, and hemodynamically stable: analgesia and follow-up
    - ruptured with significant hemoperitoneum: may require surgery
  - ovarian torsion: surgical detorsion or removal of ovary
  - uncomplicated leiomyomas, endometriosis, and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  - PID: broad spectrum antibiotics

**Disposition**
- referral: gynecological or obstetrical causes requiring surgical intervention, requiring admission, or oncological in nature
- admission: patients requiring surgery, IV antibiotics/pain management
- discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

---

**Altered Level of Consciousness**

**Definitions**
- altered mental status: collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness, including:
  - delirium (see Psychiatry, PS19)
  - dementia (see Psychiatry, PS20)
  - lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  - stupor: unresponsiveness but rousable
  - coma: a sleep-like state, not rousable to consciousness
MANAGEMENT OF ALTERED LOC

History
- obtain collateral from family, friends, police, paramedics, old chart, MedicAlert® bracelet, etc.
- onset and progression
  - antecedent trauma, seizure activity, fever
  - abrupt onset suggests CNS hemorrhage/schemia or cardiac cause
  - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- determine patient's baseline LOC
- past medical history (e.g. similar episode(s), depression, overdose)

Physical Exam
- ABCs, vitals including temperature; cardiac, respiratory, abdominal exams
- complete neurological exam; in particular, examination of the eyes ("PEARL" pupils equal and reactive to light)
- use the GCS to evaluate LOC (see Initial Patient Assessment/Management, ER2)

Investigations
- blood work
  - rapid blood sugar, CBC, electrolytes, Cr, BUN, LFTs, glucose, serum osmolality, VBG, PT/PTT/INR, troponins
  - serum EtOH, acetaminophen, and salicylate levels
- imaging
  - CXR, CT head
- other tests
  - ECG, U/A, UTox

Diagnosis
- administer appropriate universal antidotes
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished
  - one ampule D50W IV if hypoglycemic on finger-prick
  - naloxone 0.4-2 mg IV or IM if opiate overdose suspected
- distinguish between structural and toxic-metabolic coma
  - structural coma
    - pupils, extracocular movements, and motor findings, if present, are usually asymmetric
    - look for focal or lateralizing abnormalities
  - toxic-metabolic coma
    - dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
    - respiratory depression in association with an intact upper brainstem (e.g. equal and reactive pupils; see exceptions in Table 13)
    - extracocular movements and motor findings are symmetric or absent
- essential to re-examine frequently because status can change rapidly
- diagnosis may become apparent only with the passage of time
  - delayed deficit after head trauma suggestive of epidural hematoma (characteristic "lucid interval")
Table 13. Toxic-Metabolic Causes of Fixed Pupils

<table>
<thead>
<tr>
<th>Dilated</th>
<th>Dilated to Normal</th>
<th>Constricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anoxia</td>
<td></td>
<td>Cholinergic agents (e.g. organophosphates)</td>
</tr>
<tr>
<td>Anticholinergic agents (e.g. atropine, TCAs)</td>
<td>Hyperthermia</td>
<td></td>
</tr>
<tr>
<td>Methanol (rare)</td>
<td>Barbiturates</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Opioid withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinogens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disposition
- admission: if ongoing decreased LOC, admit to service based on tentative diagnosis, or transfer patient if appropriate level of care not available
- discharge: readily reversible alteration of LOC; ensure adequate follow-up care available

Table 14. Differential Diagnosis for Chest Pain

<table>
<thead>
<tr>
<th>Emergent</th>
<th>Usually Less Emergent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>MI, unstable angina, aortic dissection, cardiac tamponade, arrhythmia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>PE, pneumothorax</td>
</tr>
<tr>
<td>GI</td>
<td>Esophageal rupture, pneumomediastinum</td>
</tr>
<tr>
<td>MSK</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

History and Physical Exam
- OPQRST, previous episodes and change in pattern
- cardiac risk factors (HTN, DM, dyslipidemia, smoking, FHx)
- vitals, cardiac, respiratory, peripheral vascular, abdominal exams

Investigations
- CBC, electrolytes, Cr, BUN, glucose, PTT/INR, cardiac biomarkers (troponins, CK)
- ECG: always compare with previous; may be normal in up to 50% of PE and acute MI
- CXR: compare with previous
- CT: if indicated (e.g. aortic dissection, PE)

Management and Disposition
- ABCs, O2, cardiac monitors, IV access
- treat underlying cause and involve consultants as necessary
- consider further observation/monitoring if unclear diagnosis or risk of dysrhythmia
- discharge: patients with a low probability of life-threatening illness due to resolving symptoms and negative workup; arrange follow-up and instruct to return if SOB or increased chest pain develops

Life-Threatening Causes of Chest Pain
- PET MAP
- PE
- Esophageal rupture
- Tamponade
- MI/angina
- Aortic dissection
- Pneumothorax

Imaging is necessary for all suspected aortic dissections, regardless of BP

Angina Characteristics
- 1. Retrosternal location
- 2. Provoked by exertion
- 3. Relieved by rest or nitroglycerin

Risk for CAD
- 3/3 = "typical angina" - high risk
- 2/3 = intermediate risk for women >50 yr, all men
- 1/3 = Intermediate risk in men >40 yr, women >60 yr
### Table 15. Comparison of Chest Pain Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Classic History</th>
<th>Classic Findings</th>
<th>Diagnostic Investigations</th>
<th>Management and Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Coronary Syndrome</strong></td>
<td>New or worsening pattern of retrosternal squeezing/pressure pain, radiation to arm/neck, dyspnea, worsened by exercise, relieved by rest. N/V, syncope</td>
<td>New or worsened murmur, hypotension, diaphoresis pulmonary edema</td>
<td>ECG: ischemia (15-lead if hypotensive, AV node involvement or inferior MI), serial troponin I (sensitive 6-8 h after onset), CK-MB, CK</td>
<td>ABCs, aspirin, anticoagulation and emergent cardiology consult to consider percutaneous intervention or thrombolytic</td>
</tr>
<tr>
<td><strong>Pulmonary Embolism</strong></td>
<td>Pleuritic chest pain (75%), dyspnea; risk factors for venous thromboembolism</td>
<td>Tachycardia, hypoxemia; evidence of DVT</td>
<td>Wells’ criteria: D-dimer, CT pulmonary angiogram*, V/G scan, leg Doppler, CXR</td>
<td>ABCs, anticoagulation; consider airway management and thrombolysis if respiratory failure</td>
</tr>
<tr>
<td><strong>Aortic Dissection</strong></td>
<td>Sudden severe tearing retrosternal or midscapular pain ± focal pain/neurologic loss in extremities in context of HTN</td>
<td>HTN; systolic BP difference &gt; 20 mmHg or pulse deficit between arms; aortic regurgitant murmur</td>
<td>CT angiography; CXR: PA, lateral, expiratory views — lung edge, loss of lung markings, tracheal shift; deep sulcus sign on supine view</td>
<td>ABCs, rule out MI, high dose NSAIDs ± colchicine; consult if chronic/recurrent or non-viral cause (e.g. SLE, renal failure, requires surgery)</td>
</tr>
<tr>
<td><strong>Cardiac Tamponade</strong></td>
<td>Dyspnea, cold extremities, ± chest pain; often a recent cardiac intervention or symptoms of malignancy, connective tissue disease</td>
<td>Beck’s triad — hypotension, elevated JVP, muffled heart sounds; tachycardia, pulsus paradoxus &gt; 10 mmHg</td>
<td>Clinical diagnosis: CXR: PA, lateral, expiratory views — lung edge, loss of lung markings, tracheal shift; deep sulcus sign on supine view</td>
<td>ABCs, cardiac surgery consult; pericardiocentesis if unstable, treat underlying cause</td>
</tr>
<tr>
<td><strong>Esophageal Rupture</strong></td>
<td>Sudden onset severe pain after endoscopy, forceful vomiting, labour, or convulsion, or in context of corrosive injury or cancer</td>
<td>Subcutaneous empyema, findings consistent with sepsis</td>
<td>Clinical diagnosis: CXR: pleural effusion (75%), pneumomediastinum; CT or water soluble contrast esophagram</td>
<td>ABCs, early antibiotics, resuscitation, thoracics consult, NPO, consider chest tube</td>
</tr>
<tr>
<td><strong>Esophagitis or GERD</strong></td>
<td>Frequent heartburn, acid reflux, dysphagia, relief with antacids</td>
<td>None</td>
<td>None acutely</td>
<td>ABCs, PPI, avoid EOH, tobacco, trigger foods</td>
</tr>
<tr>
<td><strong>Herpes Zoster</strong></td>
<td>Abnormal skin sensation – itching/tingling/pain – preceding rash by 1-5 d</td>
<td>None if early; maculopapular rash developing into vesicles and pustules that crust</td>
<td>Clinical diagnosis; direct immunofluorescence assay</td>
<td>ABCs, anti-viral, analgesia ± steroids, dressing; r/o ocular involvement/refer if necessary</td>
</tr>
<tr>
<td><strong>MSK</strong></td>
<td>History of injury</td>
<td>Reproduction of symptoms with movement or palpation (not specific – present in 25% of MI)</td>
<td>MSK injury or fracture on X-rays</td>
<td>ABCs, NSAIDs, rest, orthopedics consultation for fractures</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>Symptoms of anxiety, depression, history of psychiatric disorder; may coexist with physical disease</td>
<td>Tachycardia, diaphoresis, tremor</td>
<td>Diagnosis of exclusion</td>
<td>ABCs, arrange social supports, rule out suicidality and consider psychiatry consult</td>
</tr>
</tbody>
</table>

*Addition of Clopidogrel to Aspirin® and Fibinolytic Therapy for Myocardial Infarction with ST-Segment Elevation

NEJM 2005;352:1179–91

**Purpose:** To assess the benefit of adding clopidogrel to Aspirin® and fibrinolytic therapy in ST-elevation MI.

**Methods:** Double-blind, RCT of Individuals presenting within 12 h of onset of ST-elevation MI, comparing clopidogrel (300 mg loading dose followed by 75 mg QD until day of angiogram) versus placebo, in addition to Aspirin®, a fibrinolytic agent, and heparin when appropriate. Primary outcome was composite of occluded infarct-related artery on angiography (thrombosis in MI flow grade 0 or 1), or death or recurrent MI prior to angiography. Follow-up was to 30 days. Analysis was by intention to treat.

**Results:** 3,491 patients were included (mean age 57, 80.3% male, 50.3% smokers, 9.1% previous MI). Rates of the primary endpoint were 21.7% in the placebo group and 15.0% in the clopidogrel group (95% CI 24-47%). Among the individual components of the primary endpoint, clopidogrel had a significant effect on the rate of an occluded infarct-related artery and the rate of recurrent MI, but no effect on the rate of death from any cause. At 30 clinical follow-up, there was no difference in rate of death from cardiovascular causes, a significant reduction in the odds of recurrent MI, and a non-significant reduction in recurrent ischemia with need for urgent revascularization. The rates of major bleeding and intracranial hemorrhage were similar between the two groups.

**Conclusion:** Addition of clopidogrel improves the potency rate of infarct-related arteries and reduces ischemic complications, both of which are associated with improved long-term survival after MI. The trial was not powered to detect a survival benefit, and none was seen.

**Signs of PE on CXR**

**Westermark’s sign:** abrupt tapering of a vessel on chest film

**Hampton’s hump:** a wedge-shaped infiltrate that abuts the pleura

**Effusion, atelectasis, or infiltrates 50% normal**

**Tracheal deviation is away from tension or towards non-tension pneumothorax**
Table 16. Common Life-Threatening ECG Changes

<table>
<thead>
<tr>
<th>Pathology</th>
<th>ECG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysrhythmia</strong></td>
<td></td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>Ventricular complexes in upward-pointing and downward-pointing continuum (250-350 bpm)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>6 or more consecutive premature ventricular beats (150-250 bpm)</td>
</tr>
<tr>
<td>Ventricular flutter</td>
<td>Smooth sine wave pattern of similar amplitude (250-350 bpm)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>Erratic ECG tracing, no identifiable waves</td>
</tr>
<tr>
<td><strong>Conduction</strong></td>
<td></td>
</tr>
<tr>
<td>2nd degree heart block (Mobitz Type II)</td>
<td>PR interval stable, some QRSs dropped Total AV dissociation, but stable P-P and R-R intervals</td>
</tr>
<tr>
<td>3rd degree heart block</td>
<td>Prolonged QRS complex (&gt;0.12 s) RSR' in V5 or V6</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>Monophasic I and V6 May see ST elevation Difficult to interpret, new LBBB is considered STEMI equivalent</td>
</tr>
<tr>
<td><strong>Ischemia</strong></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression)</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Tall T waves</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>P wave flattening GRS complex widening and flattening U waves appear Flattened T waves</td>
</tr>
<tr>
<td><strong>Digitalis Toxicity</strong></td>
<td>Gradual downward curve of ST At risk for AV blocks and ventricular irritability</td>
</tr>
<tr>
<td><strong>Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>Brugada</td>
<td>RBBB with ST elevation in V1, V2, and V3 Susceptible to deadly dysrhythmias, including VFib</td>
</tr>
<tr>
<td>Wellens</td>
<td>Marked T wave inversion in V2 and V3 Left anterior descending coronary stenosis</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>QT interval longer than ½ of cardiac cycle Predisposed to ventricular dysrhythmias</td>
</tr>
</tbody>
</table>

**Headache**

- see Neurology, N44

**Etiology**

- **common and less serious**
  - common migraine (without aura)/classic migraine (with aura)
    - common: unilateral, throbbing, aggravated by activity, moderate/severe, N/V, photo-/phonophobia
    - classic: varied aura symptoms, e.g. flashing lights, pins and needles (paresthesia), loss of vision, dysarthria
    - abortive treatment: fluids, NSAIDs, antiepileptic drugs, vasoactive medications
    - family doctor to consider prophylactic treatment
  - tension/muscular headache
    - mild-moderate headache with gradual onset lasting minutes to days
    - bilateral-frontal or nuchal-occipital
    - increased with stress, sleep deprivation
    - treatment: modify stressor(s), local measures, NSAIDs, tricyclic antidepressants

- **less common but potentially fatal**
  - subarachnoid hemorrhage (SAH) (see Neurosurgery, NS18)
    - sudden onset, “worst headache of life,” maximum intensity within minutes
    - increased pain with exertion, N/V, meningeval signs
    - diagnosis
      - new generation CT 100% sensitive within 6 h of onset (hyperattenuating signal around Circle of Willis)
      - LP if suspected SAH and normal CT after 6 h
    - management: urgent neurosurgery consult

**Immediate Treatment of Acute MI**

BEMOAN
- β-blocker
- Enoxaparin
- Morphine
- Oxygen
- ASA
- Nitroglycerin

**Common Therapeutic Approach to Severe Migraine**

- 1 L bolus of NS
- prochlorperazine 10 mg IV
- diphenhydramine 25 mg IV
- ketorolac 30 mg IV
- dexamethasone 10 mg IV
- Other options include haloperidol, metoclopramide, ergotamine, sumatriptan, analgesics

**Ottawa SAH Rule**

JAMA 2013;310(12): 1248-55

- Use for alert patients older than 15 yr with new severe non-traumatic headache reaching maximum intensity within 1 h
- Not for patients with new neurologic deficits, previous aneurysms, SAH, brain tumours, or history of recurrent headaches (>3 episodes over the course of ≥6 mo)
- Investigate if ≥1 high-risk variables present:
  - Age ≥40 yr
  - Neck pain or stiffness
  - Witnessed loss of consciousness
  - Onset during exertion
  - Thunderclap headache (instantly peaking pain)
  - Limited neck flexion on examination
- Subarachnoid hemorrhage can be predicted with 100% sensitivity using this rule.

**Meningitis**

- Do not delay IV antibiotics for LP
- Deliver first dose of dexamethasone with or before first dose of antibiotic therapy
• increased ICP
• worse in morning, when supine or bending down, with cough or valsalva
• physical exam: neurological deficits, cranial nerve palsies, papilledema
• diagnosis: CT head
• management: consult neurosurgery
• meningitis (see Infectious Diseases, JD18)
• flu-like symptoms (fever, N/V, malaise), meningeal signs, petechial rash
• altered LOC and confusion
• rule out increased ICP; if CT head or normal mental status, no neurological signs and no papilledema, then do LP for diagnosis
• treatment: early empiric antibiotics ± acyclovir, steroid therapy
• temporal arthritis (causes significant morbidity, blindness) (see Ophthalmology, OP35)
• vasculitis of large and mid-sized arteries, gender 3:1 F:M, most commonly age >70 yr
• headache, scalp tenderness, jaw claudication, arthralgia, myalgia, fever, malaise or weight loss
• temporal artery tender on palpation, relative afferent pupillary defect (RAPD), optic disc edema on fundoscopy
• labs: elevated ESR, CRP
• temporal artery biopsy is gold standard for diagnosis
• associated with polymyalgia rheumatica
• treatment: high-dose steroids immediately if suspected, no need to hold treatment until pathology results

Disposition
• admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atyypical presentation), or if pain is refractory to oral medications
• discharge: assess for risk of narcotic misuse; most patients can be discharged with appropriate analgesia and follow-up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

Joint Pain and Back Pain

JOINT PAIN (see Rheumatology, RI3)

rule out life threatening causes: septic joint (see Orthopedics, OR10)

History and Physical Exam
• associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
• patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
• inflammatory symptoms: morning stiffness ≥30 min, pain/stiffness that ease with activity, midday fatigue, soft tissue swelling
• non-inflammatory symptoms: morning stiffness <30 min, stiffness short-lived after inactivity, increasing pain with activity
• assess ROM, localized joint pain, effusion, erythema, warmth, swelling with pain on active ROM, inability to bear weight, fever; may indicate presence of septic joint

Investigations
• blood work: CBC, ESR, CRP, WBC, INR/PTT, blood cultures, urate
• joint x-ray ± contralateral joint for comparison
• bedside US to identify effusion
• test joint aspirate for: WBC, protein, glucose, Gram stain, crystals

Management
• septic joint: IV antibiotics ± joint decompression and drainage
• antibiotics can be started empirically if septic arthritis cannot be ruled out
• crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids
• do not use allopurinol, as it may worsen acute attack
• acute polyarthritis: NSAIDs, analgesics (acetaminophen ± opioids), local or systemic corticosteroids
• osteoarthritis: NSAIDs, acetylsalicylic acid
• soft tissue pain: allow healing with enforced rest ± immobilization
• non-pharmacologic treatment: local heat or cold, electrical stimulation, massage
• pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

BACK PAIN (see Family Medicine, FM38)

rule out vascular emergencies: aortic dissection, AAA, PE, MI, retroperitoneal bleed
rule out spinal emergencies using red flags (see sidebar): osteomyelitis, cauda equina, epidural abscess or hematoma
evaluate risk for fracture (osteoporosis, age), infection (IV drug user recent spinal intervention, immunosuppression), cancer, vascular causes (cardiac risk factors)
typical benign back pain is moderate, dull, aching, worse with movement or cough
palpate spine for bony tenderness, precordial, respiratory, abdominal and neurological exams guided by history
reserve imaging for suspicion of emergencies, metastases, and patients at high risk of fracture, infection, cancer, or vascular causes

Which Patients can Safely Undergo Lumbar Percutaneous Needle Biopsy Without Screening CT?

Purpose: To investigate whether the absence of certain clinical features at baseline may be used to identify adults with suspected meningitis who are unlikely to have abnormal computed tomography (CT) findings.
Methods: Adults with suspected meningitis seen in the Emergency Department were prospectively studied. Baseline features for the following characteristics were collected: sociodemographic characteristics, co-existing conditions (based on Clarion clinically relevant), presence/absence of neuroimaging, specific clinical features, neurological abnormalities, laboratory results and management decisions. CT was performed, and results were interpreted in duplicate by staff radiologists and neuroradiologists aware of the patients' clinical findings.
Results: 351 adults with suspected meningitis were included, of which 235 underwent a CT head scan prior to a lumbar puncture. Baseline clinical features associated with abnormal CT findings were an age of 65 years or older, immunosuppressed state, history of current or previous cerebrovascular disease, and history of cancer or infection. On multivariate analysis, the following variables were identified as independent predictors of abnormal CT findings: age ≥ 70 years (OR: 2.57, 95% CI: 1.36 to 4.86), immunosuppression (OR: 2.64, 95% CI: 1.31 to 5.33) and recent infection (OR: 5.06, 95% CI: 2.31 to 10.93). The sensitivity of the CT head scan was normal in 89% of the 165 patients (negative predictive value 97%).
Conclusion: It is safe to avoid a CT scan in patients with selected clinical features who are unlikely to have abnormal CT findings.

Parenteral Dexamethasone for Preventing Recurrence of Acute Severe Migraine Headache
BMJ 2015;356:g4761

Purpose: To examine effectiveness of parenteral corticosteroids for the prevention of acute severe migraine headache and prevention of recurrent headaches.
Methods: Meta-analysis of RCTs comparing corticosteroids (alone or in combination with standard abortive therapy) to placebo or any other standard treatment for acute migraine in adults.
Results: Seven RCTs met eligibility criteria, all of which used standard abortive therapy and subsequently compared a single dose of parenteral dexamethasone to placebo. At trials examined pain relief and recurrence of headache within 72 h. All 7 trials demonstrated dexamethasone was associated with statistically significant reduction in pain relief at 2 h (OR: 0.37, 95% CI: 0.24 to 0.56) and side effect profiles, dexamethasone provided lower recurrence rates (relative risk 0.69, 95% CI: 0.60 to 0.80; number needed to treat 9).
Conclusion: Single dose parenteral dexamethasone is standard abortive therapy is associated with a 30% relative reduction in headache recurrence within 72 h.

CT Head within 6 h ± 100% Sensitivity for Diagnosis of Subarachnoid Hemorrhage (SAH)
BMJ 2012;343:d4277

Purpose: To measure the sensitivity of CT in emergency patients being evaluated for possible SAH, particularly when carried out within 6 h of headache onset.
Methods: A prospective multicentre cohort study was conducted in 11 tertiary and emergency departments across Canada to measure the sensitivity of CT head in the evaluation of ED patients for SAH. Neurologically intact adults were screened with a new onset non-traumatic headache meeting maximal intensity in less than one hour who had head CT as part of their diagnostic workup to rule out SAH were considered eligible. Patients were deemed positive for SAH if there was subarachnoid blood on CT, suturectomies in the C-spine or CT of blood cells in the final level of CFT collected. Some patients with normal results on CT received IV dexamethasone as a result of the treating physician's subjective judgment. Patients with a negative result on CT and a plausible cause for the headache identified through questioning patients were followed for six months to characterize their outcome. Primary outcome was CT results interpreted by a staff radiologist.
Results: 1,158 adults were enrolled (median age 45 yr; 1:2.57 (72.5%) reporting worst headache ever). Overall sensitivity of CT head within 6 h of headache onset was 93% (93% CI: 92% to 94%). Specificity was 99% (99% CI: 99% to 100%). Negative predictive value was 99.99% (99.99% CI: 99.98% to 100%). Positive predictive value was 99.99% (99.99% CI: 99.99% to 100%). For patients scanned within 6 h of symptom onset (n = 172), sensitivity was 99% (99% CI: 99% to 100%). Specificity was 100% (95% CI: 100% to 100%). Negative predictive value was 100% (99.99% CI: 100% to 100%) and positive predictive value was 100% (99.99% CI: 100% to 100%).
Conclusion: CT within 6 h is highly sensitive in identifying subarachnoid hemorrhage when it is causal and within 6 h after headache onset and interpreted by a qualified radiologist.
Management
• treat underlying cause
• lumbosacral spine and disc herniation: analgesia and continue daily activities as much as tolerated; discuss red flags and organize follow-up
• spinal infection: early IV antibiotics and ID consultation
• cauda equina: dexamethasone, early neurosurgical consultation

Seizures
• see Neurology, N18

Definition
• paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons
• status epilepticus: continuous or intermittent seizure activity for greater than 5 min without regaining consciousness (life threatening)

Categories
• generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
• partial seizure (focal): simple partial, complex partial
• causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP) metabolic disturbance (hypo-/hyperglycemia, hypo-/hypernatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
• differential diagnosis: syncope, pseudoseizures, migraines, movement disorders, narcolepsy/cataplexy, myoclonus

History
• from patient and bystander: flaccid and unconscious, often with deep rapid breathing
• preceding aura, rapid onset, loss of bladder/bowel control, tongue-biting (sides of the tongue)
• length of seizure and post-ictal symptoms (e.g. cognitive impairments, migraine, focal symptoms: aphasia, hemiparesis)

Physical Exam
• injuries to head and spine and bony prominences (e.g. elbows), tongue laceration, aspiration, urinary incontinence

Table 17 Concurrent Investigation and Management of Status Epilepticus

<table>
<thead>
<tr>
<th>Timing</th>
<th>Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>Protect airway with positioning; intubate if airway compromised or elevated ICP  Monitor: vital signs, ECG, oximetry; bedside blood glucose  Establish IV access  Benzodiazepine - IV lorazepam 0.1 mg/kg up to 4 mg/dose at 2 mg/min preferred over IV diazepam 0.15 mg/kg up to 10 mg/dose at 5 mg/min; repeat at 5 min if ineffective  Fluid resuscitation  Give 50 mL 50% glucose (preceded by thiamine 100 mg IM in adults)  Obtain blood samples for glucose, CBC, electrolytes, Ca++, Mg++, toxins, and antiepileptic drug levels; consider prolactin, β-hCG  Vasopressor support if sBP &lt; 90 or MAP &lt; 70 mmHg</td>
</tr>
<tr>
<td>Urgent</td>
<td>Establish second IV line, urinary catheter  If status persists, phenytoin 20 mg/kg IV at 25-50 mg/min in adults; may give additional 10 mg/kg IV 10 min after loading infusion  If seizure resolves, antiepileptic drug still required to prevent recurrence  EEG monitoring to evaluate for non-convulsive status epilepticus</td>
</tr>
<tr>
<td>Refractory</td>
<td>If status persists after maximum doses above, consult ICU and start one or more of:  Phenobarbital 20 mg/kg IV at 50 mg/min  Midazolam 0.2 mg/kg IV loading dose and 0.05-0.5 mg/kg/h  Propofol 2-5 mg/kg IV loading dose then 2-10 mg/kg/h</td>
</tr>
<tr>
<td>Post-Seizure</td>
<td>Investigate underlying cause: consider CT, LP, MRI, intracranial pressure monitoring</td>
</tr>
</tbody>
</table>

Note: All interventions should be done as soon as possible
Adapted from Brophy et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocrit Care 2012;17:3-23

Disposition
• decision to admit or discharge should be based on the underlying disease process identified
• if a patient has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
• first-time seizure patients being discharged should be referred to a neurologist for follow-up
• admitted patients should generally have a neurology consult
• patient should not drive until medically cleared (local regulations vary)
• complete notification form to appropriate authority regarding ability to drive
• warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)
Shortness of Breath

- see Respirology, R3 and Cardiology and Cardiac Surgery, C5

### Table 18. Differential Diagnosis for Dyspnea

<table>
<thead>
<tr>
<th></th>
<th>High Mortality/Morbidity</th>
<th>Usually Less Emergent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td>Airway obstruction (foreign body, epiglottitis, abscess, anaphylaxis)</td>
<td>Chronic obstructive, interstitial or restrictive lung disease</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td></td>
<td>Gas exchange –Pulmonary edema, PE, pneumonia, Acute exacerbations of COPD</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>CHF, MI, valvular disease, tamponade, arrhythmia</td>
<td>Chronic CHF, angina</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Metabolic acidosis NYD, carbon monoxide inhalation</td>
<td>Anemia, Hemoglobinopathy</td>
</tr>
<tr>
<td><strong>Neuromuscular</strong></td>
<td>Myasthenia gravis, diaphragmatic paralysis</td>
<td>CNS lesion, primary muscle weakness</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td>Anxiety, deconditioning</td>
</tr>
</tbody>
</table>

### History and Physical Exam
- acute SOB is often due to a relatively limited number of conditions; associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischemia
  - fever, cough, and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
  - environmental or occupational exposures
- dyspnea may be the sole complaint and the physical exam may reveal few abnormalities (e.g. PE, pneumothorax)
- vitals including pulse oximetry
- wheeze and stridor (airway) vs. crackles (parenchymal), JVP, and murmurs

### Investigations
- blood work
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider VBG
  - serial cardiac enzymes and ECG if considering cardiac source
  - Wells scores to consider appropriateness of D-dimer
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection, or interstitial fluid)
  - CT chest usually is not indicated in the initial evaluation of patients with dyspnea, but can be valuable in patients with interstitial lung disease, occult emphysema, or chronic thromboembolic disease (i.e. PE)

### Management of Life-Threatening Dyspnea NYD
- see Primary and Secondary Surveys, ER2-3
- treat underlying cause

### Disposition
- the history and physical exam lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified
- consider intubation in CO2 retainers (e.g. COPD)
- if discharging, organize follow-up and educate regarding signs to return to hospital

### Syncope

**Definition**
- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system hypoperfusion

**Etiology**
- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)
History
- gather details from witnesses, and clarify patient’s experience (e.g. dizziness, ataxia, or true syncope)
  - two key historical features: prodrome and situation
- distinguish between syncope and seizure (see Neurology, N19)
  - some patients may have myoclonic jerks with syncope – NOT a seizure
  - signs and symptoms during presyncope, syncope, and postsyncope
- past medical history, drugs
- think anatomically in differential; pump (heart), blood vessels, brain
- syncope is cardiogenic until proven otherwise if
  - there is sudden loss of consciousness with no warning or prodrome
- syncope is accompanied by chest pain

Physical Exam
- postural BP and HR
- cardiac, respiratory, and neurological exams
- examine for signs of secondary injury caused by syncopal episode (e.g. head injury)

Investigations
- ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval, Brugada Syndrome, RV strain), bedside glucose
- consider blood work: CBC, electrolytes, BUN/Cr, ABGs, troponin, Ca²⁺, Mg²⁺, β-hCG, D-dimer
- consider toxicology screen

Management
- ABCs, IV, O₂, monitor
- cardiogenic syncope: admit to medicine/cardiology
- low risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

Disposition
- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow-up with family physician
  - educate about avoiding orthostatic or situational syncope
  - evaluate patient for fitness to drive or work
  - patients with recurrent syncope should avoid high-risk activities (e.g. driving)

Sexual Assault

Epidemiology
- 1 in 4 women and 1 in 10 men will be sexually assaulted in their lifetime; only 7% are reported

General Approach
- ABCs, treat acute, serious injuries; physician priority is to treat medical issues and provide clearance
- ensure patient is not left alone and provide ongoing emotional support
- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained)
- Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests or if <16 yr old (legally required)

History
- ensure privacy for the patient – others should be asked to leave
- questions to ask: who, when, where did penetration occur, what happened, any weapons, or physical assault?
- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
  - gravidity, parity, last menstrual period
  - contraception use
  - last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

Physical Exam
- never re-traumatize a patient with the examination
- general examination
  - mental status
  - sexual maturity
  - patient should remove clothes and place in paper bag
  - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
pelvic exam and specimen collection
  • ideally before urination or defecation
  • examine for seminal stains, hymen, signs of trauma
  • collect moistened swabs of dried seminal stains
  • pubic hair combings and cuttings
  • speculum exam
    • lubricate with water only
    • vaginal lacerations, foreign bodies
    • Pap smear, oral/cervical/rectal culture for gonorrhea and chlamydia
    • posterior fornix secretions if present or aspiration of saline irrigation
    • immediate wet smear for motile sperm
    • air-dried slides for immotile sperm, acid phosphatase, ABO group
  • fingernail scrapings and saliva sample from victim

Investigations
  • Venereal Disease Research Lab (VDRL): repeat in 3 mo if negative
  • serum β-hCG
  • blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

Management
  • involve local/regional sexual assault team
  • medical
    • suture lacerations, tetanus prophylaxis
    • gynecology consult for foreign body, complex lacerations
    • assume positive for gonorrhea and chlamydia
      • management: azithromycin 1 g PO x 1 dose (alt: doxycycline 100 mg PO bid x 7 d) and cefixime 800 mg PO x 1 dose (alt: ceftriaxone 250 mg IM x 1 dose)
      • may start prophylaxis for hepatitis B and HIV
      • pre and post counselling for HIV testing
      • pregnancy prophylaxis offered
        • levonorgestrel 0.75 mg PO STAT, repeat within 12 h (Plan B’)
  • psychological
    • high incidence of psychological sequelae
    • have victim change and shower after exam completed

Disposition
  • discharge if injuries/social situation permit
  • follow up with physician in rape crisis centre within 24 h
  • best if patient does not leave ED alone

DOMESTIC VIOLENCE
  • women are usually the victims, but male victimization also occurs
  • identify the problem (need high index of suspicion)
    • suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns, or other injuries; often inconsistent with history provided)
    • somatic symptoms (chronic and vague complaints)
    • psychosocial symptoms
      • clinician impression (your ‘gut feeling’, e.g. overbearing partner that won’t leave patient’s side)
  • if disclosed, be supportive and assess danger
  • patient must consent to follow-up investigation/reporting (unless for children)

Management
  • treat injuries and document findings
  • ask about sexual assault and children at home (encourage notification of police)
  • safety plan with good follow-up with family physician/social worker

Medical Emergencies

Anaphylaxis and Allergic Reactions

Etiology
• anaphylaxis is an exaggerated immune mediated hypersensitivity reaction that leads to systemic histamine release, increased vascular permeability, and vasodilation; regardless of the etiology, the presentation and management of anaphylactic reactions are the same
• allergic (re-exposure to allergen)
• non-allergic (e.g. exercise induced)
**Diagnostic Criteria**

- **anaphylaxis** is highly likely with any of:
  1. acute onset of an illness (min to hrs) with involvement of the skin, mucosal tissue and at least one of:
     - respiratory compromise (e.g. dyspnea, wheeze, stridor, hypoxemia)
     - hypotension/end-organ dysfunction (e.g. hypotonia, collapse, syncope, incontinence)
  2. two or more of the following after exposure to a LIKELY allergen for that patient (min to hrs)
     - involvement of the skin-mucosal tissue
     - respiratory compromise
     - hypotension or associated symptoms
     - persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
  3. hypotension after exposure to a KNOWN allergen for that patient (min to hrs)
     - management is also appropriate in cases which do not fulfill criteria, but who have had previous episodes of anaphylaxis
     - life-threatening differentials for anaphylaxis include asthma and septic shock
     - angioedema may mimic anaphylaxis but tends not to improve with standard anaphylaxis treatment

**Management**

- **moderate reaction:** generalized urticaria, angioedema, wheezing, tachycardia
  - epinephrine (1:1000) 0.3-0.5 mg (IM in lateral thigh)
  - antihistamines: diphenhydramine (Benadryl®) 25-50 mg IM
  - salbutamol (Ventolin®) 1 cc via MDI
- **severe reaction/evolution:** severe wheezing, laryngeal/pulmonary edema, shock
  - ABCs, may need definitive airway (e.g. ETT) due to airway edema
  - epinephrine (1:1000) 0.1-0.3 mg IV (or via ETT if no IV access) to start, repeat as needed
  - antihistamines: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg)
  - corticosteroids: hydrocortisone (Solucortef®) 100 mg IV (~1.5 mg/kg) or methylprednisolone (Solumedrol®) 1 mg/kg IV q6h x 24 h
  - large volumes of crystalloid may be required

**Disposition**

- monitor for 4-6 h in ED (minimum) and arrange follow-up with family physician in 24-48 h
- can have second phase (biphasic) reaction up to 48 h later, patient may need to be supervised
- educate patient on avoidance of allergens
  - H1 antagonist (cetirizine 10 mg PO OD or Benadryl 50 mg PO q4-6h x3d)
  - H2 antagonist (ranitidine 150 mg PO OD x3d)
  - corticosteroid (prednisone 50 mg PO OD x5d) to prevent secondary reaction

**Asthma**

- see Respiriology, R7
- chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction

**History and Physical**

- find cause(s) of asthma exacerbation (viral, environmental, etc.)
- history of asthma control; severity of exacerbations (ICU, intubation history)
- signs of respiratory distress
- vitals, specifically $O_2$

**Investigations**

- peak flow meter
- ± ABG if in severe respiratory distress
- CXR if diagnosis in doubt to rule out pneumonia, pneumothorax, etc.
Table 19. Asthma Assessment and Management

<table>
<thead>
<tr>
<th>Classifications</th>
<th>History and Physical Exam</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Arrest</strong></td>
<td>Exhausted, confused, diaphoretic, cyanotic</td>
<td>100% O2, cardiac monitor, IV access</td>
</tr>
<tr>
<td>Imminent</td>
<td>Silent chest, ineffective respiratory effort</td>
<td>Intubate (consider induction with ketamine)</td>
</tr>
<tr>
<td></td>
<td>Decreased HR, RR &gt;30, pCO2 &gt;45 mmHg</td>
<td>Short acting β-agonist (Ventolin®): nebulizer 5 mg</td>
</tr>
<tr>
<td></td>
<td>O2 sat &lt;90% despite supplemental O2</td>
<td>continually</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-acting anticholinergic (Atrovent®): nebulizer 0.5 mg x 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV steroids: methylprednisolone 125 mg</td>
</tr>
<tr>
<td><strong>Severe Asthma</strong></td>
<td>Agitated, diaphoretic, laboured respirations</td>
<td>Anticipate need for intubation</td>
</tr>
<tr>
<td></td>
<td>Speaking in words</td>
<td>Similar to above management</td>
</tr>
<tr>
<td></td>
<td>No relief from β agonist</td>
<td>Magnesium sulphate 2 g IV</td>
</tr>
<tr>
<td></td>
<td>O2 sat &lt;90%, FEV1 &lt;50%</td>
<td>O2 to achieve O2 sat &gt;92%</td>
</tr>
<tr>
<td><strong>Moderate Asthma</strong></td>
<td>SOB at rest, cough, congestion, chest tightness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Speaking in phrases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inadequate relief from β-agonist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1 50-80%</td>
<td></td>
</tr>
<tr>
<td><strong>Mild Asthma</strong></td>
<td>Exertional SOB/cough with some nocturnal symptoms</td>
<td>β agonist</td>
</tr>
<tr>
<td></td>
<td>Difficulty finishing sentences</td>
<td>Monitor FEV1</td>
</tr>
<tr>
<td></td>
<td>FEV1 &gt;80%</td>
<td>Consider steroids (MDI or PO)</td>
</tr>
</tbody>
</table>

**Disposition**

- discharge safe in patients with FEV1 or PEF > 60% predicted, and may be safe if FEV1 or PEF 40-60% predicted based on patient’s risk factors for recurrence of severe attack
- risk factors for recurrence: frequent ED visits, frequent hospitalizations, recent steroid use, recent exacerbation, poor medication compliance, prolonged use of high dose β-agonists
- β-agonist MDI with aerochamber 2-4 puffs q2-4h until symptoms controlled, then prn
- initiate inhaled corticosteroids with aerochamber if not already prescribed
- if moderate to severe attack, administer prednisone 30-60 mg/d for 7 d with no taper
- counsel on medication adherence and educate on use of aerochamber
- follow-up with primary care physician or asthma specialist

### Cardiac Dysrhythmias

- **see Cardiology and Cardiac Surgery, C16**

### Bradydysrhythmias and AV Conduction Blocks

- **AV conduction blocks**
  - 1st degree: prolonged PR interval (>200 msec), no treatment required
  - 2nd degree
    - Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - Mobitz II: PR interval constant with dropped QRS complex, can progress to 3rd degree AV block
  - 3rd degree: P wave unrelated to QRS complex, PP and RR intervals constant
  - atropine and transcatheter pacing (atropine with caution)
  - if transcatheter pacing fails consider IV dopamine, epinephrine
  - long-term treatment for Mobitz II and 3rd degree block – internal pacemaker

- **sinus bradycardia** (rate <60 bpm)
  - can be normal (especially in athletes)
  - causes: vagal stimulation, vomiting, myocardial infarction/ischemia, increased ICP, sick sinus node, hypothyroidism, drugs (e.g. β-blockers, calcium channel blockers)
  - treat if symptomatic (hypotension, chest pain)
  - acute: atropine ± transcatheter pacing
  - sick sinus: transcatheter pacing
  - drug induced: discontinue/reduce offending drug, consider antidotes

### Supraventricular Tachydysrhythmias (narrow QRS)

- **sinus tachycardia** (rate >100 bpm)
  - causes: increased sympathetic tone, drugs, fever, hypotension, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause, consider β-blocker if symptomatic

- **regular rhythm** (i.e. not sinus tachycardia)
  - vagal maneuvers (carotid massage, Valsalva), adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once
  - rhythm converts: probable re-entry tachycardia (AVNRT more common than AVRT)
  - monitor for recurrence
  - treat recurrence with adenosine or longer acting medications
  - rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
  - rate control (diltiazem, β-blockers) and consult cardiology

- **irregular rhythm**
  - probable AFib, atrial flutter, or multifocal atrial tachycardia
  - rate control (diltiazem, β-blockers)
Atrial Fibrillation
- most common sustained dysrhythmia; no organized P waves (atrial rate >300/min), irregularly irregular heart rate, narrow QRS (typically)
- etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday hear), valvular disease, pericarditis, cardiomyopathy, sick sinus syndrome
- treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
- decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
- acute management
  - if unstable: immediate synchronized cardioversion
  - if onset of Afib is >48 h: rate control, anticoagulate 3 wk prior to and 4 wk after cardioversion, or do transesophageal echocardiogram to rule out clot
  - if onset <48 h or already anticoagulated: may cardiovert
  - electrical cardioversion: synchronized direct current (DC) cardioversion
  - chemical cardioversion: procainamide, lithium, propafenone
- long-term management: rate or rhythm control, consider anticoagulation (CHADS2 score, see Cardiology and Cardiac Surgery, C20)

Ventricular Tachydysrhythmias (wide QRS)
- VTach (rate usually 140-200 bpm)
  - definition: 3 or more consecutive ventricular beats at >100 bpm
  - etiology: CAD with MI is most common cause
  - treatment: sustained VTach (>30 s) is an emergency
    - hemodynamic compromise: synchronized DC cardioversion
    - no hemodynamic compromise: synchronized DC cardioversion, amiodarone, procainamide
- VFib: call a code blue, follow ACLS for pulseless arrest
- Torsades de pointes
  - looks like VTach but QRS ‘rotates around baseline’ with changing axis and amplitude (twisted ribbon)
  - etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
  - treatment
    - IV Mg²⁺, temporary overdrive pacing, isoproterenol
    - correct cause of prolonged QT

Acute Exacerbation of COPD (AECOPD)
- for chronic management of COPD see Respirology, R9
- progressive development of irreversible airway obstruction, typically caused by smoking

History and Physical Exam
- cardinal symptoms of AECOPD: increased dyspnea, increased coughing frequency or severity, increased sputum volume or purulence
- triggers: virus, pneumonia, urinary tract infection, PE, CHF, MI, drugs
- characterize previous episodes and hospitalizations, smoking history
- vital signs, LOC, signs of respiratory distress, respiratory exam

Investigations
- CBC, electrolytes, ABG, CXR, ECG
- PFTs are NOT useful in managing acute exacerbations

Management
- oxygen: keep O₂ sat 88-92% (be aware when giving O₂ to chronic hypercapnic/CO₂ retainers but do not withhold O₂ if hypoxic)
- bronchodilators: short-acting β-agonist (salbutamol 4-8 puffs via MDI with spacer q15min x 3 prn) ± short-acting anticholinergic (ipratropium 4-8 puffs via MDI q15min x 3 prn)
- steroids: prednisone 40-60 mg PO for 7-14 d, or methylprednisolone 125 mg IV bid-qid if severe exacerbation, or unable to take PO
- antibiotics: TMP-SMX, cephalosporins, respiratory quinolones (given if all 3 cardinal symptoms present or 2 cardinal symptoms with increased sputum purulence or mechanical ventilation)
- ventilation: apply noninvasive positive-pressure ventilation (CPAP or BiPAP) if severe distress or signs of fatigue, arterial pH <7.35, or hypercapnic
- if life-threatening, ICU admission for intubation and ventilation (chance of ventilation dependency)

Disposition
- no guidelines for admission - based on clinical judgement and comorbidities
- lower threshold to admit if comorbid illness (diabetes, CHF, CAD, alcohol abuse)
- if discharging, use antibiotics, taper steroids, up to 4-6 puffs qid of ipratropium and salbutamol and organize follow-up
**Acute Decompensated Heart Failure (ADHF)**

- for chronic management of CHF [see Cardiology and Cardiac Surgery, C36]

**Etiology**
causes of CHF: decreased myocardial contractility (ischemia, infarction, cardiomyopathy, myocarditis), pressure overload states (HTN, valve abnormalities, congenital heart disease), restricted cardiac output (myocardial infiltrative disease, cardiac tamponade)

- precipitants of acute decompensation of CHF
  - cardiac (ischemia, infarction, arrhythmia - Afib)
  - medications (β-blockers, CCBs, NSAIDs, steroids, non-compliance)
  - dietary (increased sodium and/or water intake)
  - high output (anemia, infection, pregnancy, hyperthyroid)
  - other (renal failure, hypertensive crisis, iatrogenic fluid overload - blood transfusions or IV fluids)

**Presentation**
- left-sided heart failure
  - dyspnea, SOB, orthopnea, PND, nocturia, fatigue, altered mental status, presyncope/syncope, angina, systemic hypotension
  - hypoxia, decreased air entry to lungs, crackles, S3 or S4, pulmonary edema (on CXR), pleural effusion (usually right-sided)
- right-sided heart failure
  - dependent bilateral pitting edema, JVP elevation and positive AJR, ascites, hepatomegaly
- patients often present with a combination of right-sided and left-sided symptoms

**Investigations**
- blood work: CBC, electrolytes, AST, ALT, bilirubin, Cr, BUN, cardiac enzymes, brain natriuretic peptide
- CXR: most useful test (see sidebar)
- ECG: look for MI, ischemia (ST elevation/depression, T-wave inversion), LVH, atrial enlargement, conduction abnormalities
- ABG: if severe or refractory to treatment
  - hypoxemia, hypercapnia, and acidosis are signs of severe CHF
- echocardiogram: not usually used in emergency evaluation, previous results may aid in diagnosis
- rule out serious differentials: PE, pneumothorax, pneumonia/empyema, acute exacerbations COPD

**Management**
- ABCs, may require intubation if severe hypoxia
- sit upright, cardiac monitoring, and continuous pulse oximetry
- saline lock IV, Foley catheter (to follow effectiveness of diuresis)
- 100% O2 by mask
- if poor response, may require BiPAP or intubation
- medical
  - diuretic (if volume overloaded): furosemide 40-80 mg IV
  - vasodilators (if sBP >100): nitroglycerin 0.3 mg SL q5min ± topical Nitrodur* patch (0.4-0.8 mg/h)
    - if not responding or signs of ischemia (angina): nitroglycerine 10-20 µg/min IV, titrate to response
    - if severe or refractory hypertension: nitroprusside 0.5 µg/kg/min, titrate to response
  - inotropes/vasopressors (if sBP <90)
    - without signs of shock: dobutamine 2.5 µg/kg/min IV, titrate up to sBP >90 mmHg
    - with signs of shock: dopamine 5-10 µg/kg/min IV, titrate up to sBP >90 mmHg
- treat precipitating factor - e.g. rate control (β-blocker, calcium channel blockers) or rhythm-control (electrical or chemical cardioversion) if new Afib
- cardiology or medicine consult

**Hospital Management Required if**
- Acute MI
- Pulmonary edema or severe respiratory distress
- Severe complicating medical illness (e.g. pneumonia)
- Anasarca
- Symptomatic hypotension or syncope
- Refractory to outpatient therapy
- Thromboembolic complications requiring intervention
- Clinically significant dysrhythmias
- Inadequate social support for safe outpatient management
- Persistent hypoxia requiring supplemental oxygen

**Precipitants of CHF Exacerbation**

| FAILURE |
|---|---|
| F | Forgot medication |
| A | Arrhythmia (Dysrhythmia)/Anemia |
| I | Ischemia/Infarction/Infection |
| L | Lifestyle (e.g. high salt intake) |
| U | Uptregulation of cardiac output |
| R | Renal failure |
| E | Embolism (pulmonary) |

**CHF on CXR**

- Pulmonary vascular redistribution
- Perihilar infiltrates
- Interstitial edema, Kerley B lines
- Alveolar edema, bilateral infiltrates
- May see cardiomegaly, pleural effusions
- Peribronchial cuffing
- Fissural thickening (fluid in fissure)

**Acute Treatment of CHF**

| LMNOP |
|---|---|
| L | Lasix® (furosemide) |
| M | Morphine |
| N | Nitroglycerin |
| O | Oxygen |
| P | Position (sit upright), Pressure (BiPAP) |

**Hospital Management Required if**

- Acute MI
- Pulmonary edema or severe respiratory distress
- Severe complicating medical illness (e.g. pneumonia)
- Anasarca
- Symptomatic hypotension or syncope
- Refractory to outpatient therapy
- Thromboembolic complications requiring intervention
- Clinically significant dysrhythmias
- Inadequate social support for safe outpatient management
- Persistent hypoxia requiring supplemental oxygen
Venous Thromboembolism (VTE)

- see Respirology, R20

Risk Factors
- Virchow’s triad: alterations in blood flow (venous s asis), injury to endothelium, hypercoagulable state (including pregnancy, use of OCP, malignancy)
- clinical risk factors (see sidebar)

DEEP VEIN THROMBOSIS (DVT)

Presentation
- calf pain, unilateral leg swelling/erythema/edema, palpable cord along the deep venous system on exam; can be asymptomatic
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT; investigation often needed

Investigations
- use Wells’ criteria for DVT to guide investigations (see Figure 12)
- D-dimer is only useful at ruling out DVT if it’s negative in low-moderate risk patients (highly sensitive)
  - high risk of false positives in: elderly, infection, recent surgery, trauma, hemorrhage, late in pregnancy, liver disease, cancer
  - U/S has high sensitivity & specificity for proximal clot but only 73% sensitivity for calf DVT (may need to repeat in 1 wk)
  - if positive – treat for DVT regardless of risk
  - if negative and low risk – rule out DVT
  - if negative and moderate to high risk – repeat U/S in 5-7 d to rule out DVT

Management
- LMWH unless patient also has renal failure
  - dalteparin 200 IU/kg SC q24h or enoxaparin 1.5 mg/kg SC q24h
  - warfarin started at same time as LMWH (5 mg PO OD initially followed by dosing based on INR)
  - LMWH discontinued when INR has been therapeutic (2-3) for 2 consecutive days
  - DOAC can be used in acute management of symptomatic DVT
    - apixaban: 15 mg PO bid for first 21 d; 20 mg PO daily for remaining treatment (taken with food at the same time each day)
    - rivaroxaban: 15 mg PO bid for first 7 d; 5 mg PO bid for remaining treatment
    - consider thrombolyis if extensive DVT causing limb compromise
    - IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
    - duration of anticoagulation: 3 mo if transient coagulopathy; 6 mo if unprovoked DVT; life-long if ongoing coagulopathy

PULMONARY EMBOLISM (PE)

Presentation
- dyspnea, pleuritic chest pain, hemoptysis, tachypnea, cyanosis, hypoxia, fever
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT; investigation often needed

Investigations
- use Wells’ criteria for PE to guide investigations (see Figure 13)
- PERC score alone can rule out PE in low risk patients (as determined by Wells’ criteria) unless patient is pregnant
- ECG and CXR are useful to rule out other causes (e.g. ACS, pneumonia, pericarditis) or to support diagnosis of PE
  - ECG changes in PE: sinus tachycardia, right ventricular strain (S1Q3T3), T wave inversions in anterior and inferior leads
  - CXR findings in PE: Hampton’s hump (triangular density extending from pleura) or Westermark’s sign
- D-dimer is only useful at ruling out a PE if it is negative in low-moderate risk patients (highly sensitive)
  - if positive D-dimer or high-probability patient, then pursue CT angiography or V/Q scan
- CT angiography has high sensitivity and specificity for PE, may also suggest other etiology
- V/Q scan useful in pregnancy, when CT angiography not available, or IV contrast contraindicated

Management of PE
- treatment of PE with anticoagulation and duration of treatment is the same as for DVT (see above)
- consider thrombolysis if extensive PE causing hemodynamic compromise or cardiogenic shock
- catheter-directed thrombolysis or surgical thrombectomy rarely considered in massive PE or contraindication to anticoagulation
- often can be treated as outpatient, may require analgesia for chest pain (narcotic or NSAID)
- admit if hemodynamically unstable, require supplemental O2, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy
- referral to medicine for coagulopathy and malignancy workup

Wells’ Criteria for DVT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SCoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Paralysis, paresis or recent immobilization of leg</td>
<td>+1</td>
</tr>
<tr>
<td>Recently bedridden x 3 d or major surgery within 4 wk</td>
<td>+1</td>
</tr>
<tr>
<td>Local tenderness</td>
<td>+1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>+1</td>
</tr>
<tr>
<td>Calf swelling 3cm</td>
<td>+1</td>
</tr>
<tr>
<td>&gt; asymptomatic leg</td>
<td>+1</td>
</tr>
<tr>
<td>Unilateral pitting edema</td>
<td>+1</td>
</tr>
<tr>
<td>Collateral superficial veins</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative Dx more likely</td>
<td>-2</td>
</tr>
</tbody>
</table>

Wells’ Criteria for PE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SCoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Hx of DVT/PE</td>
<td>+1.5</td>
</tr>
<tr>
<td>HR &gt; 100</td>
<td>+1.5</td>
</tr>
<tr>
<td>Recent immobility or surgery</td>
<td>+1.5</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>+3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+1</td>
</tr>
<tr>
<td>Cancer</td>
<td>+1</td>
</tr>
</tbody>
</table>

PERC Score

- Age >50 yr
- HR >100 bpm
- O2 sat on RA <94%
- Prior history DVT/PE
- Recent trauma or surgery
- Hemoptysis
- Exogenous estrogen
- Clinical signs suggesting DVT

Score 1 for each question; a score >3 means patient has <1.5% chance having a PE and avoids further investigation. Caution using the PERC score in pregnant women as the original study excluded pregnant women.

D-dimer is only useful if it is negative; negative predictive value >99%
Diabetic Emergencies

• Diabetic Ketoacidosis
  • triad of hyperglycemia, ketosis, and acidosis due to severe insulin deficiency and counter regulatory hormone excess
  • clinical presentation
    • often young, Type 1 DM patients, (may rarely be first presentation of undiagnosed Type 2 DM) with symptoms evolving within a day
    • early signs and symptoms: polyuria, polydipsia, malaise, nocturia, weight loss
    • late signs and symptoms
      ■ GI: anorexia, nausea, vomiting, abdominal pain
      ■ neurological: fatigue, drowsiness, stupor, coma
      ■ respiratory: Kussmaul's respiration, dyspnea (often due to acidosis), fruity ketotic breath
  • investigations
    • blood work: CBC, electrolytes, Ca++, Mg++, PO43-, Cr, BUN, glucose, ketones, osmolality, AST/ALT/ALP, amylase, troponin
    • urine: glucose and ketones
    • ABG or VBG
    • ECG (MI is possible precipitant; electrolyte disturbances may predispose to dysrhythmia)
  • management
    • rehydration
      • bolus of NS, then high rate NS infusion (beware of overhydration and cerebral edema, especially in pediatric patients)
      • beware of a pseudohyponatremia due to hyperglycemia (add 3 Na+ per 10 glucose over 5.5 mmol/L)
  • potassium
    • essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial K+ <5.5 mmol/L)
    • use cardiac monitoring if potassium levels normal or low

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

Purpose: To compare the efficacy and safety of rivaroxaban alone as anticoagulation therapy for PE.  
Methods: A randomized, open-label, event-driven, non-inferiority trial was undertaken to compare rivaroxaban (10 mg twice daily for 3 wk, followed by 20 mg once daily) with standard therapy of enoxaparin followed by an adjusted-dose vitamin K antagonist, in patients with PE.  
Results: 3,432 patients were enrolled. Rivaroxaban was non-inferior to standard therapy (non-inferiority margin, 2.0; p=0.003) for preventing recurrent VTE (HR: 1.92; 95% CI 1.07-3.48). Major bleeding occurred less in the rivaroxaban group (hazard ratio, 0.49; 0.31-0.76; p=0.003). Rates of other adverse events were similar in the two groups.  
Conclusions: A fixed-dose regimen of rivaroxaban alone was non-inferior to standard therapy for the initial and long-term treatment of PE.
- insulin
  - critical, as this is the only way to turn off gluconeogenesis/ketosis
  - do not give insulin if K⁺ < 3.3 mmol/L.
  - initial bolus of 5-10 U short-acting/regular insulin (or 0.2 U/kg) IV in adults (controversial – may just start with infusion)
  - followed by continuous infusion at 5-10 U (or 0.1 U/kg) per h
  - once the blood glucose < 14 mmol/L, patient should receive their regular insulin SC injection and the infusion stopped in 1 h
  - add D5W to IV fluids when blood glucose < 15 mmol/L to prevent hypoglycemia
- bicarbonate is not given unless patient is at risk of death or shock (typically pH < 7.0)

**Hyperosmolar Hyperglycemic State**
- state of extreme hyperglycemia (44-133.2 mmol/L) due to relative insulin deficiency, counter-regulatory hormones excess, gluconeogenesis, and dehydration (due to osmotic diuresis)
- often older, Type 2 DM patients with more co-morbid illnesses and larger fluid losses with symptoms evolving over days to weeks, less GI symptoms and more neurological deficits than DKA including: mental disturbances, coma, delirium, seizures
- polyuria, N/V
- investigations
  - blood work: CBC, electrolytes, Ca²⁺, Mg²⁺, PO₄³⁻, Cr, BUN, glucose, ketones, osmolality
  - urine: glucose and ketones
  - ABG or VBG
  - find underlying cause: ECG, CXR, blood and urine C&S
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O₂ and cardiac monitoring, frequent electrolyte and glucose monitoring
  - insulin is controversial
  - identify and treat precipitant if present (the 5 Is)

**Hypoglycemia**
- characterized by Whipple's triad: low plasma glucose, symptoms suggestive of hypoglycemia, prompt resolution of symptoms with glucose
- clinical presentation
  - neuroglycopenic symptoms: headaches, confusion, seizures, coma
  - autonomic symptoms: diaphoresis, nausea, hunger, tachycardia, palpitations
- history and physical exam
  - last meal, known DM, prior similar episodes, drug therapy, and compliance
  - liver/renal/endocrine/neoplastic disease
  - depression, alcohol or drug use
- management
  - IV access and rapid blood glucose measurement
  - D50W 50 mL IV push, glucose PO if mental status permits
  - if IV access not possible, glucagon 1-2 mg IM, repeat x 1 in 10-20 min
  - O₂, cardiac, frequent blood glucose monitoring
  - thiamine 100 mg IM
  - full meal as soon as mental status permits
  - if episode due to long-acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long t½ (may require admission for monitoring)
  - search for cause (most often due to exogenous insulin, alcohol, or sulfonylureas)
**Electrolyte Disturbances**

- see Nephrology, NP7 and Endocrinology, E36

<table>
<thead>
<tr>
<th>Electrolyte Disturbance</th>
<th>Common Causes</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatremia</td>
<td>Inadequate H₂O intake (elderly/disabled) or inappropriate excretion of H₂O (diuretics, Li, and DI)</td>
<td>Lethargy, weakness, irritability, and edema; seizures and coma occur with severe elevations of Na⁺ levels (&gt;158 mmol/L)</td>
<td>Salt restrict and give free water</td>
<td>No more than 12 mmol/L in 24 h drop in Na⁺ (0.5 mmol/L/h) due to risk of cerebral edema, seizures, death</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Hypovolemic (GI renal, skin, blood fluid loss), euovolemic (SIADH/stress, adrenal insufficiency, hypothyroid, diet/intake), hypervolemic (CHF, cirrhosis, nephrotic syndrome)</td>
<td>Neurologic symptoms 2° to cerebral edema, headache, decreased LOC depressed reflexes; chronic milder than acute</td>
<td>Water restrict/NPD; Seizure/Coma: 100 cc 3% NaCl; Treat hypovolemic with RL and hypervolemic with furosemide</td>
<td>Limit total rise to 8 mmol/L in 24 h (0.5 mmol/L/h maximum) as patients are at risk of central pontine myelolysis</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Rhabdomyolysis, insulin deficiency, metabolic acidosis (e.g. acute renal failure, missed dialysis)</td>
<td>Nausea, palpitations, muscle stiffness, areflexia</td>
<td>Protect heart: calcium gluconate; Shift K⁺ into cells: D50W + Insulin, NaHCO₃, salbutamol; Remove K⁺: Fluids + furosemide, dialysis</td>
<td>High risk of dysrhythmia - ECG: peaked/narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, AV block, VFib</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Metabolic alkalosis (e.g. diarhoea), insulin, diuretics, anorexia, salbutamol</td>
<td>N/V, fatigue, muscle cramps, constipation</td>
<td>K-Dur³, K⁺ sparing diuretics, IV solutions with 20-40 mEq/L KCl over 3-4 h</td>
<td>ECG: U waves most important, flattened/inverted T waves, prolonged QT, depressed ST; May need to restore Mg²⁺</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Hyper-PTH and malignancy account for ~90% of cases</td>
<td>Multisystem including CVS, GI (gastrointestinal), MSK (bones), psychiatric (mood)</td>
<td>Isotonic saline (+ furosemide if hypervolemic); Bisphosphonates, dialysis, chelation (EDTA or oral PDi³)</td>
<td>Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Iatrogenic, low Mg²⁺; liver dysfunction, 1° hypo-PTH</td>
<td>Laryngospasm, hyperreflexia, paresthesia, tetany, Chvostek’s and Trouseau’s sign</td>
<td>Acute (ionized Ca²⁺ &lt;0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion</td>
<td>Prolonged QT interval can arise, leading to dysrhythmia as can upper airway obstruction</td>
</tr>
</tbody>
</table>

**Hypertensive Emergencies**

- definition: severe elevation of BP with evidence of end-organ damage (CNS, retinal, CVS, renal, GI) etiology
  - essential HTN, emotional exertion, pain, use of sympathomimetic drugs (cocaine, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), etc.
- preeclampsia
- HELLP Syndrome (seen only in preeclampsia/ eclampsia)
- Hemolytic anemia
- Elevated Liver enzymes
- Low Platelet count

**Table 21. Signs and Symptoms of Hypertensive Emergencies**

<table>
<thead>
<tr>
<th>CNS</th>
<th>Retinal</th>
<th>Renal</th>
<th>Cardiovascular</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication</td>
<td>Stroke/TIA, headache, altered mental status, seizures, hemorrhage</td>
<td>Vision change, hemorrhage, exudates, papilledema</td>
<td>Nectaria, elevated Cr, proteinuria, hematuria, oliguria</td>
<td>Ischemia/angina, infarction, dissection (back pain), CHF</td>
</tr>
</tbody>
</table>

- investigations
  - blood work: CBC, electrolytes, BUN, Cr
  - urinalysis
  - peripheral blood smear: to detect microangiopathic hemolytic anemia
  - CXR: if SOB or chest pain
  - ECG, troponins, CK: if chest pain
  - CT head: if neurological findings or severe headache
  - toxicology screen if sympathomimetic overdose suspected
- management
  - in general, strategy is to gradually and progressively reduce BP in 24-48 h
  - lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually nitroprusside and labetalol)
  - if preeclampsia, immediately consult OB/GYN (see Obstetrics OB24)
  - establish arterial line; transfer to ICU for further reduction in BP if monitored setting
  - in case of ischemic stroke: do not rapidly reduce BP; maintain BP >150/100 for 5 d
  - in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
  - in case of excessive catecholamines: avoid β-blockers (except labetalol)
  - in case of ACS: address ischemia initially, then BP
Hypertensive Urgency
- definition: severely elevated BP (usually sBP >180, dBP >110) with no evidence of end-organ damage
- most commonly due to non-adherence with medications
- treatment: initiate/adjust antihypertensive therapy, monitor in ED (up to 6 h) and discharge with follow-up for 48-72 h
- goal: differentiate hypertensive emergencies from hypertensive urgencies

Table 22. Commonly Used Agents for the Treatment of Hypertensive Crisis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Adverse Effects*</th>
<th>Special Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Nitroprusside</td>
<td>0.25-10 µg/kg/min</td>
<td>Immediate</td>
<td>3-5 min</td>
<td>N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome</td>
<td>Most hypertensive emergencies (especially CHF, aortic dissection)</td>
</tr>
<tr>
<td>Nicardipine (CCB)</td>
<td>2 mg IV bolus, then 4 mg/kg/h IV</td>
<td>15-30 min</td>
<td>40 min</td>
<td>Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, RF, eclampsia, sympathetic crisis)</td>
<td>Most hypertensive emergencies Caution with acute CHF</td>
</tr>
<tr>
<td>Fenoldopam Mesylate</td>
<td>0.05-0.1 µm/kg/min IV</td>
<td>&lt;5 min</td>
<td>8-10 min</td>
<td>Tachycardia, headache, nausea, flushing (e.g. acute RF)</td>
<td>Most hypertensive emergencies Caution with glaucoma</td>
</tr>
<tr>
<td>Enalapril (ACEI)</td>
<td>0.625-1.25 mg IV q6h</td>
<td>15-30 min</td>
<td>12-24 h</td>
<td>Theoretical fall in p essure in high renin states not seen in studies</td>
<td>Acute LV failure Avoid in acute MI, pregnancy, acute RF</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-20 µg/min IV</td>
<td>1-2 min</td>
<td>3-5 min</td>
<td>Hypotension, bradycardia, headache, lightheadedness, dizziness</td>
<td>MI/pulmonary edema</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5-10 mg IV/IM q20min (max 20 mg)</td>
<td>5-20 min</td>
<td>2-6 h</td>
<td>Dizziness, drowsiness, headache, tachycardia, Na+ retention</td>
<td>Eclampsia</td>
</tr>
<tr>
<td>Labetolol</td>
<td>20 mg IV bolus q10min or 0.5-2 mg/min</td>
<td>5-10 min</td>
<td>3-6 h</td>
<td>Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension</td>
<td>Most hypertensive emergencies (especially eclampsia) Avoid in acute CHF, heart block &gt;1st degree</td>
</tr>
<tr>
<td>Esmolol</td>
<td>250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat</td>
<td>1-2 min</td>
<td>10-20 min</td>
<td>Hypotension, nausea bronchospasm</td>
<td>Aortic dissection, acute MI SVT dysrhythmias, perioperative HTN Avoid in acute CHF, heart block &gt;1st degree</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>5-15 mg q5-15min</td>
<td>1-2 min</td>
<td>3-10 min</td>
<td>Tachycardia, headache, flushing</td>
<td>Catecholamine excess (e.g. pheochromocytoma)</td>
</tr>
</tbody>
</table>

*Hypotension may occur with all of these agents

Acute Coronary Syndrome
- see Cardiology and Cardiac Surgery, C27
- definition: new onset of chest pain, or acute worsening of previous chest pain, or chest pain at rest with:
  - negative cardiac biomarkers and no ECG changes = Unstable angina (UA)
  - positive cardiac biomarkers (elevated troponin) and no ECG changes = NSTEMI
  - positive cardiac biomarkers (elevated troponin) and ST segment elevation on ECG = STEMI
- investigations
  - ECG STAT (as soon as ACS is suspected on history), troponin (2-6 h after symptom onset), CXR (to rule out other causes)
- management
  - stabilize: ABCs, oxygen, IV access, cardiac monitors, oximetry
  - ASA 162-325 mg chewed and swallowed
  - nitroglycerin 0.3 mg SL q5min x 3; IV only if persistent pain, CHF, or hypertensive
  - contraindications: hypotension, phosphodiesterase inhibitor use, right ventricular infarctions (⅓ of all inferior MIs)
anticoagulation: choice of anticoagulation (unfractionated heparin, LMWH, or fondaparinux) and additional antiplatelet therapy (clopidogrel, ticagrelor, or prasugrel) depends on STEMI vs. NSTEMI and reperfusion strategy
- early cardiology consultation for reperfusion therapy
- UA/NSTEMI: early coronary angiography recommended if high TIMI risk score
- STEMI: primary percutaneous coronary intervention (within 90 min) preferred; thrombolytics if unavailable within 120 min of medical contact, symptoms <12 h and no contraindications
- atorvastatin 80 mg to stabilize plaques
- β-blocker if no signs of CHF, hemodynamic compromise, bradycardia, or severe reactive airway disease
- ACEI initiated within 24 h

Sepsis
- see Infectious Diseases, ID21 and Respiratory, R34
- definitions
  - sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection
    - organ dysfunction defined as a change in baseline SOFA score ≥2 points
  - septic shock: profound circulatory, cellular, and metabolic abnormalities with greater risk of mortality than with sepsis alone
  - require vasopressors to maintain MAP ≥65 mmHg
  - serum lactate ≥2 mmol/L without hypovolemia
- management
  - early recognition of sepsis and investigations to locate source of infection
  - identify severe sepsis with lactate or evidence of tissue hypoperfusion
  - early “goal-directed” therapy: ensure adequate organ perfusion
  - treatment priorities:
    - ABCs, monitors, lines
    - aggressive fluid resuscitation; consider ventilatory and inotropic support
    - cultures, then early empiric appropriate antibiotics - consider broad spectrum and atypical coverage
    - source control - e.g. remove infected Foley or surgery for ischemic gut
    - monitor adequate resuscitation with vital signs, inferior vena cava on U/S, and serial lactates

Stroke and TIA
- see Neurology, N48
- definitions
  - stroke: sudden loss of brain function due to ischemia (80%) or hemorrhage (20%) with persistence of symptoms >24 h or neuroimaging evidence
  - TIA: transient episode of neurologic dysfunction from focal ischemia without acute infarction typically lasting <1 h, but defined as <24 h
- clinical presentation

Table 23. Signs and Symptoms of Stroke

<table>
<thead>
<tr>
<th>Signs/ Symptoms</th>
<th>General</th>
<th>Language/Throat</th>
<th>Vision</th>
<th>Coordination</th>
<th>Motor</th>
<th>Sensation</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased LOC, changed mental status, confusion, neglect</td>
<td>Dysarthria, aphasia, swallowing difficulty</td>
<td>Diplopia, eye deviation, asymmetric pupils, visual field defect</td>
<td>Ataxia, intention tremor, lack of coordination</td>
<td>Increased tone, loss of power, spasticity</td>
<td>Loss of sensation</td>
<td>Hyper-reflexia, clonus</td>
<td></td>
</tr>
</tbody>
</table>

- patients with hemorrhagic stroke can present with sudden onset thunderclap headache that is usually described as “worst headache of life”
- stroke mimics: seizure, migraine, hypoglycemia, Todd’s paresis, peripheral nerve injury, Bell’s palsy, tumour, syncope

Table 24. Stroke Syndromes

<table>
<thead>
<tr>
<th>Region of Stroke</th>
<th>Stroke Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>Contralateral hemianesthesia and hemiparesis (legs &gt; arms/face), gait apraxia, altered mental status, impaired judgement</td>
</tr>
<tr>
<td>MCA</td>
<td>Contralateral hemianesthesia and hemiparesis (arms/face &gt; legs), contralateral homonymous hemianopsia, ipsilateral gaze</td>
</tr>
<tr>
<td>PCA</td>
<td>Contralateral homonymous hemianopsia, cortical blindness, impaired memory</td>
</tr>
<tr>
<td>VBA</td>
<td>Wide variety of cranial nerve, cerebellar, and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hyposthesia, syncope, ataxia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Loss of pain and temperature sensation in ipsilateral face and contralateral body</th>
<th>7 Causes of Emboli from the Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFib</td>
<td>Muscle groups</td>
</tr>
<tr>
<td>MI</td>
<td>Increased</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Increased</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>Decreased</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>absent</td>
</tr>
<tr>
<td>Left heart myxoma</td>
<td>Present</td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td>Present</td>
</tr>
</tbody>
</table>

Differentiation of UMN Disease vs. LNM Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>UMN Disease</th>
<th>LNM Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular deficit</td>
<td></td>
<td>Individual</td>
</tr>
<tr>
<td>Reflexes</td>
<td></td>
<td>muscles</td>
</tr>
<tr>
<td>Tone</td>
<td></td>
<td>Decreased</td>
</tr>
<tr>
<td>Fasciculations</td>
<td></td>
<td>absent</td>
</tr>
<tr>
<td>Atrophy</td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Babinski</td>
<td></td>
<td>Present</td>
</tr>
</tbody>
</table>

| Upgoing | | Downgoing |
Investigations
- CBC, electrolytes, blood glucose, coagulation studies ± cardiac biomarkers ± toxicology screen
- non-contrast CT head: look for hemorrhage, ischemia
- ECG ± echocardiogram: rule out AFib, acute MI as source of emboli
- other imaging: carotid Doppler, CTA, MRA as appropriate

Management
- ABCs: intubation with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protection reflexes
- thrombolysis: immediate assessment for eligibility; need acute onset, <4.5 h from drug administration time AND compatible physical findings AND normal CT with no bleed
- elevating head of bed if risk of elevated ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV ± cardiac monitoring
  - judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischemic penumbra)
  - BP control: only treat severe HTN (sBP >200, dBP >120, mean arterial BP >140) or HTN associated with hemorrhagic stroke transformation, cardiac ischemia, aortic dissection, or renal damage; use IV nitroprusside or labetalol
  - glycemic control: keep fasting glucose <6.5% in acute phase (5 d)
- cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- consult neurosurgery, neurology, medicine as indicated

Medications
- acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 4.5 h of symptom onset with no evidence of hemorrhage on CT scan
- antiplatelet agents: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin® (1st line); clopidogrel, Aggrenox® (2nd line)
- anticoagulation: DVT prophylaxis if immobile; treat AFib if present
- follow-up for consideration of carotid endarterectomy, cardiovascular risk optimization

Dizziness and Vertigo
- distinguish four types of dizziness: vertigo (“room spinning”), lightheadedness (“disconnected from environment”), presyncope (“almost blacking out”), dysequilibrium (“unstable, off-balance”)
- broad differential and diverse management (see Family Medicine, FM25; see Otolaryngology, OT6)
  - consider medication adverse effects

Otalgia (see Otolaryngology, OT6)
- differential diagnosis
  - infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis externa in diabetics, herpes simplex/zoster, auricular cellulitis, external canal abscess, dental disease
  - others: trauma, temporomandibular joint dysfunction, neoplasm, foreign body, cerumen impactions, trigeminal neuralgia, granulomatosis with polyangiitis
  - observe for otorrhea, palpation of outer ear/mastoid, otoscope to see bulging erythematous tympanic membrane, perforation
  - C&S of ear canal discharge, if present
  - CT head ± suspicion of mastoiditis, malignant otitis externa
  - antibiotics/antifungals/antivirals for respective infections

Hearing Loss (see Otolaryngology, OT7)
- differentiate conductive vs. sensorineural hearing loss
- rule out sudden sensorineural hearing loss (SSNHL), a medical emergency requiring high dose steroids and urgent referral
- in elderly, unilateral tinnitus or SNHL is acoustic neuroma until proven otherwise
- consider audiogram and referral or follow-up with family physician
Epistaxis
- see Otolaryngology, O26
- 90% of nosebleeds stem from the anterior nasal septum (at Kiesselbach’s plexus located in Little’s area)
- can be life-threatening

Etiology
- most commonly caused by trauma (digital, blunt, foreign bodies)
- other causes: barometric changes, nasal dryness, chemicals (cocaine, Otrivin®), or systemic disease (coagulopathies, HTN, etc.)

Investigations
- blood work: CBC, PT/PTT (as indicated)
- imaging: X-ray, CT as needed

Treatment
- aim is to localize bleeding and achieve hemostasis
- first-aid: ABCs, clear clots by blowing nose or suctioning, lean forward, pinch cartilaginous portion of nose for 20 min twice
- assess blood loss: vitals, IV NS, cross match 2 units pRBC if significant
- if first aid measures fail twice, proceed to packing
- apply an anterior pack
  - clear nose of any clots
  - apply topical anesthetics/vasoconstrictors (lidocaine with epinephrine, cocaine, or soaked pledgets)
  - insert either a traditional Vaseline® gauze pack or a commercial nasal tampon or balloon
  - if bleeding stops, arrange follow-up in 48-72 h for reassessment and pack removal
  - if packing both nares, prophylactic anti-staphylococcal antibiotics to prevent sinusitis or toxic shock syndrome
  - if bleeding is controlled with anterior pressure, cautery with silver nitrate can be performed if the site of bleeding is identified (one side of septum only because if both are cauterized this can lead to septal perforation)
  - if suspect posterior bleed or anterior packing does not provide hemostasis, consult ENT for posterior packing and further evaluation
  - posterior packing requires monitoring; can cause significant vagonal response and posterior bleeding source can lead to significant blood loss, therefore usually requires admission

Disposition
- discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. humidifiers, saline spray, topical ointments, avoiding irritants, managing HTN)
- admission: severe cases of refractory bleeding, and most cases of posterior packing

Gynecologic/Urologic Emergencies

Vaginal Bleeding
- see Gynecology, GY10 and Obstetrics, OB13

Etiology
- pregnant patient
  - 1st/2nd trimester pregnancy: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause)
  - 2nd/3rd trimester pregnancy: placenta previa, placental abruption, premature rupture of membranes, preterm labour
  - other: trauma, bleeding cervical polyp, passing of mucous plug
- postpartum
  - postpartum hemorrhage, uterine inversion, retained placental tissue, endometritis
  - non-pregnant patients
  - Structural (PALM- polyps, adenomyosis, leiomyoma, malignancies/hyperplasia), non-structural (COEIN - coagulopathy ovulatory, endometrial, iatrogenic, and not yet diagnosed)

History
- characterize bleeding (frequency, duration, number of pads/tampons, cyclicity)
- pain, if present (OPQRSTU)
- menstrual history, sexual history, STI history, syncope/pre syncope
- details of pregnancy, including gush of fluid and fetal movement (>20 wk)

Complications of Nasal Packing
- Hypoxemia
- Toxic-shock syndrome
- Aspiration
- Pharyngeal fibrosis/stenosis
- Alar/septal necrosis

Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removabale pack
Physical Exam
- ABC (especially noting postural BP/HR and mucous membrane)
- abdominal examination (peritoneal signs, tenderness, distension, mass)
- speculum examination (NOT IF 2nd/3rd trimester bleeding; perform only when placenta previa is ruled out with U/S)
  - look for active bleeding, trauma/anomaly, and cervical dilation
- bimanual examination (cervical tenderness, size of uterus, cervical length/dilation)
- sterile gloves and speculum if pregnant

Investigations
- β-hCG test for all patients with childbearing potential
- CBC, blood and Rh type, quantitative β-hCG, PTT, INR
- type and cross if significant blood loss
- transvaginal U/S (rule out ectopic pregnancy and spontaneous abortion)
- abdominal U/S (rule out placenta previa, fetal demise, or retained products post-partum)

Management
- ABCs
- pulse oximeter and cardiac monitors if unstable
- Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
- 1st/2nd trimester pregnancy
  - ectopic pregnancy: definitive treatment with surgery or methotrexate
  - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
  - U/S indeterminate or β-hCG >1,000-2,000 IU: further workup and/or gynecology consult
  - abortions: if complete, discharge if stable; for all others, consult gynecology
- 2nd/3rd trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type and cross 4 units of blood, consult OB/GYN immediately
- non-pregnant
  - if unstable admit to gynecology for IV hormonal therapy, possible D&C
  - non-structural abnormalities
    - tranexamic acid (Cyklokapron®) to stabilize clots
    - Provera® 10 mg PO OD x 10 d, warn patient of a withdrawal bleed
    - stable structural abnormalities (fibroids, polyps, endometrial thickening, adenomyosis), outpatient gynecology referral once stable

Disposition
- decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult gynecology for patients requiring admission
- if patient can be safely discharged, ensure follow-up with family physician or gynecologist
- instruct patient to return to ED for increased bleeding, presyncope

Pregnant Patient in the ED

Table 25. Complications of Pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Fetal</th>
<th>Maternal</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Pregnancy failure</td>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>1-12 wk</td>
<td>Spontaneous abortion</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Fetal demise</td>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td></td>
<td>Gestational trophoblastic disease</td>
<td>UTI/pyelonephritis</td>
</tr>
<tr>
<td>Second</td>
<td>Disorders of fetal growth</td>
<td>Gestational DM</td>
</tr>
<tr>
<td>13-27 wk</td>
<td>IUGR</td>
<td>Rh incompatibility</td>
</tr>
<tr>
<td></td>
<td>Oligo/polyhydramnios</td>
<td>UTI/pyelonephritis</td>
</tr>
<tr>
<td>Third</td>
<td>Vasa previa</td>
<td>Preterm labour/PPROM</td>
</tr>
<tr>
<td>28-41 wk</td>
<td>Placenta previa</td>
<td>Pre-eclampsia/eclampsia</td>
</tr>
<tr>
<td></td>
<td>Placental abruption</td>
<td>Placenta previa</td>
</tr>
<tr>
<td></td>
<td>Uterine rupture</td>
<td>DVT</td>
</tr>
<tr>
<td></td>
<td>DVT</td>
<td></td>
</tr>
</tbody>
</table>
Nephrolithiasis (Renal Colic)

- see Urology, U17

Epidemiology and Risk Factors
- 10% of population (twice as common in males)
- recurrence 50% at 5 yr
- peak incidence 30-50 yr of age
- 75% of stones <5 mm pass spontaneously within 2 wk, larger stones may require consultation

Clinical Features
- urinary obstruction \(\rightarrow\) upstream distention of ureter or collecting system \(\rightarrow\) severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- whirring, N/V, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis
- peritoneal findings/anterior abdominal tenderness usually absent

Differential Diagnosis of Renal Colic
- acute ureteric obstruction
- acute abdomen: biliary, bowel, pancreas, AAA
- urogynecological: ectopic pregnancy, torsion, rupture of ovarian cyst, testicular torsion
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1): herpes zoster, nerve root compression

Investigations
- screening
- CBC: elevated WBC in presence of fever suggests infection
- electrolytes, Cr, BUN to assess renal function
- U/A: R&M (WBCs, RBCs, crystals), C&S
- imaging
- non-contrast spiral CT is the study of choice
- abdominal U/S may demonstrate stone or hydronephrosis (consider in females of childbearing age)
- AXR will identify large radio-opaque stones (calcium, struvite, and cystine stones) but may miss smaller stones, uric acid stones, or stones overlaid by bony structures; consider as an initial investigation in patients who have a history of radio-opaque stones and similar episodes of acute flank pain (CT necessary if film is negative)
- strain all urine for stone analysis

Management
- analgesics: NSAIDs (usually ketorolac [Toradol\(^\text{\textregistered}\)], preferable over opioids), antiemetics, IV fluids
- urology consult may be indicated, especially if stone >5 mm, or if patient has signs of obstruction or infection
- \(\alpha\)-blocker (e.g. tamsulosin) may be helpful to increase stone passage in select cases

Disposition
- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and able to tolerate oral medications
- may advise hydration and limitation of protein, sodium, oxalate, and alcohol intake

Ophthalmologic Emergencies

- see Ophthalmology, OP5

History and Physical Exam
- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital X-rays, U/S, or CT scan to exclude presence of intraocular metallic foreign body
- visual acuity in both eyes, pupils, extraocular structures, fundoscopy, tonometry, slit lamp exam

Management of Ophthalmologic Foreign Body
- copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab or sterile needle
- antibiotic drops qid until healed
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only
- consider tetanus prophylaxis
- ophthalmology consult if globe penetration suspected
### Table 26. Differential Diagnosis of Red Eye in the Emergency Department

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Serious Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light Sensitivity</td>
<td>Iritis, keratitis, abrasion, ulcer</td>
</tr>
<tr>
<td>Unilateral</td>
<td>Above + herpes simplex, acute angle closure glaucoma</td>
</tr>
<tr>
<td>Significant Pain</td>
<td>Above + scleritis</td>
</tr>
<tr>
<td>White Spot on Cornea</td>
<td>Corneal ulcer</td>
</tr>
<tr>
<td>Non-Reactive Pupil</td>
<td>Acute glaucoma, iritis</td>
</tr>
<tr>
<td>Copious Discharge</td>
<td>Gonococcal conjunctivitis</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>All of the above</td>
</tr>
</tbody>
</table>

### Table 27. Select Ophthalmologic Emergencies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Signs and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Angle Closure Glaucoma</td>
<td>Unilateral red, painful eye</td>
<td>Ophthalmology consult for laser iridotomy</td>
</tr>
<tr>
<td></td>
<td>Decreased visual acuity, halos around lights</td>
<td>Topical β-blockers, adrenergics, and cholinergics</td>
</tr>
<tr>
<td></td>
<td>Fixed, mid-dilated pupil</td>
<td>Systemic carbonic anhydrase inhibitors and hyperosmotic agents</td>
</tr>
<tr>
<td></td>
<td>N/V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marked increase in IOP (&gt;40 mmHg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shallow anterior chamber ± cells</td>
<td></td>
</tr>
<tr>
<td>Chemical Burn</td>
<td>Known exposure to acids or alkali (worse)</td>
<td>Irrigate at site of accident</td>
</tr>
<tr>
<td></td>
<td>Pain, decreased visual acuity</td>
<td>IV NS drip in ED with eyelid retracted</td>
</tr>
<tr>
<td></td>
<td>Vascularization or defects of cornea</td>
<td>Swab fornices</td>
</tr>
<tr>
<td></td>
<td>Iris and lens damage</td>
<td>Cycloplegic drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical antibiotics and patching</td>
</tr>
<tr>
<td>Orbital Cellulitis</td>
<td>Red, painful eye, decreased visual acuity</td>
<td>Admission, ophthalmology consult</td>
</tr>
<tr>
<td></td>
<td>Headache, fever</td>
<td>Blood cultures, orbital CT</td>
</tr>
<tr>
<td></td>
<td>Lid erythema edema, and difficulty opening eye</td>
<td>IV antibiotics (ceftriaxone + vancomycin)</td>
</tr>
<tr>
<td></td>
<td>Conjunctival injection and chemosis</td>
<td>Drainage of abscess</td>
</tr>
<tr>
<td></td>
<td>Proptosis, opthalmoplegia ± RAPD</td>
<td></td>
</tr>
<tr>
<td>Retinal Artery Occlusion</td>
<td>Sudden, painless, monocular vision loss</td>
<td>Restore blood flow &lt;2 h</td>
</tr>
<tr>
<td></td>
<td>RAPD</td>
<td>Massage globe</td>
</tr>
<tr>
<td></td>
<td>Cherry red spot and retinal pallor on funduscopy</td>
<td>Decrease IOP (topical β-blockers, inhaled O2/CO2-mix, IV Diamox®, IV mannitol, drain aqueous fluid)</td>
</tr>
<tr>
<td>Retinal Detachment</td>
<td>Flashes of light, floaters, and curtains of blackness/ peripheral vision loss</td>
<td>Ophthalmology consult for scleral buckle/ pneumatic retinopexy</td>
</tr>
<tr>
<td></td>
<td>Painless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of red reflex, decreased IDP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detached areas are grey</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAPD ±</td>
<td></td>
</tr>
</tbody>
</table>

### Dermatologic Emergencies

#### Rash Characteristics

**A. Diffuse Rashes**

- **Staphylococcal Scalded Skin Syndrome (SSSS)**
  - caused by an exotoxin from infecting strain of coagulase-positive *S. aureus*
  - mostly occurs in children
  - prodrome: fever, irritability, malaise, and skin tenderness
  - sudden onset of diffuse erythema: skin is red, warm, and very tender
  - flaccid bullae that are difficult to see, then desquamate in large sheets
  - Nikolskay’s sign: gentle lateral stroking of skin causes epidermis to separate
- **Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)**
  - see Dermatology, D22
  - caused by drugs (e.g. phenytoin, sulfas, penicillins, and NSAIDs), bone marrow transplantation, and blood product transfusions
  - usually occurs in adults
  - diffuse erythema followed by necrosis
  - severe mucous membrane blistering
  - entire epidermis desquamation
  - high mortality (>50%)
- **Toxic Shock Syndrome (TSS)**
  - see Infectious Diseases, ID23
  - caused by superantigen from *S. aureus* or GAS activating T cell and cytokines
  - patient often presents with onset of shock and multi organ failure, fever
  - diffuse erythematous macular rash
  - at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, and skin (necrotizing fascitis, gangrene)
Dermatologic Emergencies

- vesicobullous lesions
- Erythema Multiforme (EM)
  - see Dermatology, D29
  - immunologic reaction to herpes simplex
  - viral prodrome 1-14 d before rash
  - “target lesion”: central grey bulla or wheal surrounded by concentric rings of erythema and normal skin

B. Discrete Lesions
- pyoderma gangrenosum
  - often associated with immunocompromised patients (HIV, leukemia, or lymphoma) with Gram-negative sepsis
  - often occurs in arms, hands, feet, or perineal region
  - usually begins as painless macule/vesicle pustule/bulla on red/blue base sloughing, leaving a gangrenous ulcer
- disseminated gonococcal infection
  - see Dermatology, D22
  - fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), and septic arthritis (in larger joints, such as knees, ankles, and elbows)
  - most commonly in gonococcus positive women during menstruation or pregnancy
  - skin lesions usually appear in extremities and resolve quickly (<7 d)
- meningococcemia
  - flu-like symptoms of headache, myalgia, N/V
  - petechial, macular, or maculopapular lesions with grey vesicular centres
  - usually a few millimeters in size, but may become confluent and hemorrhagic
  - usually appear in extremities, but may appear anywhere
  - look for signs of meningeal irritation: Brudzinski, Kernig, nuchal rigidity, jolt accentuation

History and Physical Exam
- determine onset, course, and location of skin lesions
- fever, joint pain
- associated symptoms: CNS, respiratory, GU, GI, renal, liver, mucous membranes
- medication history
- vitals

Investigations
- immediate consultation if patient unstable
- CBC, electrolytes, Cr, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)

Management
- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevention of infection
- determine if admission and consult needed: dermatology or infectious diseases
- specific management is determined by etiology
  - SSSS, TSS, DGI, and meningococcemia
  - IV antibiotics
  - EM, SJS, and TEN
  - stop precipitating medication
  - fluids
  - symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir consider IVIG
  - TEN: debride necrotic tissue

Disposition
- most cases will require urgent care and hospitalization
- TEN: early transfer to burn centre improves outcome
Environmental Injuries

Heat Exhaustion and Heat Stroke

HEAT EXHAUSTION
- Clinical features relate to loss of circulating volume caused by exposure to heat stress
  - "water depletion": heat exhaustion occurs if lost fluid not adequately replaced
  - "salt depletion": heat exhaustion occurs when losses replaced with hypotonic fluid

HEAT STROKE
- Life-threatening emergency resulting from failure of normal compensatory heat shedding mechanisms
- Divided into classical and exertional subtypes
- If patient does not respond relatively quickly to cooling treatments, consider other possible etiologies
  of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, other infections)

<table>
<thead>
<tr>
<th>Table 28. Heat Exhaustion vs. Heat Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat Exhaustion</td>
</tr>
<tr>
<td>Clinical Features</td>
</tr>
<tr>
<td>Body temp &lt;40.5°C (usually normal)</td>
</tr>
<tr>
<td>No coma or seizures</td>
</tr>
<tr>
<td>Dehydration (HR, orthostatic hypotension)</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Hypothermia and Cold Injuries

HYPOTHERMIA
- Hyperthermia is an increase in temperature by thermoregulatory failure, whereas fever is mediated by cytokine activity
- Predisposing factors: young persons who overexert themselves, older adults who cannot dissipate heat at rest (e.g. using anticholinergic drugs such as antihistamines or TCAs), and patients who are using anticholinergic or antiepileptic medications
- Treatment based on re-warming and supporting cardiopulmonary function
- Complications: coagulopathy, acidosis, ventricular dysrhythmias (VTib), asystole, volume and electrolyte depletion
- Labs: CBC, electrolytes, ABG, serum glucose, Cr/BUN, Mg2+, Ca2+, amylase, coagulation profile
- Imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- Monitors: ECG, rectal thermometer, Foley catheter, NG tube, monitor metabolic status frequently

<table>
<thead>
<tr>
<th>Table 29. Classification of Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
</tbody>
</table>

Re-warming Options
- Gentle fluid and electrolyte replacement in all (due to cold diuresis)
- Passive external re-warming
  - Suitable for most stable patients with core temperature >32.2°C
  - Involves covering patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
Environmental Injuries

- **active external re-warming**
  - involves use of warming blankets
  - beware of "afterdrop" phenomenon
  - safer when done in conjunction with active core re-warming

- **active core re-warming**
  - generally for patients with core temperature <32.2°C, and/or with cardiovascular instability
  - avoids "afterdrop" seen with AER alone
  - re-warm core by using
    - warmed humidified oxygen, IV fluids
    - peritoneal dialysis with warm fluids
    - gastric/colonic/pleural irrigation with warm fluids
    - external circulation (cardiopulmonary bypass machine) is most effective and fastest

Approach to Cardiac Arrest in the Hypothermic Patient
- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 min; may have profound bradycardia
- if any pulse at all (even very slow) do NOT do CPR
  - if in VFib try to defibrillate up to maximum 3 shocks if core temperature <30°C
  - intubate if required, ventilate with warmed, humidified O₂
- medications (vasopressors, antidysrhythmics) may not be effective at low temperatures controversial; may try one dose
- focus of treatment is re-warming

**FROSTBITE**

**Classification**
- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
  - 1st degree
    - symptoms: initial paresthesia, pruritus
    - signs: erythema, edema, hyperemia, no blisters
  - 2nd degree
    - symptoms: numbness
    - signs: blistering (clear), erythema, edema
  - 3rd degree
    - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
    - signs: hemorrhagic blisters, skin necrosis, edema, no movement
  - 4th degree
    - extension into subcuticular, osseous, and muscle tissues

**Management**
- treat for hypothermia: O₂, IV fluids, maintenance of body warmth
- remove wet and constrictive clothing
- immerse in 40-42°C agitated water for 10-30 min (very painful; administer adequate analgesia)
- clean injured area and leave it open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin
- tetanus prophylaxis
- consider penicillin G as frost bite injury has high risk of infection
- surgical intervention may be required to release restrictive eschars
- never allow a thawed area to re-chill/freeze

**Burns**
- see Plastic Surgery, PL18

**Clinical Presentation/Physical Exam Findings**
- burn size
  - rule of nines; does not include 1st degree burns
- burn depth
  - superficial (1st degree): epidermis only (e.g. sunburn), painful and tender to palpation
  - superficial partial thickness (2nd degree): extends to epidermis and superficial dermis, blister formation occurs, very painful
  - deep partial thickness (2nd degree): involves hair follicles, sebaceous glands; skin is blistered, exposed dermis is white to yellow, absent sensation
  - full thickness (3rd degree): epidermis and all dermal layers; skin is pale, insensate, and charred or leathery
  - deep (4th degree): involvement of fat, muscle, even bone

**Management**
- remove noxious agent/stop burning process
- establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury)
- resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)
Fluid boluses if unstable
- Parkland Formula: Ringer’s lactate 4 cc/kg/%BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
- urine output is best measure of resuscitation, should be 40-50 cc/h or 0.5 cc/kg/h; avoid diuretics
- pain relief: continuous morphine infusion with breakthrough bolus
- investigations: CBC, electrolytes, U/A, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, systemic antibiotics infrequently indicated
- tetanus prophylaxis if burn is deeper than superficial dermis

Disposition
- admit
  - 2nd degree burns >10% BSA, or any significant 3rd degree burns
  - 2nd degree burns on face, hands, feet, perineum, or across major joints
  - electrical, chemical burns, and inhalation injury
  - burn victims with underlying medical problems or immunosuppressed patients

Inhalation Injury

Etiology
- CO or cyanide poisoning
- direct thermal injury: limited to upper airway (above the vocal cords)
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

History and Physical Exam
- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin (unreliable, usually post-mortem finding)
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO2 normal but O2 saturation low suggests CO poisoning

Investigations
- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± bronchoscopy

Management
- CO poisoning: 100% O2 ± hyperbaric O2 (controversial)
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators, and mucolytics (N-acetylcysteine)

Bites

MAMMALIAN BITES
- see Plastic Surgery, PL11

History
- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, rabies risks HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, “fight bites”

Physical Exam
- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status

Investigations
- if bony injury or infection suspected, check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds ± CT to rule out cranial perforation
- ultrasound may be helpful for identifying abscess formation as well as locating radiolucent foreign bodies in infected wounds

Initial Management
- wound cleansing and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
• culture wound if signs of infection (erythema, necrosis, or pus) obtain anaerobic cultures if wound foul smelling, necrotizing, or abscess; notify lab that sample is from bite wound
• suturing
  • vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  • allow avascular structures (i.e. pretilial regions, hands, and feet) to heal by secondary intention
  • tetanus immunization if >10 yr or incomplete primary series

**Prophylactic Antibiotics**

• types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
• a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present (efficacy not proven)
• dog and cat bites (pathogens: *Pasteurella multocida, S. aureus, S. viridans*)
  • 10-50% of cat bites, 5% of dog bites become infected
• human bites (pathogens: *Eikenella corrodens, S. aureus, S. viridans, oral anaerobes*)
  • 1st line: amoxicillin + clavulanic acid
• rabies (see Infectious Diseases, ID20)
  • reservoirs: warm-blooded animals except rodents, lagomorphs (e.g. rabbits)
  • post-exposure vaccine is effective; treatment depends on local prevalence

**INSECT BITES**

• bee stings
  • 5 types of reactions to stings (local, large local, systemic, toxic, unusual)
  • history and physical exam key to diagnosis; no lab test will confirm
  • investigations: CBC, electrolytes, BUN, Cr, glucose, ABGs, ECG
  • ABC management, epinephrine 0.1 mg IV over 5 min if shock, antihistamines, cimetidine 300 mg IV/IM/PO, steroids, β-agonists for SOB/wheezing 3 mg in 5 mL NS via nebulizer, local site management
  • West Nile virus (see Infectious Diseases, ID24)

**Near Drowning**

• most common in children <4 yr and teenagers
• causes lung damage, hypoxemia, and may lead to hypoxic encephalopathy
• must also assess for shock, C-spine injuries, hypothermia, and scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
• complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

**Physical Exam**

  ABCs, vitals: watch closely for hypotension
  • respiratory: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
  • CVS: murmurs, dysrhythmias, JVP (CHF, pneumothorax)
  • H&N: assess for C-spine injuries
  • neurological: GCS or AVPU, pupils, focal deficits

**Investigations**

  • labs: CBC, electrolytes, ABGs, Cr, BUN, INR, PTT, U/A (drug screen, myoglobin)
  • imaging: CXR (pulmonary edema, pneumothorax) ± C-spine imaging
  • ECG

**Management**

  • ABCs, treat for trauma, shock, hypothermia
  • cardiac and O₂ monitors, IV access
  • intensive respiratory care
    • ventilator assistance if decreased respirations, pCO₂ >50 mmHg, or pO₂ <60 mmHg on maximum O₂
    • may require intubation for airway protection, ventilation, pulmonary toilet
    • high flow O₂/CPAP/BiPAP may be adequate but some may need mechanical ventilation with positive end-expiratory pressure
  • dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, and acidosis
  • vomiting: very common, NG suction to avoid aspiration
  • convulsions: usually respond to O₂; if not, diazepam 5-10 mg IV slowly
  • bronchodilator: bronchodilators
  • bacterial pneumonia: prophylactic antibiotics not necessary unless contaminated water or hot tub (*Pseudomonas*)
  • always initiate CPR in drowning-induced cardiac arrest even if patient hypothermic; continue CPR until patient is fully rewarmed

**Disposition**

  • non-significant submersion: discharge after short observation
  • significant submersion (even if asymptomatic): long period of observation (24 h) as pulmonary edema may appear late
  • CNS symptoms or hypoxemia: admit
  • severe hypoxemia, decreased LOC: ICU
Toxicology

“ABCD₃EFG” of Toxicology

- basic axiom of care is symptomatic and supportive treatment
- address underlying problem only once patient is stable

A  Airway (consider stabilizing the C-spine)
B  Breathing
C  Circulation
D1  Drugs
   - ACLS as necessary to resuscitate the patient
   - universal antidotes
D2  Draw bloods
D3  Decontamination (decrease absorption)
E  Expose (look for specific toxidromes)/Examine the patient
F  Full vitals, ECG monitor, Foley, X-rays
G  Give specific antidotes and treatments

- reassess
- call Poison Information Centre
- obtain corroborative history from family, bystanders

D1 – Universal Antidotes

- treatments that will not harm patients and may be essential

**Dextrose (glucose)**
- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W
- children: 0.25 g/kg (2-4 mL/kg) IV of D25W

**Oxygen**
- do not deprive a hypoxic patient of oxygen no matter what the antecedent medical history (i.e. even COPD with CO₂ retention)
- if depression of hypoxic drive, intubate and ventilate
- exception: paraquat or diquat (herbicides) inhalation or ingestion (oxygen radicals increase morbidity)

**Naloxone** (central µ-receptor competitive antagonist, shorter t½ than naltrexone)
- antidote for opioids: administration is both diagnostic and therapeutic (1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    - response to naloxone can be drastic, so stepwise delivery of initial 2 mg bolus is recommended
    - draw up 2 mg to deliver IV/IM/SL/SC or via ETT (ETT dose = 2.5x IV dose)
      - 1st dose 0.4 mg
      - if no response, deliver second dose 0.6 mg
      - if still no response, deliver remaining 1 mg
  - child
    - 0.01 mg/kg initial bolus IV/OE/ETT
    - 0.1 mg/kg if no response and opioid still suspected to max of 10 mg
- maintenance dose
  - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
  - hourly infusion rate at 2/3 of initial dose that allowed patient to be roused

**Thiamine** (Vitamin B1)
- 100 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke’s encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke’s encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine unavailable
- must assume all undifferentiated comatose patients are at risk

---

**Toxicology**

**Universal Antidotes**

- DONT
  - Dextrose
  - Oxygen
  - Naloxone
  - Thiamine (must give BEFORE dextrose)

**Principles of Toxicology**

4 principles to consider with all ingestions:
- Resuscitation (ABCD₃EFG)
- Screening (toxidromes? clinical clues?)
- Decrease absorption of drug
- Increase elimination of drug

**Administration of naloxone can cause opioid withdrawal in chronic users:**

- Minor withdrawal may present as lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, HTN, and tachycardia
- Severe withdrawal may present as hot and cold flashes, arthralgias, myalgias, N/V, and abdominal cramps

**Thiamine is deficient in the malnourished.**

Consider in patients with alcohol use disorder, anorexia, or malnutrition states
D2 – Draw Bloods

- **essential tests**
  - CBC, electrolytes, BUN/CR, glucose, INR/PTT, osmolality
  - ABGs, measure O₂ sat
  - ASA, acetaminophen, EtOH levels
- **potentially useful tests**
  - drug levels – this is NOT a serum drug screen
  - Ca²⁺, Mg²⁺, PO₄³⁻
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical presentation

**Serum Drug Levels**

- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only)

**Table 30 Toxic Gaps (see Nephrology, NP16)**

<table>
<thead>
<tr>
<th>METABOLIC ACIDOSIS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased AG: “MUDPILES CAT” (* = toxic)</td>
<td>Increased POG: “MAE DIE” (if it ends in “-ol”, it will likely increase the POG)</td>
</tr>
<tr>
<td>Methanol*</td>
<td>Methanol</td>
</tr>
<tr>
<td>Uremia</td>
<td>Acetone</td>
</tr>
<tr>
<td>Diabetic ketoacidosis/Starvation ketoacidosis</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Phenformin*/Paraldehyde*</td>
<td>Diuretics (glycerol, mannitol, sorbitol)</td>
</tr>
<tr>
<td>Isoniazid, Iron, Ibuprofen</td>
<td>Isoxpropanol</td>
</tr>
<tr>
<td>Lactate (anything that causes seizures or shock)</td>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Ethylene glycol*</td>
<td>Note: normal POG does not rule out toxic alcohol; only an elevated gap is helpful</td>
</tr>
<tr>
<td>Salicylates*</td>
<td></td>
</tr>
<tr>
<td>Cyanide, CO*</td>
<td></td>
</tr>
<tr>
<td>Alcoholic ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>Toluene, theophylline*</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased AG</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte imbalance (increased Na⁺/K⁺/Mg²⁺)</td>
<td>Increased O₂ saturation gap</td>
</tr>
<tr>
<td>Hypoalbuminemia (50% fall in albumin ~5.5 mmol/L decrease in the AG)</td>
<td>Carboxyhemoglobin</td>
</tr>
<tr>
<td>Lithium, br mine elevation</td>
<td>Methemoglobin</td>
</tr>
<tr>
<td>Paraproteins (multiple myeloma)</td>
<td>Suffmethemoglobin</td>
</tr>
</tbody>
</table>

**Normal AG**
- High K⁺: pyelonephritis, obstructive nephropathy, renal tubular acidosis IV, TPN
- Low K⁺: small bowel losses, acetazolamide, renal tubular acidosis I, II

**Table 31. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning**

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
<th>Selected Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Hypoventilation (pCO₂)</td>
<td>CNS depressants (opioids, sedative-hypnotics, phenothiazines, EtOH)</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation (pCO₂)</td>
<td>Salicylates, CO, other asphyxiants</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>AG metabolic acidosis</td>
<td>“MUDPILES CAT”: see Table 30</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Digitals, fluoride, potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hypoglycemia</td>
<td>Oral hypoglycemic agents, insulin, EtOH, ASA</td>
</tr>
<tr>
<td>Osmolality and Osmolar Gap</td>
<td>Elevated osmolar gap</td>
<td>“MAE DIE”: see Table 30</td>
</tr>
<tr>
<td>ECG</td>
<td>Wide QRS complex</td>
<td>TCAs, quinidine, other class 1a and 1c antiarrhythmic agents</td>
</tr>
<tr>
<td></td>
<td>Prolonged QT interval</td>
<td>Terfenadine, astemizole, antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Atrioventricular block</td>
<td>Ca²⁺ antagonists, digitals, phenylpropanolamine</td>
</tr>
<tr>
<td>Abdominal X-Ray</td>
<td>Radioopaque pills or objects</td>
<td>“CHIPES”: Calcium, Chloral hydrate, CCr, Heavy metals, Iron, Potassium, Enteral coated Salicylates, and some foreign bodies</td>
</tr>
<tr>
<td>Serum Acetaminophen</td>
<td>Elevated level (&gt;140 mg/L or 1,000 µmol/L 4 h after ingestion)</td>
<td>May be only sign of acetaminophen poisoning</td>
</tr>
</tbody>
</table>
D3 – Decontamination and Enhanced Elimination

Ocular Decontamination
- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

Dermal Decontamination (Wear Protective Gear)
- remove clothing, brush off toxic agents, irrigate all external surfaces

Gastrointestinal Decontamination
- single dose activated charcoal
  - adsorption of drug/toxin to activated charcoal prevents availability
  - contraindications: caustics, small bowel obstruction, perforation
  - dose: 10 g/g drug ingested or 1g/kg body weight
  - odourless, tasteless, prepared as slurry with H2O
- whole bowel irrigation
  - 500 mL/h (child) to 2,000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
  - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated
- indications
  - awake, alert, can be nursed upright OR intubated and airway protected
  - delayed release product
  - drug/toxin not bound to charcoal
  - drug packages (if any evidence of breakage emergency surgery)
  - recent toxin ingestion
- contraindications
  - evidence of ileus, perforation, or obstruction
  - surgical removal in extreme cases
  - indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
  - no evidence for the routine use of cathartics (i.e. ipecac)

Urine Alkalization
- may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
- weakly acidic substances can be trapped in alkali urine (pH >7.5) to increase elimination

Multidose Activated Charcoal
- may be used for: carbamazepine, phenobarbital, quinine, theophylline
- for toxins which undergo enterohepatic recirculation
- removes drug that has already been absorbed by drawing it back into GI tract
- various regimens: 12.5 g (1/4 bottle) PO q1h or 25 g (1/2 bottle) PO q2h until non-toxic

Hemodialysis
- indications/criteria for hemodialysis
  - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution, or rapid plasma equilibration
  - removal of toxin will lead to clinical improvement
  - advantage is shown over other modes of therapy
  - predicted that drug or metabolite will have toxic effects
  - impairment of normal routes of elimination (cardiac, renal, or hepatic)
  - clinical deterioration despite maximal medical support
- useful for the following toxins
  - methanol
  - ethylene glycol
  - salicylates
  - lithium
  - phenobarbital
  - chloral hydrate (trichloroethanol)
  - others include theophylline, carbamazepine, valproate, methotrexate

E – Expose and Examine the Patient
- vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours, and CNS
- head-to-toe survey including
  - C-spine
  - signs of trauma, seizures (incontinence, “tongue biting”, etc.), infection (meningismus), or chronic alcohol/drug abuse (track marks, nasal septum erosion)
- mental status
Table 32. Specific Toxidromes

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Overdose Signs and Symptoms</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>Hyperthermia</td>
<td>Antidepressants (e.g. TCAs)</td>
</tr>
<tr>
<td></td>
<td>&quot;Hot as a hare&quot;</td>
<td>Cycllobenzaprine (Flexeril*)</td>
</tr>
<tr>
<td></td>
<td>Dilated pupils</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>&quot;Blind as a bat&quot;</td>
<td>Antihistamines (e.g. diphenhydramine)</td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td></td>
<td>&quot;Dry as a bone&quot;</td>
<td>Antispasmodics</td>
</tr>
<tr>
<td></td>
<td>Vasodilation</td>
<td>Belladonna alkaloids (e.g. atropine)</td>
</tr>
<tr>
<td></td>
<td>&quot;Red as a beet&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Agitation/hallucinations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Mad as a hatter&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;The bowel and bladder lose their tone and the heart goes on alone*&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Hot as a hare&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Blind as a bat&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Dry as a bone&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Red as a beet&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Mad as a hatter&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;The bowel and bladder lose their tone and the heart goes on alone*&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td>Cholinergic</td>
<td>&quot;DUMBELS&quot;</td>
<td>Natural plants: mushrooms, trumpet flower</td>
</tr>
<tr>
<td></td>
<td>Diaphoresis, Diarrhea, Decreased BP</td>
<td>Anticholinesterases phystostigmine</td>
</tr>
<tr>
<td></td>
<td>Urination</td>
<td>Insecticides (organophosphates, carbamates)</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
<td>Nerve gases</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm, Bronchorrhea, Bradycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emesis, Excitation of skeletal muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salivation, Seizures</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal</td>
<td>Dysphonia, dysphagia</td>
<td>Major tranquilizers</td>
</tr>
<tr>
<td></td>
<td>Rigidity and tremor</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Motor restlessness, crawling sensation (aka hisia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant movements (dyskinesia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Increased respiratory rate</td>
<td>CO poisoning (carboxyhemoglobin)</td>
</tr>
<tr>
<td>Derangements</td>
<td>Decreased LOC</td>
<td>Drug ingestion (methemoglobin, sulfmethemoglobin)</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyanosis unresponsive to O₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Opioid, Sedative/</td>
<td>Hypothermia</td>
<td>EtOH</td>
</tr>
<tr>
<td>Hypnotic, EtOH</td>
<td>Hypotension</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td>Opioids (morphine, heroin, fentanyl, etc.)</td>
</tr>
<tr>
<td></td>
<td>Dilated or constricted pupils (pinpoint in opioid)</td>
<td>Barb turates</td>
</tr>
<tr>
<td></td>
<td>CNS depression</td>
<td>Gamma hydroxybutyrate</td>
</tr>
<tr>
<td>Sympathomimetic</td>
<td>Increased temperature</td>
<td>Amphetamines, caffeine, cocaine, LSD, phencyclidine</td>
</tr>
<tr>
<td></td>
<td>CNS excitation (including seizures)</td>
<td>Ephedrine and other decongestants</td>
</tr>
<tr>
<td></td>
<td>Tachycardia, HTN</td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>N/V</td>
<td>Sedative or EtOH withdrawal</td>
</tr>
<tr>
<td>Serotonin Syndrome</td>
<td>Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, hyperthermia, diarrhea, HTN</td>
<td>MAOI, TCA, SSRI, opiate analgesics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough medicine, weight reduction medications</td>
</tr>
</tbody>
</table>

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

---

F – Full Vitals, ECG Monitor, Foley, X-Rays

G – Give Specific Antidotes and Treatments

Urine Alkalization Treatment for ASA Overdose
- urine pH >7.5
- fluid resuscitate first, then 3 amps NaHCO₃/L of D5W at 1.5x maintenance
- add 20-40 mEq/L KCl if patient is able to urinate

Table 33. Protocol for Warfarin Overdose

<table>
<thead>
<tr>
<th>INR</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.0</td>
<td>Cessation of warfarin administration, observation, serial INR/PT</td>
</tr>
<tr>
<td>5.1–9.0</td>
<td>If no risk factors for bleeding, hold warfarin x 1-2 d and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding</td>
</tr>
<tr>
<td>9.1–20.0</td>
<td>Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary</td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4h) if needed</td>
</tr>
<tr>
<td>Toxin</td>
<td>Treatment</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Decontaminate (activated charcoal) N-acetylcysteine</td>
</tr>
<tr>
<td>Acute Dystonic Reaction</td>
<td>Benztropine: 1-2 mg IM/IV then 2 mg PO x 3 d OR Diphenhydramine 1-2 mg/kg IV then 25 mg PO qid x 3 d</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Decontaminate (activated charcoal) Supportive care</td>
</tr>
<tr>
<td>ASA</td>
<td>Decontaminate (activated charcoal) Alkalize urine; want urine pH &gt; 7.5</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Decontaminate (activated charcoal) Fluromazenil Supportive care</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Decontaminate (activated charcoal) Consider high dose insulin euglycemia therapy Some dialyzable, some use intralipids</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Decontaminate (activated charcoal) CaCl₂ 1-4 g of 10% solution IV if hypotensive Other: high dose insulin euglycemia inotropes or intralipids</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Decontaminate (activated charcoal) if oral Aggressive supportive care</td>
</tr>
<tr>
<td>CO Poisoning</td>
<td>See Inhalation Injury, ER47 Supportive care 100% O₂</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Hydroxocobalamin</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Decontaminate (activated charcoal) Digoxin-specific Ab fragments 10-20 vials IV if acute; 3-6 if chronic 1 vial (40 mg) neutralizes 0.5 mg of toxin</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Thiamine 100 mg IM/IV Manage airway and circulatory support</td>
</tr>
<tr>
<td>Ethylene Glycol/ Methanol</td>
<td>Fornepazole (4-methylpyrazole) 15 mg/kg IV load over 30 min, then 10 mg/kg q12h OR Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate 25-50 mg IV</td>
</tr>
<tr>
<td>Insulin IM/SC/ Oral Hypoglycemic</td>
<td>Glucose IV/PO/NG tube Glucagon: 1-2 mg IM (if no access to glucose)</td>
</tr>
<tr>
<td>MDMA</td>
<td>Decontaminate (activated charcoal), supportive care</td>
</tr>
<tr>
<td>Opioids</td>
<td>See Universal Antidotes, ER49</td>
</tr>
<tr>
<td>TCAs</td>
<td>Decontaminate (activated charcoal) Aggressive supportive care NaHCO₃ bolus for wide QRS/seizures</td>
</tr>
</tbody>
</table>

* Call local Poison Information Centre for specific doses and treatment recommendations
Alcohol Related Emergencies

- see Psychiatry PS23

**Acute Intoxication**
- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia may progress to coma
- hypotension (peripheral vasodilation)
- if obtunded, rule out
  - head trauma/intracranial hemorrhage
  - associated depressants/street drugs, toxic alcohols
  - may also contribute to respiratory/cardiac depression
- hypoglycemia (screen with bedside glucometer)
- hepatic encephalopathy: confusion, altered LOC, coma
  - precipitating factors: GI bleed, infection, sedation, electrolyte abnormalities, protein meal
- Wernicke's encephalopathy (ataxia, ophthalmoplegia, delirium)
- post-ictal state, basilar stroke

**Withdrawal**
- beware of withdrawal signs
- treatment
  - diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1h until calm
  - frequency of dosing may have to be increased depending on clinical response
  - may use CIWA protocol and give benzodiazepines as above until CIWA <10
  - thiamine 100 mg IM/IV then 50-100 mg/d
  - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  - admit patients with DT or multiple seizures

**Table 35. Alcohol Withdrawal Signs**

<table>
<thead>
<tr>
<th>Time Since Last Drink</th>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8 h</td>
<td>Mild withdrawal</td>
<td>Generalized tremor, anxiety, agitation, but no delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autonomic hyperactivity (sinus tachycardia), insomnia, N/V</td>
</tr>
<tr>
<td>1-2 d</td>
<td>Alcoholic hallucinations</td>
<td>Visual (most common), auditory, and tactile hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitals often normal</td>
</tr>
<tr>
<td>8 h-2 d</td>
<td>Withdrawal seizures</td>
<td>Typically brief generalized tonic-clonic seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May have several within a few hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT head if focal seizures have occurred</td>
</tr>
<tr>
<td>3-5 d</td>
<td>DT</td>
<td>5% of untreated withdrawal patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severely confused state, fluctuating LOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitation, insomnia, hallucinations/delusions, tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia, hyperpyrexia, diaphoresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High mortality rate</td>
</tr>
</tbody>
</table>

**Cardiovascular Complications**
- HTN
- cardiomyopathy: SOB, edema
- dysrhythmias ("holiday heart")
- AFib (most common), atrial flutter, SVT, VTach (especially Torsades if hypomagnesemic/hypokalemic)

**Metabolic Abnormalities**
- alcoholic ketoacidosis
  - AG metabolic acidosis, urine ketones, low glucose, and normal osmolality
  - history of chronic alcohol intake with abrupt decrease/cessation
  - malnourished, abdominal pain with N/V
  - treatment: dextrose, thiamine (100 mg IM/IV prior to dextrose), volume repletion (with NS)
  - generally resolves in 12-24 h
- other alcohols
  - ethylene glycol CNS, CVS, renal findings
  - methanol
    - early: lethargy, confusion
    - late: headache, visual changes, N/V, abdominal pain, tachypnea
  - both ethylene glycol and methanol produce severe metabolic acidosis with anion gap (as the alcohol is metabolized) and osmolar gap (initially after ingestion but before metabolism)
  - EtOH co-ingestion is protective
• treatment
  - urgent hemodialysis required
  - fomepizole 15 mg/kg IV bolus OR EtOH 10% IV bolus and infusion to achieve blood level of 22 mmol/L (EtOH loading may be done PO)
  - consider folic acid for methanol, and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites

• other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

**Gastrointestinal Abnormalities**
• gastritis
  - common cause of abdominal pain and GI bleed in chronic alcohol users
• pancreatitis
  - serum amylase very unreliable in patients with chronic pancreatitis, may need serum lipase
  - hemorrhagic form (15%) associated with increased mortality
  - fluid resuscitation very important
• hepatitis
  - AST/ALT ratio >2 suggests alcohol as the cause as well as elevated GGT with acute ingestion
• peritonitis/spontaneous bacterial peritonitis
  - leukocytosis, fever, generalized abdominal pain/tenderness
  - occasionally accompanies cirrhosis
  - paracentesis for diagnosis (common pathogens: \(E\ coli\), Klebsiella, Streptococcus)
• GI bleeds
  - most commonly gastritis or ulcers, even if patient known to have varices
  - consider Mallory-Weiss tear secondary to retching
  - often complicated by underlying coagulopathies
  - minor: treat with antacids
  - severe or recurrent: endoscopy

**Disposition**
• before patient leaves ED ensure stable vital signs, can walk unassisted, and fully oriented
• offer social services to find shelter or detox program
• ensure patient can obtain any medications prescribed and can complete any necessary follow-up

---

**Approach to the Overdose Patient**

**History**
• age, weight, underlying medical problems, medications
• substance, route, and quantity
• time and symptoms since exposure determines prognosis and need for decontamination
• route
• intention, suicidality

**Physical Exam**
• focus on: ABCs, LOC/GCS, vitals, pupils

**Disposition from the Emergency Department**
• methanol, ethylene glycol
  - delayed onset, admit and watch clinical and biochemical markers
• TCAs
  - prolonged/delayed cardiotoxicity warrants admission to monitored (ICU) bed
  - if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  - sinus tachycardia alone (most common finding) with history of overdose warrants observation in ED
• hydrocarbons/smoke inhalation
  - pneumonitis may lag 6-8 h
  - consider observation for repeated clinical and radiographic examination
• ASA, acetaminophen
  - if borderline level, get second level 2-4 h after first
  - for ASA, must have at least 2 levels going down before discharge (3 levels minimum)
• oral hypoglycemics
  - admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  - observe asymptomatic patient for at least 8 h

**Psychiatric Consultation**
• once patient medically cleared, arrange psychiatric intervention if required
• beware – suicidal ideation may not be expressed
Psychiatric Emergencies

Approach to Common Psychiatric Presentations

• see Psychiatry, PS4
• before seeing patient, ensure your own safety; have security/police available if necessary

History

• safety
  • assess suicidality: suicidal ideation (SI), intent, plan, lethal means, and past attempts
  • assess homicidality: homicidal ideation (HI), access to weapons, intended victim, and history of violence
  • driving and children
  • command hallucinations
  • identify current stressors and coping strategies
  • mood symptoms: manic, depressive
  • anxiety: panic attacks, generalized anxiety, phobias, obsessive-compulsive disorder, post-traumatic stress disorder
  • psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
  • substance use history: most recent use, amount, previous withdrawal reactions
  • past psychiatric history, medications, adherence with medications
  • medical history: obtain collateral if available

Physical Exam

• complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder
• mental status exam: general appearance, behaviour, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability

Investigations

• investigations vary with age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
• as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, biliubin, serum Cr, BUN, and osmolality
• blood levels of psychiatric medications
• CT head if suspect neurological etiology
  LP if indicated

Acute Psychosis

Differential Diagnosis

• primary psychotic disorder (e.g. schizophrenia)
• secondary to medical condition (e.g. delirium)
• drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
• infectious (CNS)
• metabolic (hypoglycemic, hepatic, renal, thyroid)
• structural (hemorrhage, neoplasm)

Management

• violence prevention
  • remain calm, empathic, and reassuring
  • ensure safety of staff and patients, have extra staff and/or security on hand
  • patients demonstrating escalating agitation or overt violent behaviour may require physical restraint and/or chemical tranquilization
  • treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
  • benzodiazepines: lorazepam 2 mg PO/IM/SL
  • antipsychotics: olanzapine 5 mg PO, haloperidol 5 mg PO/IM
• treat underlying medical condition
• psychiatry or Crisis Intervention Team consult

Key Functions of Emergency Psychiatric Assessment

• Is the patient medically stable?
• Rule out medical cause
• Is psychiatric consult needed?
• Are there safety issues (SI, HI)?
• Is patient certifiable? (must demonstrate risk [present/past test] and apparent mental illness [future test])

Psychiatric Review of Systems

MOAPS
Mood
Organic
Anxiety
Psychosis
Safety
Intoxication

booksfree.com
mebook.com
freebook.com
Suicidal Patient

Epidemiology
- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr

Management
- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), previous attempts
- admit if there is evidence of active intent and organized plan, access to lethal means, psychiatric disorder, intoxication (suicidal ideation may resolve with few days of abstinence)
- patient may require certification if unwilling to stay voluntarily
- do not start long-term medications in the ED
- psychiatry or Crisis Intervention Team consult

Common Pediatric ED Presentations

Modified Glasgow Coma Score

Table 36. Modified GCS

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 – spontaneously</td>
<td>5 – coos, babbles</td>
<td>6 – normal, spontaneous movement</td>
</tr>
<tr>
<td>3 – to speech</td>
<td>4 – irritable cry</td>
<td>5 – withdraws to touch</td>
</tr>
<tr>
<td>2 – to pain</td>
<td>3 – cries to pain</td>
<td>4 – withdraws to pain</td>
</tr>
<tr>
<td>1 – no response</td>
<td>2 – moans to pain</td>
<td>3 – decorticate flexion</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
<td>2 – decerebrate extension</td>
</tr>
</tbody>
</table>

Modified GCS for Children <4 years

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 – spontaneously</td>
<td>5 – oriented, social, speaks, interacts</td>
<td>6 – normal, spontaneous movement</td>
</tr>
<tr>
<td>3 – to speech</td>
<td>4 – confused speech, disoriented, consolable</td>
<td>5 – localizes to pain</td>
</tr>
<tr>
<td>2 – to pain</td>
<td>3 – inappropriate words, not consolable/aware</td>
<td>4 – withdraws to pain</td>
</tr>
<tr>
<td>1 – no response</td>
<td>2 – incomprehensible, agitated, restless, not aware</td>
<td>3 – decorticate flexion</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
<td>2 – decerebrate extension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 – no response</td>
</tr>
</tbody>
</table>

Respiratory Distress

- see Pediatrics, P79

History and Physical Exam
- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
- see Pediatrics, P3 for age specific vital signs
- pulse paradoxus
- wheezing, grunting, vomiting

Table 37 Stridorous Upper Airway Diseases: Diagnosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group</th>
<th>Bacterial Tracheitis</th>
<th>Epiglottitis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Range (yr)</td>
<td>0.5-4</td>
<td>5-10</td>
<td>2-8</td>
</tr>
<tr>
<td>Prodrome</td>
<td>Days</td>
<td>Hours to days</td>
<td>Minutes to hours</td>
</tr>
<tr>
<td>Temperature</td>
<td>Low grade</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Radiography</td>
<td>Steeple sign</td>
<td>Exudates in trachea</td>
<td>Thumb sign</td>
</tr>
<tr>
<td>Etiology</td>
<td>Parainfluenza</td>
<td>S. aureus/GAS</td>
<td>H. influenzae type b</td>
</tr>
<tr>
<td>Barky Cough</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drooling</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Appear Toxic</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intubation/ICU</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NOTE
- Oral exam
- Oral exam
- No oral exam, consult ENT

¹Now rare with Hb vaccine in common use
Management

- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - dexamethasone x 1 dose
  - if moderate-severe, add nebulized epinephrine (racemic has limited availability)
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
  - humidified O₂ should not be given (no evidence for efficacy)
- bacterial tracheitis
  - airway maintenance - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g. cloxacillin), pending C&S
- epiglottitis
  - 4 D's: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
  - do not examine oropharynx or agitate patient
  - immediate anesthesiology, ENT call – intubate
  - then IV fluids, antibiotics, blood cultures
- asthma
  - supplemental O₂ if saturation <90% or PaO₂ <60%
  - bronchodilator therapy: salbutamol (Ventolin®) 0.15 mg/kg x3 by mask q20min
  - give corticosteroid therapy as soon as possible after arrival (prednisolone 2 mg/kg, dexamethasone 0.6 mg/kg, 2 doses 24 h apart)
  - if severe, add 250-500 µg ipratropium (Atrovent®) to first 3 doses salbutamol if critically ill, not responding to inhaled bronchodilators or steroids: give IV bolus, then infusion of MgSO₄
  - IV ß₂-agonists if critically ill and not responding to above

FEBRILE INFANT and FEBRILE SEIZURES

FEBRILE INFANT
- see Pediatrics, P46
- for fever >38°C without obvious focus
  - <28 d
    - admit
    - full septic workup (CBC and differential, blood C&S, urine C&S, LP ± stool C&S, CXR if indicated)
    - treat empirically with broad spectrum IV antibiotics
  - 28-90 d
    - as above unless infant meets Rochester criteria, partial septic workup (CBC and differential, blood C&S, urine C&S, CXR if indicated)
  - >90 d
    - toxic: admit, treat, full septic workup
    - non-toxic and no focus: investigate as indicated by history and physical

FEBRILE SEIZURES
- see Pediatrics, P77

Etiology

- children aged 6 mo-6 yr with fever or history of recent fever
- typical vs. atypical febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- relatively well-looking after seizure

Investigations and Management

- if it is a febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
  - note: may also have fever but may not meet criteria for febrile seizure
  - ± EEG (especially if first seizure), head U/S (if fontanelle open)

Table 38. Typical vs. Atypical Febrile Seizures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>&lt;15 min</td>
<td>&gt;15 min</td>
</tr>
<tr>
<td>Type of Seizure</td>
<td>Generalized</td>
<td>Focal features</td>
</tr>
<tr>
<td>Frequency</td>
<td>1 in 24 h</td>
<td>&gt;1 in 24 h</td>
</tr>
</tbody>
</table>
Abdominal Pain

- see Pediatrics, P38

History
- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake

Physical Exam
- HEENT, respiratory, abdominal exam including DRE, testicular/genital exam

Table 39. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents

<table>
<thead>
<tr>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colic</td>
<td>Malrotation with volvulus</td>
</tr>
<tr>
<td>UTI</td>
<td>Hirschsprung’s disease</td>
</tr>
<tr>
<td>Constipation</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Incarcerted hemia</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Duodenal atresia</td>
</tr>
<tr>
<td>IBD</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
<td>Cholecytitis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Strept throat</td>
<td>Testicular torsion</td>
</tr>
<tr>
<td>Sickle cell disease crisis</td>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>DKA</td>
<td>Trauma</td>
</tr>
<tr>
<td>Functional</td>
<td>Pyloric stenosis</td>
</tr>
</tbody>
</table>

Red Flags for Abdominal Pain
- Significant weight loss or growth retardation (need growth chart)
- Fever
- Joint pain with objective physical findings
- Rash
- Rectal bleeding
- Rebound tenderness and radiation of pain to back, shoulders, or legs
- Pain wakes from sleep
- Severe diarrhea and encopresis
- Trauma or suspected trauma patient <1 yr of age with a large, boggy scalp hematoma requires U/S or CT

Common Infections

- see Pediatrics, P50

Table 40. Antibiotic Treatment of Pediatric Bacterial Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MENINGITIS SEPSIS</td>
<td>Neontal: GBS, E. coli, Listeria, Gram-negative bacilli</td>
<td>ampicillin + cefotaxime</td>
</tr>
<tr>
<td></td>
<td>1-3 mo: Same pathogens as above and below</td>
<td>ampicillin + cefotaxime + vancomycin</td>
</tr>
<tr>
<td></td>
<td>&gt;3 mo: S. pneumoniae, H. influenzae type b (&gt;5 yr), meningococcus</td>
<td>ceftriaxone + vancomycin</td>
</tr>
<tr>
<td>OTITIS MEDIA</td>
<td>1st line: S. pneumoniae, H. influenzae type b, M. catarrhalis</td>
<td>amoxicillin 80-90 mg/kg/d</td>
</tr>
<tr>
<td></td>
<td>2nd line: clarithromycin 15 mg/kg/d bid (for penicillin allergy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment failure: 90 mg/kg/d amoxicillin and 6.4 mg/kg/d clavulanate divided into bid dosage</td>
<td></td>
</tr>
<tr>
<td>STREP PHARYNGITIS</td>
<td>Group A β-hemolytic Streptococcus</td>
<td>penicillin/amoxicillin or erythromycin (penicillin allergy)</td>
</tr>
<tr>
<td>UTI</td>
<td>E. coli, Proteus, H. influenzae, Pseudomonas, S. saprophyticus, Enterococcus, GBS</td>
<td>Oral: cephalixin (older children) IV: ampicillin and aminoglycoside</td>
</tr>
<tr>
<td>PNEUMONIA</td>
<td>1-3 mo: Viral, S. pneumoniae, C. trachomatis, B. pertussis, S. aureus, H. influenzae</td>
<td>cefuroxime ± macrolide (erythromycin) OR ampicillin ± macrolide</td>
</tr>
<tr>
<td></td>
<td>3 mo-5 yr: Viral, S pneumoniae, S. aureus, H. influenzae, Mycoplasma pneumoniae</td>
<td>ampicillin/amoxicillin or cefuroxime</td>
</tr>
<tr>
<td></td>
<td>&gt;5 yr: As above</td>
<td>ampicillin/amoxicillin + macrolide or cefuroxime + macrolide</td>
</tr>
</tbody>
</table>
Child Abuse and Neglect

- see Pediatrics, P14
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - HI: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken Baby Syndrome: diffuse brain injury, subdural/SAH, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures age <1 yr, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - GU/GI injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea

Common Medications

Table 41. Commonly Used Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>325-650 mg PO q4-6h pm</td>
<td>Pain control</td>
<td>Max 4 g daily</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>30-100 g PO in 250 mL H2O</td>
<td>Poisoning/overdose</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>325-650 mg PO q6h max 4g/d stroke/MI risk: 81-325 mg PO OD 180 mg chewed</td>
<td>Pain control Cardiac prevention ACS</td>
<td></td>
</tr>
<tr>
<td>β-blockers (metoprolol)</td>
<td>5 mg slow IV q5min x 3 if no contraindications</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>anxiety: 2-10 mg PO tid/qid alcohol withdrawal: 10-20 mg PO/IV q1h titrated to signs/symptoms</td>
<td>Anxiety Alcohol withdrawal</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg SC bid</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>anaphylaxis: 0.1-0.5 mg IM; can repeat q10-15min</td>
<td>Anaphylaxis Max 1 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5-1.0 µg/kg IV</td>
<td>Procedural sedation Very short acting narcotic (complication=apnea)</td>
<td></td>
</tr>
<tr>
<td>Flumazenil</td>
<td>0.3 mg IV bolus q5min x 3 doses</td>
<td>Reversal of procedural sedation Benzozeazepine antagonist Can cause seizures/status epilepticus in chronic benzodiazepine users</td>
<td></td>
</tr>
<tr>
<td>Furosemide (Lasix®)</td>
<td>CHF: 40-80 mg IV HTN: 10-40 mg PO bid</td>
<td>Monitor for electrolyte imbalances</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>0.5-1.0 g/kg (1-2 mL/kg) IV of D50W</td>
<td>Hypoglycemia/DKA</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2.5-5.0 mg PO/IM initial effective dose 6-20 mg/d</td>
<td>Psychosis Monitor with Parkinson’s; results in CNS depression</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200-800 mg PO tid pm max 1,200 mg/d</td>
<td>Mild to moderate acute pain Analgesic and anti-inflammatory properties</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per h</td>
<td>Hyperglycemia Monitor blood glucose levels Consider K+ replacement, also measure blood glucose levels before administration</td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>2-3 puffs inhaled tid-qid, max 12 puffs/d</td>
<td>Asthma Contraindicated with peanut/soy allergy Caution with narrow-angle glaucoma</td>
<td></td>
</tr>
<tr>
<td>Lidocaine with epi</td>
<td>max 7 mg/kg SC</td>
<td>Local anesthetic Not to be used in fingers, nose, toes, penis, ears</td>
<td></td>
</tr>
<tr>
<td>Lidocaine w/o epi</td>
<td>max 5 mg/kg SC</td>
<td>Local anesthetic</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>anxiety: 0.5-2 mg PO/IM/IV q6-8h status epilepticus: 4 mg IV repeat up to q5min</td>
<td>Anxiety Status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>50 µg/kg IV</td>
<td>Procedural sedation Short acting benzodiazepine (complication=apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation</td>
<td></td>
</tr>
</tbody>
</table>
### Table 41. Commonly Used Medications (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td>15-30 mg PO q6-12h 10-0.2 mg/kg max 15 mg IV q4h</td>
<td>Mild to moderate acute/chronic pain</td>
<td>GI and constipation side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prescribed in combination with NSAIDs or acetylsalicylic acid</td>
<td>DO NOT CRUSH, CUT, or CHEW</td>
</tr>
<tr>
<td><strong>Naloxone</strong></td>
<td>0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg</td>
<td>Comatose patient Opioid overdose Reversal in procedural sedation</td>
<td></td>
</tr>
<tr>
<td><strong>Nitroglycerin</strong></td>
<td>acute angina: 0.3-0.6 mg SL q5min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5min</td>
<td>Angina Acute MI</td>
<td>Not to be used with other antihypertensives Not in right ventricular MI</td>
</tr>
<tr>
<td><strong>Percocet 10/325®</strong></td>
<td>1-2 tabs PO q6h pm</td>
<td>Moderate pain control</td>
<td>Oxycodeone + acetylsalicylic acid Max 4 g acetylsalicylic acid daily</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td>Status epilepticus: see Table 17</td>
<td>Status epilepticus</td>
<td>Begin maintenance dose 12 h after loading dose Continuous ECG, BP monitoring mandatory</td>
</tr>
<tr>
<td><strong>Polysporin®</strong></td>
<td>Apply to affected area bid-tid</td>
<td>Superficial infections</td>
<td></td>
</tr>
<tr>
<td><strong>Propofol</strong></td>
<td>0.25-1 mg/kg IV</td>
<td>Procedural sedation</td>
<td>Short acting Anesthetic/sedative (complication = apnea, decreased BP)</td>
</tr>
<tr>
<td><strong>Salbutamol</strong></td>
<td>2 puffs inhaled q4-6h max 12 puffs/d</td>
<td>Asthma</td>
<td>Caution with cardiac abnormalities</td>
</tr>
<tr>
<td><strong>Thiamine</strong></td>
<td>100 mg IV/IM initially, then 50-100 mg IM/IV/PO OD x 3d</td>
<td>To treat/prevent Wernicke’s encephalopathy</td>
<td>Caution use in pregnancy</td>
</tr>
<tr>
<td><strong>Tylenol #3®</strong></td>
<td>1-2 tabs PO q4-6h pm</td>
<td>Pain control</td>
<td>Max 4 g acetylsalicylic acid daily</td>
</tr>
</tbody>
</table>

---
References


# Endocrinology

## Acronyms

- Acronym: Definition

## Basic Anatomy Review

- Major Endocrine Organs

## Dyslipidemias

- Overview of Lipid Transport
- Hypertriglyceridemia (Elevated Triglycerides)
- Hypercholesterolemia
- Low High-Density Lipoprotein
- Dyslipidemia and the Risk for Coronary Artery Disease
- Treatment of Dyslipidemias

## Disorders of Glucose Metabolism

- Overview of Glucose Regulation
- Pre-Diabetes (Impaired Glucose Tolerance/Impaired Fasting Glucose)
- Diabetes Mellitus
- Treatment of Diabetes
- Acute Complications
- Macrovascular Complications
- Microvascular Complications
- Other Complications
- Hypoglycemia (BG <4.0 mmol/L or 72 mg/dL)
- Metabolic Syndrome

## Obesity

- FM7

## Pituitary Gland

- Pituitary Hormones
- Growth Hormone
- Prolactin
- Thyroid Stimulating Hormone
- Adrenocorticotropic Hormone
- Luteinizing Hormone and Follicle Stimulating Hormone
- Antidiuretic Hormone
- Pituitary Pathology

## Thyroid

- Thyroid Hormones
- Tests of Thyroid Function and Structure
- Thyrotoxicosis
- Graves’ Disease
- Subacute Thyroiditis (Thyrotoxic Phase)
- Toxic Adenoma/Toxic Multinodular Goitre
- Thyrotoxic Crisis/Thyroid Storm
- Hypothyroidism
- Hashimoto’s Thyroiditis
- Myxedema Coma
- Sick Euthyroid Syndrome
- Non-Toxic Goitre
- Thyroid Nodules
- Thyroid Malignancies

## Adrenal Cortex

- Adrenocorticotropic Hormone
- Adrenocortical Hormones
- Adrenocortical Functional Workup
- Mineralocorticoid Excess Syndromes
- Cushing’s Syndrome
- Congenital Adrenal Hyperplasia
- Hyperandrogenism
- Adrenocortical Insufficiency

## Adrenal Medulla

- Catecholamine Metabolism
- Pheochromocytoma

## Disorders of Multiple Endocrine Glands

- Multiple Endocrine Neoplasm

## Calcium Homeostasis

- Hypercalcemia
- Hypocalcemia

## Metabolic Bone Disease

- Osteoporosis
- Osteomalacia and Rickets
- Renal Osteodystrophy
- Paget’s Disease of Bone

## Male Reproductive Endocrinology

- Androgen Regulation
- Tests of Testicular Function
- Hypogonadism and Infertility
- Erectile Dysfunction
- Gynecomastia

## Female Reproductive Endocrinology

## Paraneoplastic Syndrome

## Common Medications

- Diabetes Medications
- Dyslipidemia Medications
- Thyroid Medications
- Metabolic Bone Disease Medications
- Adrenal Medications

## Landmark Endocrinology Trials

## References
**Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab</td>
<td>Ab antibody</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin-creatinine ratio</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ADH</td>
<td>Antidiuretic hormone</td>
</tr>
<tr>
<td>AG</td>
<td>Anion gap</td>
</tr>
<tr>
<td>AVP</td>
<td>Arginine vasopressin</td>
</tr>
<tr>
<td>BG</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CAH</td>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>CHO</td>
<td>Carbohydrates</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegaviral</td>
</tr>
<tr>
<td>C Santorini</td>
<td>Captopril</td>
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<tr>
<td>CHD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotropin-releasing hormone</td>
</tr>
<tr>
<td>CVL</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DDAVP</td>
<td>Desmopressin (1-deamino-8-D-arginine vasopressin)</td>
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<tr>
<td>DHEA</td>
<td>Dehydroepiandrosterone</td>
</tr>
<tr>
<td>DHT</td>
<td>Dihydrotestosterone</td>
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<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>DEX</td>
<td>Dexamethasone</td>
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<tr>
<td>ECG</td>
<td>Extracellular fluid</td>
</tr>
<tr>
<td>EGF</td>
<td>Epidermal growth factor</td>
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<tr>
<td>EFGH</td>
<td>Ethanol-glyceraldehyde-3-phosphate dehydrogenase</td>
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<tr>
<td>EGF</td>
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<td>EGK</td>
<td>Lactic dehydrogenase</td>
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<td>EL</td>
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<td>Fibroblast growth factor</td>
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<td>FSH</td>
<td>Follicle-stimulating hormone</td>
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</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
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<td>Growth hormone</td>
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<td>Human chorionic gonadotropin</td>
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<tr>
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<td>High density lipoprotein</td>
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<tr>
<td>HHS</td>
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<tr>
<td>HMG-CoA</td>
<td>3-Hydroxy-3-methylglutaryl-coenzyme A</td>
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<td>HPA</td>
<td>Hypothalamic pituitary adenohypophysis</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>High sensitivity C-reactive protein</td>
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<tr>
<td>HVA</td>
<td>Homovanillic acid</td>
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<td>ICF</td>
<td>Intracellular fluid</td>
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<td>IEL</td>
<td>Intermediate density lipoprotein</td>
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<td>IM</td>
<td>Insulin-like growth factor</td>
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<td>ION</td>
<td>Intracellular osmolyte network</td>
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<tr>
<td>LCAT</td>
<td>Lecithin-cholesterol acyltransferase</td>
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<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
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<td>LH</td>
<td>Luteinizing hormone</td>
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<td>LS</td>
<td>Local signaling</td>
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<td>LP</td>
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<td>Metabolism</td>
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<td>Metabolism</td>
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<tr>
<td>MIR</td>
<td>Microcirculation</td>
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<tr>
<td>MTC</td>
<td>Medullary thyroid cancer</td>
</tr>
<tr>
<td>NS</td>
<td>Normal saline</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral arterial disease</td>
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<tr>
<td>PCOS</td>
<td>Polycystic ovarian syndrome</td>
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<tr>
<td>PRL</td>
<td>Prolactin</td>
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<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
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<tr>
<td>PTU</td>
<td>Propylthiouracil</td>
</tr>
<tr>
<td>RAU</td>
<td>Radioactive iodine uptake</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
</tr>
<tr>
<td>RAIU</td>
<td>Radioactive iodine uptake</td>
</tr>
<tr>
<td>RHC</td>
<td>Retinol binding protein</td>
</tr>
<tr>
<td>SHBG</td>
<td>Sex hormone binding globulin</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
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<tr>
<td>Tg</td>
<td>Thyroglobulin</td>
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<tr>
<td>THG</td>
<td>Thymus growth hormone</td>
</tr>
<tr>
<td>THN</td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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<tr>
<td>TSI</td>
<td>Thyroid stimulating immunoglobulin</td>
</tr>
<tr>
<td>Tm</td>
<td>Testosterone metabolizing enzyme</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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<tr>
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<td>Thyroxine</td>
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</table>
| T3            | Triiodothyro
Table 1. Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Apolipoproteins</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td><strong>Exogenous Pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylomicron</td>
<td>B-48, C, E, A-I, A-II, A-IV</td>
<td>Transports dietary TG from gut to adipose tissue and muscle</td>
</tr>
<tr>
<td><strong>Endogenous Pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>B-100, C, E</td>
<td>Transports hepatic synthesized TG from liver to adipose tissue and muscle</td>
</tr>
<tr>
<td>IDL</td>
<td>B-100, E</td>
<td>Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core. Enriched in cholesterol esters.</td>
</tr>
<tr>
<td>LDL</td>
<td>B-100</td>
<td>Formed by further removal of residual TG from IDL core by hepatic lipase resulting in greater enriched particles with cholesterol esters. Transports cholesterol from liver to peripheral tissues (gonads, adrenals)</td>
</tr>
<tr>
<td>HDL</td>
<td>A-I, A-II, C, E</td>
<td>Transports cholesterol from peripheral tissues to liver. Acts as a reservoir for apolipoproteins</td>
</tr>
</tbody>
</table>

Figure 2. Exogenous and endogenous biosynthetic lipid pathways

**Hypertriglyceridemia (Elevated Triglycerides)**

**PRIMARY HYPERTRIGLYCERIDEMIA**

Table 2. Primary Hypertriglyceridemias

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipase Deficiency</td>
<td></td>
<td>Moderate ↑ in VLDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial Hypertriglyceridemia</td>
<td>Autosomal dominant for inactivating mutations of the LP lipase gene and several genetic defects resulting in ↑ hepatic VLDL synthesis or ↓ removal of VLDL</td>
<td>↑ TG, ↑ VLDL</td>
<td>Possible premature CAD. Develop syndrome of obesity, hypertriglyceridemia, hyperinsulinemia, and hyperuricemia in early adulthood.</td>
<td>Decrease dietary simple carbohydrates and fat intake. Abstain from EtOH. Fibre x or niacin.</td>
</tr>
</tbody>
</table>
SECONDARY HYPERTRIGLYCERIDEMIA

Etiology
- endocrine: obesity/metabolic syndrome, hypothyroidism (more for high LDL, not TG), acromegaly, Cushing's syndrome, DM
- renal: chronic renal failure, polyclonal and monoclonal hypergammaglobulinemia
- hepatic: chronic liver disease, hepatitis, glycogen storage disease
- drugs: alcohol, corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
- other: pregnancy

Hypercholesterolemia

PRIMARY HYPERCHOLESTEROLEMIA

Table 3. Primary Hypercholesterolemia

<table>
<thead>
<tr>
<th>Hypercholesterolemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>1/500 in U.S. population Autosomal codominant with high penetrance More prevalent in French Canadian, Dutch Afrikanner, Christian Lebanese populations Most commonly due to defects in the normal LDL receptor on cell membranes</td>
<td>↑ LDL ↑ TC</td>
<td>Tendinous xanthomatosis (Achilles, patellar, and extensor tendons of hand) Arcus cornealis Xanthelasma Heterozygotes: premature CAD, 50% risk of MI in men by age 30 Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (in &lt;20 yr olds)</td>
<td>Heterozygotes: improvement of LDL with statins, often in combination with ezetimibe or bile acid sequestrans or PCSK9 inhibitor Homozygotes: partial control with portacaval shunt or LDL apheresis in conjunction with niacin; large dose statin is modestly effective; potential liver transplant; consider lomitapide (inhibitor of the microsomal TG transfer protein) and mipomersen (inhibits ApoB gene)</td>
</tr>
<tr>
<td>Polygenic Hypercholesterolemia</td>
<td>Most common Few mild inherited defects in cholesterol metabolism</td>
<td>↑ TC</td>
<td>Asymptomatic until vascular disease develops No xanthomata</td>
<td>Statins, ezetimibe, niacin, bile acid sequesterant, PCSK9 inhibitor</td>
</tr>
<tr>
<td>Familial Combined Hyperlipidemia</td>
<td>In many cases, over-population of VLDL and associated ↑ LDL 2+ to excess hepatic synthesis of apolipoprotein B Autosomal dominant</td>
<td>↑ TC + G ↑ VLDL ↑ LDL</td>
<td>Xanthelasma CAD and other vascular disease</td>
<td>Weight reduction Decrease simple carbohydrates, fat, cholesterol, and EtOH in diet Fibrates, statins, ezetimibe, PCSK9 inhibitor</td>
</tr>
</tbody>
</table>

SECONDARY HYPERCHOLESTEROLEMIA

Etiology
- endocrine: hypothyroidism
- renal: nephrotic syndrome
- immunologic: monoclonal gammopathy
- hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)
- nutritional: diet, anorexia nervosa
- drugs: cyclosporin, anabolic steroids, carbamazepine

Low High-Density Lipoprotein

PRIMARY CAUSES

Table 4. Primary Low HDL Cholesterol Levels

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology/Pathophysiology</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypoalphalipoproteinemia or Familial HDL Deficiency</td>
<td>Autosomal dominant inheritance of a mutation in the ABCA1 or the APOA1 gene</td>
<td>Premature atherosclerosis Cerebrovascular disease Premature atherosclerosis Xanthomas</td>
<td>Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present</td>
</tr>
<tr>
<td>Tangier Disease</td>
<td>Autosomal recessive inheritance of mutations in the ABCA1 gene Impaired HDL-mediated cholesterol efflux from macrophages and impaired intracellular lipid trafficking</td>
<td>Mild hypertriglyceridemia Neuropathy Enlarged, orange-coloured tonsils Premature atherosclerosis Splenomegaly Hepatomegaly Corneal clouding Type 2 DM</td>
<td>Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present</td>
</tr>
</tbody>
</table>
SECONDARY CAUSES

Etiology
- endocrine: obesity/metabolic syndrome, DM
- drugs: β-blockers, benzodiazepines, anabolic steroids
- other: acute infections, inflammatory conditions

Dyslipidemia and the Risk for Coronary Artery Disease

- increased LDL is a major risk factor for atherosclerosis and CAD as LDL is the major atherogenic lipid particle
- increased HDL is associated with decreased cardiovascular disease and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3–9 mmol/L) is an independent risk factor for CAD, especially in people with DM and in post-menopausal women
- treatment of hypertriglyceridemia has not been shown to reduce CAD risk

Screening
- screen men >40 yr, women >50 yr or post-menopausal
- if following risk factors present, screen at any age:
  - DM
  - current cigarette smoking or COPD
  - HTN (sBP >140, dBP >90)
  - obesity (BMI >27 kg/m²)
  - family history of premature CAD
  - clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
  - evidence of atherosclerosis
  - inflammatory disease (rheumatoid arthritis, SLE, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease)
  - HIV infection on highly active antiretroviral therapy (HAART)
  - chronic kidney disease (estimated GFR <60 mL/min/1.73 m²)
  - erectile dysfunction
  - screen children with a family history of hypercholesterolemia or chylomicronemia

Factors Affecting Risk Assessment
- metabolic syndrome
- apolipoprotein B (apo B)
  - each atherogenic particle (VLDL, IDL, LDL, and lipoprotein A) contains one molecule of apo B
  - serum [apo B] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome
- C-reactive protein (hs-CRP) levels
  - highly sensitive acute phase reactant
  - may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment

Treatment of Dyslipidemias

Approach to Treatment
For clinical guidelines see Can J Cardiol 2016;32:1263-1282.
- consider treatment for patients with statin-induced conditions (listed below); risk assessment is not required
  - for primary prevention:
    - estimate 10 yr risk of CAD using Framingham Risk Score (FRS) model
    - establish treatment targets
    - low FRS does not require statin treatment

Table 5. Dyslipidemia Treatment Indications and Targets

<table>
<thead>
<tr>
<th>Indications</th>
<th>Initiate Treatment if:</th>
<th>Primary Target LDL-C</th>
<th>Alternate Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin-Indicated Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical atherosclerosis</td>
<td>Consider treatment in all patients</td>
<td>≤2 mmol/L</td>
<td>apo B ≤0.8 g/L or non-HDL-C</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td></td>
<td>or ≥50% ↓ in LDL</td>
<td></td>
</tr>
<tr>
<td>DM &gt;15 yr duration and age older than 30 yr</td>
<td></td>
<td>For LDL-C ≥5 mmol/L: 50% ↓ in LDL</td>
<td></td>
</tr>
<tr>
<td>DM with age older than 40 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM with microvascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease and age older than 50yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C ≥5 mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>Consider treatment in all patients</td>
<td>≤2 mmol/L</td>
<td>apo B ≤0.8 g/L or non-HDL-C</td>
</tr>
<tr>
<td>FRS ≥20%</td>
<td></td>
<td>or ≥50% ↓ in LDL</td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td></td>
<td>For LDL-C ≥5 mmol/L: 50% ↓ in LDL</td>
<td></td>
</tr>
<tr>
<td>FRS 10-19%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from 2016 CCS Dyslipidemia guidelines
Disorders of Glucose Metabolism

Overview of Glucose Regulation

Figure 3. Blood glucose regulation

Pre-Diabetes (Impaired Glucose Tolerance/Impaired Fasting Glucose)

- 1-5% per yr go on to develop DM
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance
- increased risk of developing macrovascular complications (IGT >IFG)
- lifestyle modifications decrease progression to DM by 58%

Diagnostic Criteria (CDA Guidelines)

- impaired fasting glucose (IFG): fasting plasma glucose (FPG) 6 1 6.9 mmol/L
- impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L
- HbA1c: 6.0-6.4%

Table 6. Treatment of Hypercholesterolemia and Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Treatment of Hypercholesterolemia</th>
<th>Treatment of Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative: 4-6 mo trial</td>
<td>Conservative: 4-6 mo trial</td>
</tr>
<tr>
<td>Diet:</td>
<td>Diet:</td>
</tr>
<tr>
<td>Decrease fat: &lt;30% calories</td>
<td>Decrease fat: &lt;30% calories</td>
</tr>
<tr>
<td>Decrease saturated fat: &lt;10% calories</td>
<td>Decrease saturated fat: &lt;10% calories</td>
</tr>
<tr>
<td>Decrease cholesterol: &lt;200 mg/d</td>
<td>Decrease cholesterol: &lt;200 mg/d</td>
</tr>
<tr>
<td>Decrease triglyceride: &lt;1.7 mmol/L</td>
<td>Decrease triglyceride: &lt;1.7 mmol/L</td>
</tr>
<tr>
<td>Control blood sugars</td>
<td>Control blood sugars</td>
</tr>
<tr>
<td>Decrease alcohol intake to &lt;1-2 drinks/d</td>
<td>Decrease alcohol intake to &lt;1-2 drinks/d</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</td>
<td>Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</td>
</tr>
<tr>
<td>Weight loss: target BMI &lt;25</td>
<td>Weight loss: target BMI &lt;25</td>
</tr>
<tr>
<td>Medical: fibres, niacin (see Common Medications, E49)</td>
<td>Medical: fibres, niacin (see Common Medications, E49)</td>
</tr>
</tbody>
</table>

Common Medications

- HMG-CoA reductase inhibitors, ezetimibe, bile acid sequestrants, niacin (see Common Medications, E49)

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (Jupiter Study)

**NEJM 2008;359(21):2195-207**

**Study:** Randomized Control Trial

**Intervention:** Statin Therapy

**Results:** Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46-0.69; P < 0.0001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.49; 95% CI, 0.40-0.58; P < 0.0001), 0.45 and 0.65 for stroke (hazard ratio, 0.52; 95% CI, 0.43-0.64; P < 0.0001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.89; 95% CI, 0.74-1.07; P = 0.19).

**Conclusion:** Statins reduce the incidence of major cardiovascular events even in healthy people without hyperlipidemia but with elevated C-reactive protein.

Three Year Efficacy of Complex Insulin Regimens in Type 2 DM: A 3Y Trial

**NEJM 2009;361:1736-1747**

**Study:** Randomized unblinded trial with 3 yr of follow-up.

**Population:** 718 patients with type 2 DM, not on insulin or thiazolidinedione therapy on maximal metformin and sulfonylurea therapy.

**Intervention:** Three-daily prandial insulin aspart, versus twice-daily biphasic insulin aspart, versus once-daily basal insulin detemir. Sulfonylurea therapy was replaced with a secondary insulin regimen specific to each arm if there was persistent hypoglycemia.

**Primary Outcome:** Three yr hemoglobin HbA1c.

**Results:** Significant difference in rates of patient withdrawal from the study: 5.1% biphasic, 11.7% prandial, 11.3% basal regimens (p = 0.04). There were no significant differences in median HbA1c levels between all three arms from yr 1-3. A smaller proportion of patients reached HbA1c <6.5% or <7.0% in the biphasic arm. The basal arm had least weight gain and least weight circumference increase, but highest rate of secondary insulin requirement. The basal arm had lowest severe hypoglycemic events per patient yr, while the biphasic had the most serious adverse effects.

**Conclusion:** Basal insulin regime provides the best glycemic control over a 3 yr study, with better HbA1c control, fewer hypoglycemic events, and less weight gain.
Diabetes Mellitus

Definition
- syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/relative deficiency of insulin, or a reduction in biological effectiveness of insulin, or both

Diagnostic Criteria (CDA Guidelines)
- any one of the following is diagnostic
  - FPG ≥7.0 mmol/L (fasting = no caloric intake for at least 8 h) OR
  - 2 h 75 g OGTT ≥11.1 mmol/L OR
  - random PG ≥11.1 mmol/L OR
  - HbA1c ≥6.5% (not for diagnosis of suspected Type 1 DM, children, adolescents, or pregnant women)
- in the presence of hyperglycemia symptoms (polyuria, polydipsia, polyphagia, weight loss, blurry vision), a confirmatory test is not required
- in the absence of hyperglycemic symptoms, a repeat confirmatory test is required to make the diagnosis of diabetes

Etiology and Pathophysiology

Table 7. Etiologic Classification of Diabetes Mellitus

| I. Type 1 DM (immune-mediated β cell destruction, usually leading to absolute insulin deficiency) |
| II. Type 2 DM (ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance 2º to β cell dysfunction) |
| III. Other Specific Causes of DM |
  | a. Genetic defects of β cell function (e.g. MODY – Maturity-Onset Diabetes of the Young) or insulin action |
  | b. Diseases of the exocrine pancreas: |
  | Pancreatitis, pancreactectomy, neoplasia, cystic fibrosis, hemochromatosis ("bronze diabetes") |
  | c. Endocrinopathies: |
  | Acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, hyperthyroidism |
  | d. Drug-induced: |
  | Glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, clozapine |
  | e. Infections: |
  | Congenital rubella, CMV, coxsackie |
  | f. Genetic syndromes associated with DM: |
  | Down’s syndrome, Klinefelter’s syndrome, Turner’s syndrome |

IV. Gestational Diabetes Mellitus (see Obstetrics, OB26)

Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Usually &lt;30 yr of age</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>More common in Caucasians</td>
</tr>
<tr>
<td></td>
<td>Accounts for &gt;90% of all DM</td>
</tr>
<tr>
<td>Etiology</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>Genetics</td>
<td>Monozygotic twin concordance is 30-40%</td>
</tr>
<tr>
<td></td>
<td>Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of type 1 DM</td>
</tr>
<tr>
<td></td>
<td>Certain DQ alleles also confer a risk</td>
</tr>
<tr>
<td></td>
<td>Non-HLA associated</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion</td>
</tr>
<tr>
<td></td>
<td>Autoimmune process is believed to be triggered by environmental factors (e.g. viruses, bovine milk protein, urea compounds)</td>
</tr>
<tr>
<td></td>
<td>Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction</td>
</tr>
<tr>
<td></td>
<td>80% of β cell mass is destroyed before features of DM present</td>
</tr>
</tbody>
</table>

Effects of Intensive Treatment of Type 1 DM on the Development and Progression of Long-Term Complications: The DCCT Study

- Study: Multicentre RCT, with 6.5 yr of mean follow-up
- Patients: 1,441 patients (aged 13-39 yr) with type 1 DM with no cardiovascular history or severe diabetic complications
- Intervention: Intensive therapy (3 or more daily insulin injections or treatment with an insulin pump with dose adjustments as needed, BG monitoring minimum q-d, monthly visits strict BG targets) vs. Conventional therapy (1 or 2 insulin injections per day with no dose adjustments, daily BG monitoring visits q-3 months).
- Outcomes: Primary outcome was development or progression of retinopathy. Secondary outcomes were development or progression of renal, neurological, cardiovascular, and neuropathological outcomes
- Results: Intensive treatment of Type 1 DM significantly reduced the risk for the development and progression of retinopathy in the primary- and secondary-intervention cohorts, respectively. Intensive therapy also reduced the occurrence of microalbuminuria, albuminuria, and clinical neophopathy. The chief adverse event associated with intensive therapy was an increase in the occurrence of severe hypoglycemia.
- Conclusions: Intensive treatment of Type 1 DM significantly reduces the development and progression of diabetic retinopathy, nephropathy, and neuropathy in patients with Type 1 DM.

Blood Glucose Control in Type 2 DM – UKPDS 33

- Study: RCT (mean follow-up 10 yr)
- Patients: 3,867 patients with newly diagnosed type 2 DM (mean age 53 yr, 61% men, 81% white, mean fasting plasma glucose [FPG] 6.1-15.0 mmol/L)
- Exclusions: included severe cardiovascular disease, renal disease, retinopathy, and others.
- Intervention: Intensive treatment with a sulfonylurea (all patients) or a sulfonylurea and metformin (target FPG ≤6.1 mmol/L without hyperglycemic symptoms). Intensive treatment with metformin alone (target FPG ≤7.0 mmol/L) vs. conventional treatment with diet alone (target FPG <15 mmol/L).
- Main Outcomes: DM-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia); DM-related death, and all-cause mortality.
- Results: Patients allocated to intensive treatment had lower median HbA1c levels (p<0.001).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RRR % (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM-related endpoint</td>
<td>0.47 (0.02)</td>
</tr>
<tr>
<td>DM-related death</td>
<td>0.34 (0.03)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.44 (0.04)</td>
</tr>
</tbody>
</table>

Patients allocated to intensive therapy had more hypoglycemic episodes and greater weight gain.
- Conclusion: Intensive blood glucose control reduces microvascular, but not macrovascular complications in type 2 DM.
Glycemic Targets
- HbA1c reflects glycemic control over 3 mo and is a measure of patient’s long-term glycemic control
- therapy in most individuals with type 1 or type 2 DM (especially younger patients) should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications
- more intensive glucose control, HbA1c <6.5%, may be targeted in type 2 DM in patients with a shorter duration of DM with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia
- less stringent HbA1c targets (7.1-8.5%) may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to attain HbA1c <7.0% despite intensified basal and bolus insulin therapy
- there may be harm associated with strategy to target HbA1c <6.0% (see ACCORD trial, E9)

Diet
- daily carbohydrate intake 45-60% of energy, protein 15-20% of energy, and fat <35% of energy
- intake of saturated fats <7% and polyunsaturated fats <10% of total calories each
- limit sodium, alcohol, and caffeine intake
- type 1: carbohydrate counting is used to titrate insulin regimen
- type 2: weight reduction
Lifestyle
- regular physical exercise to improve insulin sensitivity, lower lipid concentrations and control blood pressure
- smoking cessation

Medical Treatment: Non-insulin Antihyperglycemic Agents (Type 2 DM)
- initiate non-insulin antihyperglycemic therapy within 2-3 mo if lifestyle management does not result in glycemic control
- if initial HbA1c >8.5% at the time of diagnosis, initiate pharmacologic therapy with metformin immediately and consider combination of therapies or insulin immediately
- continue to add additional pharmacologic therapy in a timely fashion to achieve target HbA1C within 3-6 mo of diagnosis
- see Common Medications, E49 for details on antihyperglycemic agents

Medical Treatment: Insulin (Figure 5)
- used for type 1 DM at onset, may be used in type 2 DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- bolus insulins: short-acting (Insulin regular), rapid-acting analogue (Insulin aspart, Insulin glulisine, Insulin lispro)
- basal insulins: intermediate-acting (Insulin NPH), long-acting analogue (Insulin detemir, glargine)
- premixed insulins (combination of basal and bolus insulins) available but not used regularly
- estimated total daily insulin requirement: 0.5-0.7 units/kg (often start with 0.3-0.5 units/kg/d)

Table 9. Available Insulin Formulations

<table>
<thead>
<tr>
<th>Insulin Type (trade name)</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRANDIAL (BOLUS INSULINS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting insulin analogues</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Insulin aspart (NovoRapid&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>4 min</td>
<td>1 h</td>
<td>3-4 h</td>
</tr>
<tr>
<td>Insulin faster aspart (Fiasp)</td>
<td>10-15 min</td>
<td>1-2 h</td>
<td>3.5-4.75 h</td>
</tr>
<tr>
<td>Insulin lispro (Humalog&lt;sup&gt;®&lt;/sup&gt;, Humalog 200 units/mL)</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Insulin glulisine (Apidra&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin R&lt;sup&gt;®&lt;/sup&gt;</td>
<td>30 min</td>
<td>2-3 h</td>
<td>6.5 h</td>
</tr>
<tr>
<td>Novolin Toronto&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASAL INSULINS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>1-3 h</td>
<td>5-8 h</td>
<td>Up to 18 h</td>
</tr>
<tr>
<td>Humulin N&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novolin NPH&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting basal insulin analogues</td>
<td>90 min</td>
<td>Not applicable</td>
<td>Up to 24 h (glargine 24 h, detemir 16-24 h)</td>
</tr>
<tr>
<td>Insulin detemir (Levemir&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine 100 units/mL (Lantus&lt;sup&gt;®&lt;/sup&gt;/ Basaglar)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine 300 units/mL (Toujeo)</td>
<td></td>
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</tr>
</tbody>
</table>

Effects of Intensive Glucose Lowering in Type 2 DM: The ACCORD Trial

NEWS: Reducing glycemia in type 2 diabetes (Diabetes Care 2010;33: 1777-1783)

Study: Multicentre RCT.

Patients: 10,251 patients (mean age 62.2) with type 2 DM and cardiovascular risk factors.

Intervention: Intensive therapy targeting a HbA1c level of less than 6.0% or standard therapy targeting 7.0-7.9%.

Outcomes: First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.

Results: The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV mortality, nonfatal MI, and CHF in the intensive therapy group. There were increased rates of all hypoglycemic events, any hypoglycemic serious adverse events, fluid retention, and weight gain >10 kg. The annualized incidence of hypoglycemia was 3.4% (95% CI 3.3-3.5) versus 2.5% (95% CI 2.3-2.7) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 2.2%, p=0.02), especially urinary tract infections (5.2% vs. 2.4%, p<0.01) and hyperkalemia (0.4% vs. 0.2%, p=0.01). There was no significant difference in primary outcomes in the two study arms, or all cause mortality. There was a significant reduction in any stroke (2.12%/yr vs. 0.54%/yr, p=0.01), and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, p=0.03) in the intensive therapy arm.

Conclusions: Intensive BP lowering to less than 120 mmHg (80 mmHg for diabetics) versus standard therapy was an increased incidence of elevated ALT (>3x upper limit) and ACE drug use in the standard therapy group.

Additional therapy was required to control blood pressure. The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV mortality, nonfatal MI, and CHF in the intensive therapy group. There were increased rates of all hypoglycemic events, any hypoglycemic serious adverse events, fluid retention, and weight gain >10 kg. The annualized incidence of hypoglycemia was 3.4% (95% CI 3.3-3.5) versus 2.5% (95% CI 2.3-2.7) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 2.2%, p=0.02), especially urinary tract infections (5.2% vs. 2.4%, p<0.01) and hyperkalemia (0.4% vs. 0.2%, p=0.01). There was no significant difference in primary outcomes in the two study arms, or all cause mortality. There was a significant reduction in any stroke (2.12%/yr vs. 0.54%/yr, p=0.01), and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, p=0.03) in the intensive therapy arm.

Conclusions: Intensive BP lowering to less than 120 mmHg (80 mmHg for diabetics) versus standard therapy was an increased incidence of elevated ALT (>3x upper limit) and ACE drug use in the standard therapy group.
Insulin Regimens

Table 10. Insulin Regimens for Type 2 DM and Type 1 DM

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 DM</td>
<td>Non-insulin antihyperglycemic agent + basal insulin</td>
</tr>
<tr>
<td></td>
<td>Start with 10 units of basal insulin at bedtime</td>
</tr>
<tr>
<td></td>
<td>Titrate up by 1 unit until FPG &lt; 7.0 mmol/L</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>Basal-bolus (multiple daily injections)</td>
</tr>
<tr>
<td></td>
<td>Estimated total insulin requirement is 0.5-0.7 U/kg</td>
</tr>
<tr>
<td></td>
<td>40% is given as basal insulin at bedtime</td>
</tr>
<tr>
<td></td>
<td>20% is given as bolus insulin before breakfast, lunch, and dinner</td>
</tr>
<tr>
<td></td>
<td>Continue metformin but discontinue secretagogue</td>
</tr>
<tr>
<td></td>
<td>Estimated total insulin requirement is 0.5-0.7 U/kg</td>
</tr>
<tr>
<td></td>
<td>2/3 dose is given as pre-mixed insulin before breakfast, lunch, and dinner</td>
</tr>
<tr>
<td></td>
<td>Continue metformin but discontinue secretagogue</td>
</tr>
</tbody>
</table>

*Bolus insulin: Aspart, Glulisine, Lispro; *Basal insulin: Gargine, Detemir NPH *Pre-mixed insulin: Humulin 30/70, Novolin 30/70, Novomix 30, Humalog Mix25, Humalog Mix50

Variable Insulin Dose Schedule (“Supplemental/Correction Scale”)
- for patients on Basal-Bolus regimen: patient takes usual doses of basal insulin but varies doses of bolus insulin based on BG reading at time of dose
- use baseline bolus insulin dose when within BG target range; add or subtract units when above or below target
- when used in hospital (including perioperative management of DM), patient should also receive basal insulin to prevent fluctuations in blood sugar levels or long periods of hyperglycemia construction of a supplemental sliding scale for a patient on anti-hyperglycemics
  - Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD)
    - BG <4: call MD and give 15 g carbohydrates
    - BG between 4 to 8: no additional insulin
    - BG between 8 to (8 + CF): give one additional unit
    - BG between (8 + CF) to (8 + 2CF): give two additional units
    - BG between (8 + 2CF) to (8 + 3CF): give three additional units

Insulin Pump Therapy: Continuous Subcutaneous Insulin Infusion (CSII)
- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected
- coverage available for insulin pumps for individuals with Type 1 DM varies by province
### Acute Complications

#### Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Diabetic Ketoacidosis (DKA)</th>
<th>Hyperosmolar Hyperglycemic State (HHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Usually occurs in type 1 DM</td>
<td>• Occurs in type 2 DM</td>
<td></td>
</tr>
<tr>
<td>• Insulin deficiency with ↑ catabolism</td>
<td>• Often precipitated by sepsis, stroke, MI, CHF, renal failure, trauma, drugs (glucocorticoids, immunosuppressants, phenytoin, diuretics), dialysis, recent surgery, burns</td>
<td></td>
</tr>
<tr>
<td>• Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise)</td>
<td>• Partial or relative insulin deficiency decreases glucose utilization in muscle, fat, and liver while inducing hyperglycemia-cagonemia and hepatic glucose production</td>
<td></td>
</tr>
<tr>
<td>• Unopposed hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na⁺ (water shift to ECF causing pseudohyponatremia)</td>
<td>• Presence of a small amount of insulin prevents the development of ketosis by inhibiting lipolysis</td>
<td></td>
</tr>
<tr>
<td>• Fat mobilization → ↑ FFA → ketoadiposis</td>
<td>• Characterized by hyperglycemia, hyperosmolality and dehydration without ketosis</td>
<td></td>
</tr>
<tr>
<td>• Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria</td>
<td>• More severe dehydration compared to DKA due to more gradual onset and ↑ duration of metabolic decompensation plus impaired fluid intake which is common in bedridden or elderly</td>
<td></td>
</tr>
<tr>
<td>• Total body K⁺ depletion but serum K⁺ may be normal or elevated, 2° to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality</td>
<td>• Volume contraction → renal insufficiency → ↑ hyperglycemia, ↑ osmolality → shift of fluid from neurons to ECF → mental obtundation and coma</td>
<td></td>
</tr>
<tr>
<td>• Total body PO₄³⁻ depletion</td>
<td>• Total body PO₄³⁻ depletion</td>
<td></td>
</tr>
</tbody>
</table>

#### Clinical Features

| • Polypnea, polydipsia, polyphagia with marked fatigue, N/V | • Onset is insidious → preceded by weakness, polyuria, polydipsia |  |
| • Dehydration (orthostatic changes) | • History of decreased fluid intake |  |
| • LOC may be ↓ with ketoacidosis or with high serum osmolality (osm >330 mmol/L) | • History of ingesting large amounts of glucose containing fluids |  |
| • Abdominal pain | • Dehydration (orthostatic changes) |  |
| • Fruity smelling breath | • ↓ LOC → lethargy, confusion, coma due to high serum osmolality |  |
| • Kussmaul’s respiration | • Kussmaul’s respiration is absent unless the underlying precipitant has also caused a metabolic acidosis |  |

#### Serum

| • ↑ BG (typically 11-55 mmol/L, ↓ Na⁺ (2° to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in Na⁺ by 3 mmol/L) | • ↑ BG (typically 44.4-133.2 mmol/L) |  |
| • Normal or ↑ K⁺, ↓ HCO₃⁻, ↑ BUN, ↑ Cr, ketonemia, ↓ PO₄³⁻ | • In mild dehydration, may have hyponatremia (spurious 2° to hyperglycemia → for every ↑ in BG by 10 mmol/L, there is a ↓ in Na⁺ by 3 mmol/L) |  |
| • ↑ osmolality | • if dehydration progresses, may get hypernatremia |  |

#### Urine

| • Metabolic acidosis with ↑ AG, possible 2° respiratory alkalosis | • Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI) |  |
| • If severe vomiting/dehydration there may be a metabolic alkalosis | • Glycosuria |  |

#### Treatment

| • ABCs are first priority | • Same resuscitation and emergency measures as DKA |  |
| • Monitor degree of ketoacidosis with AG, not BG or serum ketone level | • Rehydration |  |
| • Rehydration | — IV fluids: 1 L/h NS initially |  |
| — 1 L/h NS in first 2 h | — evaluate corrected serum Na⁺ |  |
| — after 1st 2 L, 300-400 mL/h NS. Switch to 0.45% NaCl once euvolemic (continue NS if corrected sodium is falling faster than 3 mmol/kg/h) | — if corrected serum Na⁺ high or normal, switch to 0.45% NaCl (4.14 mL/kg/h) |  |
| — once BG reaches 13.9 mmol/L then switch to DSW to maintain BG in the range of 12-14 mmol/L | — if corrected serum Na⁺ low, maintain NS (4.14 mL/kg/h) |  |
| • Insulin therapy | — when serum BG reaches 13.9 mmol/L switch to DSW |  |
| — critical to resolve acidosis, not hyperglycemia | |  |
| — do not use with hypokalemia (see below), until serum K⁺ is corrected to >3.3 mmol/L | • K⁺ replacement |  |
| — use only regular insulin (R) | — less severe K⁺ depletion compared to DKA |  |
| — maintain on 0.1 U/kg/h insulin R infusion | — if serum K⁺ <3.3 mmol/L, hold insulin and give 40 mEq/L K⁺ replacement |  |
| — check serum glucose hourly | — if K⁺ is 3.3-5.0, give KCl 20-30 mEq/L IV fluid |  |
| • K⁺ replacement | — if serum K⁺ ≥5.5 mmol/L check K⁺ every 2 h |  |
| — with insulin administration, hypokalemia may develop | • Search for precipitating event |  |
| — if serum K⁺ <3.3 mmol/L, hold insulin and give 40 mEq/L K⁺ replacement | • Insulin therapy |  |
| — when K⁺ 3.5-5.0 mmol/L add KCl 20-40 mEq/L IV fluid to keep K⁺ in the range of 3.5-5 mEq/L | — use only regular insulin (R) |  |
| • HCO₃⁻ | — initially load 0.1 U/kg body weight insulin R bolus |  |
| — if pH <7.0 or if hypotension, arrhythmia, or coma is present with a pH of <7.1 give HCO₃⁻ in 0.45% NaCl | — maintenance 0.1 U/kg/h insulin R infusion or IM |  |
| — do not give if pH >7.1 (risk of metabolic alkalosis) | — check serum glucose hourly |  |
| — can give in case of life-threatening hyperkalemia | • K⁺ depletion in general lower insulin requirement compared to DKA |  |
| • ± mannitol (for cerebral edema) | • Overall mortality approaches 50% primarily because of the older patient population and underlying etiology/precipitant |  |

#### Prognosis

| • 2.5% mortality in developed countries | • Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children) |  |
Macrovascular Complications

- increased risk of CAD, ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- CAD (see Cardiology and Cardiac Surgery, C32)
  - risk of MI is 3-5x higher in those with DM compared to age-matched controls
  - CAD is the leading cause of death in type 2 DM
  - most patients with DM are considered “high risk” under the risk stratification for CAD (see Dyslipidemias, E3)
- ischemic stroke (see Neurology, N50)
  - risk of stroke is approximately 2.5x higher in those with DM
  - level of glycemia is both a risk factor for stroke and a predictor of a poor outcome in patients who suffer a stroke
  - HbA1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Vascular Surgery, VS2)
  - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with DM compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with DM
- treatment
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight low density lipoprotein (LDL) cholesterol control (LDL ≤2.0 mmol/L)
  - ACEI or angiotensin receptor blocker in high-risk patients
  - smoking cessation
  - for adults with CVD who do not meet glycemic targets, recommended to add anti-hyperglycemic agent with demonstrated cardiovascular benefit (empagliflozin or liraglutide) to reduce the risk of major cardiovascular events

Microvascular Complications

DIABETIC RETINOPATHY (see Ophthalmology, OP33 for a more detailed description)

Epidemiology
- type 1 DM: 25% affected at 5 yr, 100% at 20 yr
- type 2 DM: 25% affected at diagnosis, 60% at 20 yr
- leading cause of blindness in North America between the ages of 20-74
- most important factor is disease duration

Clinical Features
- nonproliferative
- preproliferative
- proliferative

Treatment and Prevention
- tight glycemic control (delays onset, decreases progression), tight lipid control, manage HTN, smoking cessation
- ophthalmological treatments available – see Ophthalmology, OP33 for more details
- annual follow-up visits with an optometrist or ophthalmologist examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of type 2 DM; 5 yr after diagnosis of type 1 DM)
- interval for follow-up should be tailored to severity of retinopathy

DIABETIC NEPHROPATHY (see Nephrology, NP31 for a more detailed description)

Epidemiology
- DM-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with type 1 DM (after 5-10 yr) and 4-20% with type 2 DM have progressive nephropathy

Screening
- serum creatinine
- random urine test for albumin to creatinine ratio (ACR) plus urine dipstick test for all type 2 DM patients at diagnosis, then annually, and for postpubertal type 1 DM patients with ≥5 yr duration of DM

Treatment and Prevention
- appropriate glycemic control
- appropriate blood pressure control (<130/80 mmHg)
- use either ACEI or ARB (often used first line for their CVD protection)
- limit use of nephrotoxic drugs and dyes
DIABETIC NEUROPATHY

Epidemiology
• approximately 50% of patients within 10 yr of onset of type 1 DM and type 2 DM

Pathophysiology
• can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy
• mechanism poorly understood
• acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerve
• the more common motor and sensory neuropathies are thought to be related to metabolic or osmotic toxicity secondary to increased sorbitol and/or decreased myoinositol (possible mechanisms include accumulation of advanced glycation end products [AGE], oxidative stress, protein kinase C, nerve growth factor deficiency)

Screening
• 128 Hz tuning fork or 10 g monofilament at diagnosis and annually in people with type 2 DM and after 5 yr duration of type 1 DM

Clinical Features

<table>
<thead>
<tr>
<th>Peripheral Sensory Neuropathy</th>
<th>Motor Neuropathy</th>
<th>Autonomic Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation</td>
<td>Less common than sensory neuropathy</td>
<td>Postural hypotension tachycardia, decreased cardiovascular response to Valsalva maneuver</td>
</tr>
<tr>
<td>Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands</td>
<td>Delayed motor nerve conduction and muscle weakness/atrophy</td>
<td>Gastroparesis and alternating ileus</td>
</tr>
<tr>
<td>Decreased ankle reflex</td>
<td>May involve one nerve trunk (mononeuropathy) or more (mononeuropathies multiplex)</td>
<td>Urinary retention and erectile dysfunction</td>
</tr>
<tr>
<td>Symptoms may first occur in entrapment syndromes e.g. carpal tunnel syndrome</td>
<td>Some of the motor neuropathies spontaneously resolve after 6-8 wk</td>
<td></td>
</tr>
<tr>
<td>May result in neuropathic ulceration of foot</td>
<td>Reversible CN palsies: III (ptosis/ ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell’s palsy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetic amyotrophy: refers to pain, weakness, and wasting of hip flexors or extensors</td>
<td></td>
</tr>
</tbody>
</table>

Treatment and Management
• tight glycemic control
• for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anti-epileptics (e.g. carbamazepine, gabapentin) and capsaicin
• foot care education
• Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
• treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), erythromycin (stimulates motilin receptors)
• medical, mechanical, and surgical treatment for erectile dysfunction (see Urology, U30)

Other Complications

Dermatologic
• diabetic dermopathy: atrophic brown spots commonly in pretibial region known as “skin spots”, secondary to increased glycosylation of tissue proteins or vasculopathy
• eruptive xanthomas secondary to increased triglycerides
• necrobiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

Bone and Joint Disease
• juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
• Dupuytren’s contracture
• bone demineralization: bone density 10-20% below normal
• adhesive capsulitis (“frozen shoulder”)

Cataracts
• subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

Infections
• see Infectious Diseases, ID14

Toronto Notes 2018

Back to Top
Hypoglycemia (BG <4.0 mmol/L or 72 mg/dL)

Etiology and Pathophysiology
- hypoglycemia occurs most frequently in people with DM receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without DM, care must be taken to distinguish fasting from post-prandial hypoglycemia as each invokes separate differential diagnoses

Table 14. Common Causes of Hypoglycemia

<table>
<thead>
<tr>
<th>Fasting</th>
<th>Without Hyperinsulinism</th>
<th>Post-Prandial (Nonfasting, Reactive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperinsulinism</td>
<td>Exogenous insulin</td>
<td>Severe hepatic dysfunction</td>
</tr>
<tr>
<td>Sulfonylurea or meglitinide reaction</td>
<td>Chronic renal insufficiency</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor)</td>
<td>Alcohol use</td>
<td>Noninsulinoma pancreaticogenic hypoglycemic syndrome</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Inborn error of carbohydrate metabolism, glycogen storage disease, glucokinase enzyme deficiency</td>
<td>Leucine sensitivity</td>
</tr>
<tr>
<td>Pancreatic β cell tumour – insulinoma</td>
<td></td>
<td>Hereditary fructose intolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Galactosaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Newborn infant of diabetic mother</td>
</tr>
</tbody>
</table>

Clinical Features
- Whipple's triad
  1. serum glucose <2.5 mmol/L in males and <2.2 mmol/L in females
  2. neuroglycopenic symptoms
  3. rapid relief provided by administration of glucose
- adrenergic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia
- neuroglycopenic symptoms (caused by decreased activity of CNS)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations
- electrolytes, creatinine, LFTs, drugs/toxins, cortisol
- if concerned about possible insulinoma
  - blood work to be drawn when patient is hypoglycemic (e.g. during hospitalized 72-h fast) for glucose, serum ketones, insulin, pro-insulin, C-peptide, insulin antibodies

Treatment
for fasting hypoglycemia, must treat underlying cause
- for post-prandial (reactive) hypoglycemia, frequent small feeds
- see Emergency Medicine, ER35
treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV or 1 mg glucagon SC (if no IV available)
  - may need ongoing glucose infusion once BG >5 mmol/L

Metabolic Syndrome
- several definitions exist
- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, HTN, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include DM, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Obesity
- see Family Medicine, FM7
Pituitary Gland

Pituitary Hormones

Figure 7. Hypothalamic-pituitary hormonal axes
CRH = corticotropin-releasing hormone; GHRH = growth hormone-releasing hormone; GnRH = gonadotropin-releasing hormone; PRH = prolactin-releasing hormone; TRH = thyrotropin-releasing hormone

Hypothalamic Control of Pituitary
- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control by dopamine, as well as GH and TSH which are inhibited by somatostatin
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

Anterior Pituitary Hormones
- growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and prolactin (PRL)

Posterior Pituitary (Hypothalamic) Hormones
- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus, these hormones are stored and released from the posterior pituitary

Table 15. The Physiology and Action of Pituitary Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Stimulates growth of adrenal cortex and secretion of its hormones</td>
<td>Polypeptide Pulsatile and diurnal variation (highest in AM, lowest at midnight)</td>
<td>Dexamethasone Cortisol</td>
<td>CRH Metyrapone Insulin-induced hypoglycemia Vasopressin Fever, pain, stress</td>
</tr>
<tr>
<td>GH</td>
<td>Needed for linear growth IGF-1 stimulates growth of bone and cartilage</td>
<td>Polypeptide Acts indirectly through serum factors synthesized in the liver: IGF-1 (somatomedins-C) Serum GH undetectable for most of the day and suppressed after meals high in glucose Sustained rise during sleep</td>
<td>Glucose challenge Glucocorticoids Hypothyroidism Somatostatin Dopamine D2 receptor agonists IGF-1 (long-loop)</td>
<td>GHRH Insulin induced hypoglycemia Exercise REM sleep Arginine, clonidine, propranolol, L-dopa</td>
</tr>
</tbody>
</table>

Features of Metabolic Syndrome
(≥ 3 measures to make a Dx)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Obesity</td>
<td>≥102 cm (40 inches)</td>
<td>≥88 cm (35 inches)</td>
</tr>
<tr>
<td>Elevated Waist Circumference</td>
<td>≥94 cm (37 inches)</td>
<td>≥80 cm (31.5 inches)</td>
</tr>
<tr>
<td>Canada, USA</td>
<td>≥90 cm (35 inches)</td>
<td>≥80 cm (31.5 inches)</td>
</tr>
<tr>
<td>Europid, Middle Eastern, Sub-Saharan Africa, Mediterranean</td>
<td>≥90 cm (35 inches)</td>
<td>≥80 cm (31.5 inches)</td>
</tr>
<tr>
<td>Asian, Japanese South &amp; Central America</td>
<td>≥90 cm (35 inches)</td>
<td>≥80 cm (31.5 inches)</td>
</tr>
<tr>
<td>Triglyceride Level</td>
<td>≥1.7 mmol/L (150 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>HDL C Level</td>
<td>&lt;1.0 mmol/L (&lt;40 mg/dL)</td>
<td>&lt;1.3 mmol/L (&lt;50 mg/dL)</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥130/85 mmHg</td>
<td></td>
</tr>
<tr>
<td>Fasting Glucose Level</td>
<td>≥5.6 mmol/L (&gt;100 mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

Drug treatment for any elevated marker is an alternate indicator
Table 15. The Physiology and Action of Pituitary Hormones (continued)

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH/FSH</td>
<td>Stimulate gonads via cAMP&lt;br&gt;Ovary: LH production of androgens (theca cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles&lt;br&gt;Testes: LH production of testosterone (Leydig cells)&lt;br&gt;FSH: growth of granulosa cells in ovarian follicle; controls estrogen production</td>
<td>Polypeptide Glycoproteins (similar α subunit as TSH and hCG) Secreted in pulsatile fashion</td>
<td>Estrogen&lt;br&gt;Testosterone&lt;br&gt;Inhibin Continuous (i.e. non-pulsatile) GnRH infusion</td>
<td>Pulsatile GnRH</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Promotes milk production&lt;br&gt;Inhibits GnRH secretion</td>
<td>Polypeptide&lt;br&gt;Episodic secretion</td>
<td>Dopamine</td>
<td>Sleep&lt;br&gt;Stress, hypoglycemia&lt;br&gt;Pregnancy, breastfeeding&lt;br&gt;Mid-menstrual cycle&lt;br&gt;Sexual activity&lt;br&gt;TRH&lt;br&gt;Drugs: psychotropics, antihypertensives, dopamine antagonists, opiates, high dose estrogen</td>
</tr>
<tr>
<td>TSH</td>
<td>Stimulates growth of thyroid and secretion of T₃ and T₄ via cAMP</td>
<td>Glycoprotein</td>
<td>Circulating thyroid hormones (T₃, T₄) Opiates, dopamine</td>
<td>TRH&lt;br&gt;Epinephrine&lt;br&gt;Prostaglandins</td>
</tr>
<tr>
<td>ADH</td>
<td>Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine</td>
<td>Octapeptide&lt;br&gt;Secreted by posterior pituitary Osmoreceptors in hypothalamus detect serum osmolality Contracted plasma volume detected by baroreceptors is a more potent stimulus than ↑ osmolality</td>
<td>↓ serum osmolality</td>
<td>Hypovolemia or ↓ effective circulatory volume&lt;br&gt;↑ serum osmolality&lt;br&gt;Stress, pain, fever, paraneoplastic Lung or brain pathology</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Causes uterine contraction&lt;br&gt;Breast milk secretion</td>
<td>Nonapeptide&lt;br&gt;Secreted by posterior pituitary</td>
<td>EtOH</td>
<td>Suckling&lt;br&gt;Distortion of female genital tract during labour via stretch receptors</td>
</tr>
</tbody>
</table>

**Growth Hormone**

**GH DEFICIENCY**
- cause of short stature in children (see Pediatrics, P26)
- controversial significance in adults; often not clinically apparent, may present as fatigue

**GH EXCESS**

**Etiology**
- GH secreting pituitary adenoma, carcinoid or pancreatic islet tumours secreting ectopic GHRH resulting in excess GH

**Pathophysiology**
- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in GH excess states, secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

**Clinical Features**
- in children (before epiphyseal fusion) leads to gigantism
- in adults (after epiphyseal fusion) leads to acromegaly
- enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, thickening of skin, increased sebum production, sweating, acne, sebaceous cysts, fibroma mollusca, acanthosis nigricans, arthralgia, carpal tunnel syndrome, degenerative osteoarthritis, barrel chest, thyromegaly, renal calculi, HTN, cardiomyopathy, obstructive sleep apnea, colonic polyps, erectile dysfunction, menstrual irregularities, and DM

**Risks Associated with GH Excess**
- Cardiac disease (e.g. CAD, cardiomegaly, cardiomyopathy) in 1/3 of patients, with a doubling of risk of death from cardiac disease
- HTN in 1/3 of patients
- Risk of cancer (particularly GI) increased 2-fold to 3-fold
Pituitary Gland

Investigations
- elevated serum insulin-like growth factor-1 (IGF-1) is usually the first line diagnostic test
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- CT, MRI, or skull x-rays may show cortical thickening or enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica
- MRI of the sella turcica is needed to look for a tumour

Treatment
- surgery, octreotide (somatostatin analogue), dopamine agonist (bromocriptine/cabergoline), GH receptor antagonist (pegvisomant), radiation

Prolactin

HYPERPROLACTINEMIA

Etiology
- pregnancy and breastfeeding
- prolactinoma: most common pituitary adenoma (prolactin-secreting tumours may be induced by estrogen and grow during pregnancy)
- pituitary masses with pituitary stalk compression causing reduced dopamine inhibition of prolactin release
- primary hypothyroidism (increased TRH)
- decreased clearance due to chronic renal failure or severe liver disease (prolactin is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics (common), antidepressants, antihypertensives, anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide/domperidone), H2-blockers (ranitidine)
- macroprolactinemia (high molecular weight prolactin also known as big big prolactin)

Clinical Features
- galactorrhea (secretion of breast milk in women and, in rare cases, men), infertility, hypogonadism, amenorrhea, erectile dysfunction

Investigations
- serum PRL, TSH, liver enzyme tests, creatinine, macroprolactin level in select cases
- MRI of the sella turcica in select cases

Treatment
- long-acting dopamine agonist: bromocriptine, cabergoline, or quinagolide
- surgery ± radiation (rare)
- prolactin-secreting tumours are often slow-growing and sometimes require no treatment
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

Thyroid Stimulating Hormone

see Thyroid, E20

Adrenocorticotropic Hormone

see Adrenal Cortex, E29

Luteinizing Hormone and Follicle Stimulating Hormone

HYPOGONADOTROPIC HYPOGONADISM

Etiology
- primary/congenital: Kallmann syndrome, CHARGE syndrome, GnRH insensitivity
- secondary: CNS or pituitary tumours, pituitary apoplexy, brain/pituitary radiation, drugs (GnRH agonists/antagonists, glucocorticoids, narcotics, chemotherapy, drugs causing hyperprolactinemia), functional deficiency due to another cause (hyperprolactinemia, chronic systemic illnesses, eating disorders, hypothyroidism, DM Cushing's disease), systemic diseases (hemochromatosis, sarcoido-sis, histiocytosis)
**Clinical Features**

- hypogonadism, amenorrhea, erectile dysfunction (see Urology, U30), loss of body hair, fine skin, testicular atrophy, failure of pubertal development

**Treatment**

- combined FSH/LH hormone therapy, human chorionic gonadotropin (hCG), rFSH, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

**HYPERGONADOTROPIC HYPOGONADISM**

- hypogonadism due to impaired response of the gonads to FSH and LH

**Etiology**

- congenital:
  - chromosomal abnormalities (Turner's syndrome, Klinefelter syndrome, XX gonadal dysgenesis)
  - enzyme defects (17α-hydroxylase deficiency, 17, 20-lyase deficiency)
  - gonadotropin resistance (Leydig cell hypoplasia, FSH Insensitivity, pseudohypoparathyroidism type 1A)

- acquired:
  - gonadal toxins (chemotherapy, radiation)
  - drugs (glucocorticoids, antiandrogens, opioids, alcohol)
  - infections (STIs, Mumps)
  - gonadal failure in adults (androgen decline and testicular failure in men, premature ovarian failure and menopause in women)

**Clinical Features**

- hypogonadism, amenorrhea, erectile dysfunction (see Urology, U30), loss of body hair, fine skin, testicular atrophy, failure of pubertal development, low libido, infertility

**Treatment**

- hormone replacement therapy consisting of androgen (for males) and estrogen (for females) administration

---

**Antidiuretic Hormone**

**DIABETES INSIPIDUS**

**Definition**

- disorder of ineffective ADH (decreased production or peripheral resistance) resulting in passage of large volumes of dilute urine

**Etiology and Pathophysiology**

- central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, stalk lesion, hydrocephalus, histiocytosis X, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI
- psychogenic polydipsia and osmotic diuresis must be ruled out

**Clinical Features**

- passage of large volumes of dilute urine, polydipsia, and dehydration; hypernatremia can develop with inadequate water consumption or secondary to an impaired thirst mechanism

**Diagnostic Criteria**

- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
- response to exogenous ADH (DDAVP) will distinguish central from nephrogenic DI

**Treatment**

- DDAVP/vasopressin for central DI
- chlorpropamide, clofibrate, thiazides, NSAIDs, or carbamazepine as second line or for partial DI
- nephrogenic DI treated with solute restriction NSAIDs and thiazide diuretics; DDAVP (if partial)

---

**SYNDROME OF INAPPROPRIATE ADH SECRETION**

**Diagnostic Criteria**

- hyponatremia with corresponding plasma hypo-osmolality, urine sodium concentration above 40 mEq/L, urine less than maximally diluted (>100 mOsm/kg), euvolemia (edema absent), and absence of adrenal, renal, or thyroid insufficiency
Etiology and Pathophysiology
- stress (pain, nausea, post-surgical)
- malignancy (lung, pancreas, lymphoma)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain Barré syndrome)
- respiratory disease (TB, pneumonia, empyema)
- drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotinamide, morphine, DDAVP, oxytocin)

Clinical Features
- symptoms of hyponatremia: headaches, nausea, vomiting, muscle cramps, tremors, cerebral edema
  If severe (confusion, mood swings, hallucinations, seizures, coma)

Treatment
- treat underlying cause, fluid restriction (800-1000 mL/day), vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), and demeclocycline (antibiotic with anti-ADH properties, rarely-used)
  fludrocortisone, furosemide

Pituitary Pathology

PITUITARY ADENOMA (see Neurosurgery, NS13)

Clinical Features
- local mass effects
  - visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies), headaches; increased ICP is rare
  - hypofunction
  - hyperfunction
    - PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing's disease = Cushing's syndrome caused by a pituitary tumour)
    - tumours secreting LH, FSH, and TSH are rare

Investigations
- radiological evaluation (MRI is imaging procedure of choice)
- formal visual field testing
- hypothalamic pituitary hormonal function

HYPOPITUITARISM

Etiology (The Eight Is)
- Invasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke's cleft, arachnoid, or dermoid), metastases
- Infarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive post-partum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache, and altered level of consciousness; can be fatal if not recognized and treated early)
- Infiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- Infectious
  - syphilis, TB, fungal (histoplasmosis), parasitic (toxoplasmosis)
- Injury
  - severe head trauma
- Immunologic
  - autoimmune destruction
- Iatrogenic
  - following surgery or radiation
- Idiopathic
  - familial forms, congenital midline defects

Clinical Features
- symptoms depend on which hormone is deficient:
  - ACTH: fatigue, weight loss, hypoglycemia, anemia, hyponatremia, failure to thrive and delayed puberty in children
  - GH: short stature in children
  - TSH: tiredness, cold intolerance, constipation, weight gain, hair loss
  - LH and FSH: oligo- or amenorrhea, infertility, decreased facial/body hair and muscle mass in men, delayed puberty
  - Prolactin: inability to breastfeed
  - ADH: symptoms of diabetes insipidus (extreme thirst, polydipsia, hypernatremia)
  - Oxytocin: usually asymptomatic- only needed during labour and breastfeeding

SIADH vs. Cerebral Salt Wasting (CSW)
CSW can occur in cases of subarachnoid hemorrhage. Na+ is excreted by malfunctioning renal tubules, mimicking findings of SIADH; hallmark is hypovolemia

Presentations of Pituitary Lesions
- Mass effect (visual field defects, diplopia, ptosis, headaches, CSF leak)
- Hyperfunction
- Hypofunction

Important Deficiencies to Recognize are:
- Adrenal insufficiency
- Hypothyroidism
- Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis

The Pituitary Hormones
Order they are usually lost with compression by a mass:
"Go Look For The Adenoma Please"
GH, LH, FSH, TSH, ACTH, PRL + posterior pituitary hormones: ADH and oxytocin

The Pituitary Gland
Endocrinology
Toronto Notes 2018
Thyroid Hormones

Figure 8. Thyroid hormone synthesis

Synthetic Function of Thyroid Gland
- The synthesis of thyroid hormones T3 (thyroxine) and T4 (triiodothyronine) by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, digestion of thyroglobulin, and release of T3 and T4.
- 85% of T4 is converted to T3 or reverse T3 (RT3) in the periphery by deiodinases.
- RT3 is metabolically inactive but produced in times of stress to decrease metabolic activity.
- The plasma T3 pool is derived from the peripheral conversion of T4.
- Calcitonin, a peptide hormone, is also produced in the thyroid, by the parafollicular cells or C cells.
- Calcitonin functions by inhibiting osteoclast activity and increasing renal calcium excretion.

Role of Thyroid Hormones
- Thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors.
- Action of these hormones is diffuse, effecting nearly every organ system.
- Thyroid hormones have different tissue-specific actions determined by the expression of the types of thyroid receptor isoform and the local production of T4.
- They increase the basal metabolic rate including: increased Na+/K+ ATPase activity, increased O2 consumption, increased respiration, heat generation, and increased cardiovascular activity.
- Thyroid hormones also play crucial role during fetal life in both neurological and somatic development.

Patterns of Hormone Levels

<table>
<thead>
<tr>
<th>Pattern</th>
<th>TSH</th>
<th>T3, T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Hyper</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>2° Hyper</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>1° Hypo</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>2° Hypo</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
Regulation of Thyroid Function
- extrathyroidal:
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
  - T3 negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
- intrathyroidal (autoregulation):
  - synthesis (Wolff-Chaikoff effect, Jod-Basedow effect)
  - there is varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T3 to T4 in iodide deficiency
  - increased activity of peripheral 5’ deiodinase in hypothyroidism increases T3 production despite low T4 levels

Tests of Thyroid Function and Structure

TSH
- sensitive TSH (sTSH) is the best test for assessing thyroid function
- hyperthyroidism:
  - primary: TSH is low because of negative feedback from increased levels of circulating T3 and T4
  - secondary: increased TSH results in increased T3 and T4
- hypothyroidism:
  - primary: increased TSH (most sensitive test) because of less negative feedback from T3 and T4
  - secondary: TSH is low or normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T3 and Free T4
- standard assessment of thyroid function measures TSH and, if necessary, free T4. Free T3 should only be measured in the small subset of patients with hyperthyroidism and suspected T3 toxicosis. TSH would be suppressed, free T4 normal, and free T3 elevated

Thyroid Autoantibodies
- thyroglobulin antibodies (TgAb), anti-thyroid peroxidase antibodies (TPOAb), and TSH receptor antibodies (TRAB) of the blocking variety are increased in Hashimoto’s disease; normal variant in 10-20% of individuals
- TRABs of the stimulating variety are also referred to as thyroid stimulating immunoglobulins (TSI) and cause Graves’ disease. However, both TRAB receptor blocking and stimulating antibodies are seen in patients with Graves’ disease

Plasma Thyroglobulin
- used to monitor for residual thyroid tissue post-thyroidectomy, e.g. tumour marker for thyroid cancer recurrence
- normal or elevated levels may suggest persistent, recurrent, or metastatic disease

Serum Calcitonin
- not routinely done to investigate thyroid nodules
- ordered if suspicion of medullary thyroid carcinoma or family history of MEN IIa or IIb syndromes
- used to monitor for residual or recurrent medullary thyroid cancer

Thyroid Imaging/Scans
- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S:
  - to measure size of gland, solid vs. cystic nodule, facilitate fine needle aspirate biopsy (FNAB)
  - radioisotope thyroid scan (Technetium-99)
  - test of structure: order if there is a thyroid nodule and patient is hyperthyroid with low TSH
  - differentiates between hot (functioning → excess thyroid hormone production) and cold (non-functioning) nodules
  - hot nodule → very low chance malignancy; treat hyperthyroidism
  - cold nodule → ~5% chance malignancy; further workup required (U/S and FNAB)
- radioactive iodine uptake (RAIU):
  - test of function: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland in vivo
  - if ↑ uptake (ie incorporated), gland is overactive (hyperthyroid)
  - if ↓ uptake (ie not incorporated), gland is leaking thyroid hormone (e.g. thyroiditis, exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye which has high iodine content)
- see Figure 9, Approach to the Evaluation of a Thyroid Nodule, E28 for further information regarding the utility of these scans

Thyroid Biopsy
- fine needle aspiration (FNA) for cytology
- differentiates between benign and malignant disease
- best done under U/S guidance
- accuracy decreased if nodule is greater than 50% cystic, or if nodule located posteriorly in the gland
Table 16. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSH</strong></td>
<td>Decreased in 1° hyperthyroidism</td>
<td>Increased in 2° hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Increased in 2° hyperthyroidism</td>
<td>Decreased in 2° hypothyroidism</td>
</tr>
<tr>
<td><strong>Free T4</strong></td>
<td>Increased in 1° hyperthyroidism</td>
<td>Decreased in 1° hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Increased in 2° hyperthyroidism</td>
<td>Increased in 2° hypothyroidism</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td>Graves': thyroid stimulating Ig (TSI)</td>
<td>Hashimoto's: antithyroid peroxidase (TPOAb, TgAb)</td>
</tr>
<tr>
<td><strong>RAIU</strong></td>
<td>Increased uptake</td>
<td>Decreased uptake</td>
</tr>
<tr>
<td></td>
<td>Graves'</td>
<td>Subacute thyroiditis</td>
</tr>
<tr>
<td></td>
<td>Toxic multinodular goitre</td>
<td>Recent iodine load</td>
</tr>
<tr>
<td></td>
<td>Toxic adenoma</td>
<td>Exogenous thyroid hormone</td>
</tr>
<tr>
<td><strong>Radioisotope Thyroid Scan</strong></td>
<td>Graves': homogenous diffuse uptake</td>
<td>Toxic multinodular goitre: heterogeneous uptake</td>
</tr>
<tr>
<td></td>
<td>Toxic adenoma</td>
<td>Toxic adenoma: single intense area of uptake with suppression elsewhere</td>
</tr>
</tbody>
</table>

Thyrotoxicosis

**Definition**
- Clinical, physiological, and biochemical findings in response to elevated thyroid hormone

**Epidemiology**
- 1% of general population have hyperthyroidism
- F:M = 5:1

**Etiology and Pathophysiology**

Table 17. Differential Diagnosis of Thyrotoxicosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>Free T4/T3</th>
<th>Antibodies</th>
<th>RAUU</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPERTHYROIDISM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves' Disease</td>
<td>Decreased</td>
<td>Increased</td>
<td>TSI</td>
<td>Increased</td>
<td>Homogenous uptake on scan</td>
</tr>
<tr>
<td>Toxic Nodular Goitre</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Heterogeneous uptake on scan</td>
</tr>
<tr>
<td>Toxic Nodule</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Intense uptake in hot nodule on scan with no uptake in the rest of the gland</td>
</tr>
<tr>
<td><strong>THYROIDITIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute, Silent, Postpartum</td>
<td>Decreased</td>
<td>Increased</td>
<td>Up to 50% of cases</td>
<td>Decreased (increases once entering hypothyroid phase, when TSH rises)</td>
<td>In classical subacute painful thyroiditis, ESR increased</td>
</tr>
<tr>
<td><strong>EXTRATHYROIDAL SOURCES OF THYROID HORMONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Exogenous (drugs)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Decreased</td>
<td>(T4 would be decreased if taking T3)</td>
</tr>
<tr>
<td><strong>EXCESSIVE THYROID STIMULATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary thyrotrophoma</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Pituitary thyroid hormone receptor resistance</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Increased hCG (e.g. pregnancy)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>DO NOT DO THIS TEST IN PREGNANCY</td>
</tr>
</tbody>
</table>

Drugs Affecting Thyroid Function

**Thyrotoxicosis**
- Lithium plays an inhibitory role in thyroid hormone release, resulting in clinical hyperthyroidism and goitre.
- Amiodarone, a class III anti-arrhythmic drug contains 2 atoms of iodine per molecule and is structurally similar to thyroid hormones, and may exert antagonistic effects on TSH receptors. It is also shown to inhibit type I deiodinases resulting in low T3 and high T4 levels. Amiodarone-induced hyperthyroidism occurs in 5-15% of patients on amiodarone. AHT can also occur in people without pre-existing thyroid dysfunction.
- Amiodarone-induced thyrotoxicosis (AIT) occurs in 2-12% of patients on amiodarone. This may be due to either an increased iodine load in patients with previously autonomous thyroid (Graves’ disease, toxic multinodular goitre), or amiodarone-induced destructive thyroiditis.

**Signs and Symptoms of HYPERthyroidism**
- Tremor
- Heart rate up
- Yawning (fatigued)
- Restlessness
- Oligomenorrhea/amenorrhea
- Intolerance to heat
- Diarrhea
- Irritability
- Sweating
- Muscle wasting/weight loss

**Common Etiologies**

<table>
<thead>
<tr>
<th>Thyrotoxicosis</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves' Disease</td>
<td>Hashimoto's</td>
</tr>
<tr>
<td>Toxic Nodular Goitre</td>
<td>Congenital</td>
</tr>
<tr>
<td>Toxic Nodule</td>
<td>Iatrogenic (thionamides, radioactive iodine, or surgery)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Hypothyroid phase of thyroiditis</td>
</tr>
</tbody>
</table>
Clinical Features

Table 18. Clinical Features of Thyrotoxicosis

<table>
<thead>
<tr>
<th>General</th>
<th>Fatigue, heat intolerance, irritability, fine tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Tachycardia, atrial fibrillation, palpitations</td>
</tr>
<tr>
<td></td>
<td>Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation</td>
</tr>
<tr>
<td>GI</td>
<td>Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)</td>
</tr>
<tr>
<td>Neurology</td>
<td>Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians)</td>
</tr>
<tr>
<td>GU</td>
<td>Oligomenorrhea, amenorrhea, decreased fertility</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema, pruritis</td>
</tr>
<tr>
<td>MSK</td>
<td>Decreased bone mass, proximal muscle weakness</td>
</tr>
<tr>
<td>Hematology</td>
<td>Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)</td>
</tr>
<tr>
<td>Eye</td>
<td>Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjunctival injection</td>
</tr>
</tbody>
</table>

Treatment
- thionamides: propylthiouracil (PTU) or methimazole (MMI); MMI recommended (except in first trimester pregnancy)
- β-blockers for symptom control
- radioactive iodine thyroid ablation for Graves' disease
- surgery in the form of hemi, subtotal, or complete thyroidectomy

Graves' Disease

Definition
- an autoimmune disorder characterized by autoantibodies to the TSH receptor that leads to hyperthyroidism

Epidemiology
- most common cause of thyrotoxicosis
- occurs at any age with peak in 3rd and 4th decade
- F:M = 7:1, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA B8 and DR3
- may be associated with other inherited autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathophysiology
- autoimmune disorder due to a defect in T-suppressor cells
- B lymphocytes produce TSI that binds and stimulates the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, lithium therapy, viral or bacterial infections, glucocorticoid withdrawal
- ophthalmopathy (thyroid associated orbitopathy) is a result of increased tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit; this leads to fluid accumulation and displacement of the eyeball forward
- dermopathy may be related to increased glycosaminoglycan deposition

Clinical Features
- signs and symptoms of thyrotoxicosis
- diffuse thyroid goitre ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity (plus signs of hyperthyroidism: lid retraction, characteristic stare)
- dermopathy (rare): pretibial myxedema (thickening of dermis that manifests as non-pitting edema)
- acropachy: clubbing and thickening of distal phalanges

Investigations
- low TSH
- increased free T4 (and/or increased T3)
- positive for TSI (specific but not sensitive for Graves' disease)
- increased radioactive iodine (I 131) uptake
- homogeneous uptake on thyroid scan (only do this test in the presence of nodule)
**Treatment**

- thionamides: propylthiouracil (PTU) or methimazole (MMI)
  - PTU and MMI inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of isotopotides
  - PTU also inhibits peripheral deiodination of T4 to T3
  - continue treatment until remission occurs (20-40% of patients achieve spontaneous remission at 6-18 mo of treatment)
- small goitre and recent onset are good indicators for long-term remission with medical therapy
- major side effects: hepatitis, agranulocytosis, and fever/arthritis
- minor side effects: rash
- iodinated contrast agents: sodium ipodate and iopanoic acid can inhibit conversion of T4 to T3 and are especially effective in combination with MMI
- MMI preferred vs. PTU due to longer duration of action (once daily for most), more rapid efficacy, and lower incidence of side effects
- in pregnancy: use PTU during first trimester and MMI during second and third trimester. MMI is contraindicated in the first trimester due to risk of aplasia cutis; MMI is preferred in the second and third trimester due to the potential risk of hepatotoxicity with PTU in the second and third trimesters
- symptomatic treatment with β-blockers
- thyroid ablation with radioactive ¹³¹I if PTU or MMI trial does not produce disease remission
- high incidence of hypothyroidism after ¹³¹I requiring lifelong thyroid hormone replacement
- con raindeicated in pregnancy
- may worsen ophthalmopathy
- subtotal or total thyroidectomy (indicated for large goitres, suspicious nodule for Ca, if patient is intolerant to thionamides and refusing RAI ablation)
- risks include hypoparathyroidism and vocal cord palsy
- ophthalmopathy/orbitopathy
  - smoking cessation is important
  - prevent drying of eyes
  - high dose prednisone in severe cases
  - orbital radiation, surgical decompression

**Prognosis**

- course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
- lifetime follow-up needed
- risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively

## Subacute Thyroiditis (Thyrotoxic Phase)

**Definition**

- acute inflammatory disorder of the thyroid gland characterized by an initial thyrotoxic state followed by hypothyroidism eventually followed by euthyroidism in most cases
- two subtypes: painful (“De Quervain’s”) and painless (“Silent”)

**Etiology and Pathophysiology**

- acute inflammation of the thyroid gland characterized by giant cells and lymphocytes
- disruption of thyroid follicles by inflammatory process results in the release of stored hormone rather than excessive production of new thyroid hormone
- painful = viral (usually preceded by URI), De Quervain’s (granulomatous thyroiditis)
- painless = postpartum, auto-immune, lymphocytic
- occurs in 5-10% of postpartum mothers and is symptomatic in 1/3 of patients

**Clinical Features**

- painful (thyroid, ears, jaw, and occiput) or painless
- fever and malaise may be present, especially in De Quervain’s
- postpartum: thyrotoxicosis 2-3 mo postpartum with a subsequent hypothyroid phase at 4-8 mo post partum
- may be mistakenly diagnosed as postpartum depression

**Laboratory Investigations**

- initial elevated free T₄, T₃, low TSH, RAIU markedly reduced
- marked elevation of ESR in painful variety only
- as disease progresses values consistent with hypothyroidism may appear

**Treatment**

- painful – high dose NSAIDs prednisone may be required for severe pain, fever, or malaise
- iodinated contrast agents (e.g. iopanoic acid, ipodate) to inhibit peripheral conversion of T₄ to T₃
- β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms in both subtypes
- if symptomatically hypothyroid, may treat short-term with thyroxine

**Prognosis**

- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis
- postpartum: most resolve spontaneously without need for supplementation, however may recur with subsequent pregnancies
Toxic Adenoma/Toxic Multinodular Goitre

Etiology and Pathophysiology
- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting T3 and T4
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre [Plummer's disease])

Clinical Features
- goitre with adenomatous changes
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- seen most frequently in elderly people, often with presentation of atrial fibrillation

Investigations
- low TSH, high T3 and T4
- thyroid scan with increased RAIU in nodule(s) and suppression of the remainder of the gland

Treatment
- initiate therapy with PTU or MMI to attain euthyroid state
- use high dose radioactive iodine (I-131) to ablate hyperfunctioning nodules
- β-blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as 1st line treatment

Thyrotoxic Crisis/Thyroid Storm

Definition
- acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism – medical emergency!
- rare, but serious with mortality rate between 10-30%

Etiology and Pathophysiology
- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

Differential Diagnosis
- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

Clinical Features
- hyperthyroidism
- extreme hyperthermia (≥40°C), tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
- tachyarrhythmia, CHF, shock
- mental status changes ranging from delirium to coma

Laboratory Investigations
- increased free T3 and T4, undetectable TSH
- ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

General Measures
- fluids, electrolytes, and vasopressor agents should be used as indicated
- a cooling blanket and acetaminophen can be used to treat the pyrexia
- propranolol or other β blockers that additionally decrease peripheral conversion of T3 → T4 can be used, but should be used with caution in CHF patients as it may worsen condition

Specific Measures
- PTU is the anti-thyroid drug of choice and is used in high doses
- give iodide, which acutely inhibits the release of thyroid hormone, one hour after the first dose of PTU is given
  - Sodium iodide 1 g IV drip over 12h q12h
  - Lugol's solution 2-3 drops q8h
  - Potassium iodide (SSKI) 5 drops q8h
- dexamethasone 2-4 mg IV q6h for the first 24-48 hours lowers body temperature and inhibits peripheral conversion of T3 → T4

Prognosis
- probably <20% mortality rate if rapidly recognized and treated
Hypothyroidism

**Definition**
- clinical syndrome caused by cellular responses to insufficient thyroid hormone production

**Epidemiology**
- 2-3% of general population
- F:M = 10:1
- 10-20% of women over age 50 have subclinical hypothyroidism (normal T₄, TSH mildly elevated)
- iodine deficiency most common cause worldwide, but not in North America

**Etiology and Pathophysiology**
- primary hypothyroidism (90%)
  - inadequate thyroid hormone production secondary to intrinsic thyroid defect
  - iatrogenic: post-ablative (1-131 or surgical thyroidectomy)
  - autoimmune: Hashimoto’s thyroiditis, chronic thyroiditis, idiopathic, burnt out Graves’
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4,000 births)
- secondary hypothyroidism: pituitary hypothyroidism
  - insufficiency of pituitary TSH
  - tertiary hypothyroidism: hypothalamic hypothyroidism
  - decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

**Table 20. Clinical Features of Hypothyroidism**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Serum TSH</th>
<th>Free T₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt Primary Hypothyroidism</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Subclinical Primary Hypothyroidism</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
<td>Decreased or not appropriately elevated</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

**Clinical Features**

**Table 20. Clinical Features of Hypothyroidism**

| General | Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroGLOSSIA |
| CVS     | Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart |
| Respiratory | Decreased exercise capacity, hyponatremia secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroGLOSSIA |
| GI      | Weight gain despite poor appetite, constipation |
| Neurology | Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes (“hung reflexes”), carpal tunnel syndrome, asymptomatic increase in CK, seizures |
| GU     | Menorrhagia, amenorrhea, impotence |
| Dermatology | Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discoloration (carotenemia) |
| Hematology | Anemia: 10% pernicious due to presence of anti-periartial cell antibodies with Hashimoto’s thyroiditis |

**Treatment**
- L-thyroxine (dose range: 0.05-0.2 mg PO OD ~1.6 μg/kg/d)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up TSH with patient annually
- secondary/tertiary hypothyroidism
  - monitor via measurement of free T₄ (TSH is unreliable in this setting)

**CONGENITAL HYPOTHYROIDISM**
- see Pediatrics P28
Hashimoto’s Thyroiditis

- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from the start
  - associated with thyroid lymphoma

Etiology and Pathophysiology

- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na+/I– symporter

Risk Factors

- female gender (F:M = 7:1)
- genetic susceptibility: increased frequency in patients with Down’s syndrome, Turner’s syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake
- stress and infection

Investigations

- high TSH, low T4 (not necessary to measure T3 as it will be low as well)
- presence of anti-thyroid peroxidase (TPOAb) and thyroglobulin antibodies (TgAb) in serum

Treatment

- if hypothyroid, replace with L-thyroxine (analog of T4)

Myxedema Coma

Definition

- severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – medical emergency!
- rare high level of mortality when it occurs (up to 40%, despite therapy)

Clinical Features

- hallmark symptoms of decreased mental status and hypothermia; hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized edema often present

Investigations

- decreased T4, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment

- aggressive treatment required
- ABCs: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated; also consider T3 therapy
- supportive measures: mechanical ventilation, vasopressor drugs, passive rewarming, IV dextrose, fluids if necessary (risk of overload)
- monitor for arrhythmia

Sick Euthyroid Syndrome

Definition

- changes in circulating thyroid hormones amongst patients with serious illness, trauma, or stress
- not due to intrinsic thyroid or pituitary disease
- initially low free T3 may be followed by low TSH and if severe illness low free T4
- with recovery of illness, TSH may overshoot and become transiently high

Pathophysiology

- abnormalities include alterations in
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
  - thyroid function itself
- may be protective during illness by reducing tissue catabolism
**Labs**
- initially decreased free T₃ followed by decreased TSH and finally decreased free T₄

**Treatment**
- treat the underlying disease; thyroid hormone replacement worsens outcomes
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

**Non-Toxic Goitre**

**Definition**
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

**Pathophysiology**
- the appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages goitre is usually diffuse
  - later stages: multinodular non-toxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

**Etiology**
- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

**Treatment**
- remove goitrogens
- radioiodine therapy (need very high doses given low iodine uptake, used as last resort)
- suppression with L-thyroxine (rarely done)
- surgery may be necessary for severe compressive symptoms

**Complications**
- compression of neck structures causing stridor, dysphagia, pain, and hoarseness
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

**Thyroid Nodules**

**Definition**
- clearly defined discrete mass, separated from the thyroid parenchyma
- palpable nodules are found in approximately 5% of women and 1% of men

**Etiology**
- benign tumours (e.g. colloid nodule, follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

**Investigations**

**Figure 9. Approach to the evaluation of a thyroid nodule**
Adapted from Dr. J Goguen, University of Toronto, MMMD 2013

**Thyroid Malignancies**
- see Otolaryngology, OT37
Adrenal Cortex

Adrenocorticotropic Hormone

- a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400; trough: 1800-2400)
- secretion regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)
- stimulates growth of adrenal cortex and release of glucocorticoids, androgens and, to a limited extent, mineralocorticoids
- some melanocyte stimulating activity

Adrenocortical Hormones

Aldosterone
- a mineralocorticoid which regulates extracellular fluid (ECF) volume through Na⁺ and K⁺ excretion (stimulates distal tubule Na⁺/K⁺ ATPase)
- regulated by the renin-angiotensin-aldosterone system (Figure 12)
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone↑ volume expansion) and short loop (angiotensin II↑ peripheral vasoconstriction)

Cortisol
- a glucocorticoid, regulated by the HPA axis
- involved in regulation of metabolism; counteracts the effects of insulin
- support blood pressure, vasomotor tone
- also involved in regulation of behaviour and immunosuppression
Table 21. Physiological Effects of Glucocorticoids

<table>
<thead>
<tr>
<th>Stimulatory Effects</th>
<th>Inhibitory Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulate hepatic glucose production (gluconeogenesis)</td>
<td>Inhibit bone formation; stimulate bone resorption</td>
</tr>
<tr>
<td>Increase insulin resistance in peripheral tissues</td>
<td>Inhibit fibroblasts, causing collagen and connective tissue loss</td>
</tr>
<tr>
<td>Increase protein catabolism</td>
<td>Suppress inflammation; impair cell-mediated immunity</td>
</tr>
<tr>
<td>Stimulate leukocytosis and lymphopenia</td>
<td>Inhibit growth hormone axis</td>
</tr>
<tr>
<td>Increase cardiac output, vascular tone, Na⁺ retention</td>
<td>Inhibit reproductive axis</td>
</tr>
<tr>
<td>Increase PTH release, urine calcium excretion</td>
<td>Inhibit vitamin D³ and inhibit calcium uptake</td>
</tr>
</tbody>
</table>

**Androgens**

- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione, and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age

**Adrenocortical Functional Workup**

**STIMULATION TEST**

- purpose: diagnosis of hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

1. **Tests of Glucocorticoid Reserve**

   - Cosyntropin (ACTH analogue) Stimulation Test
     - give 1 µg or 250 µg cosyntropin IV, then measure plasma cortisol levels at time 0, 30, and 60 min
     - physiologic response: stimulated plasma cortisol of >500 nmol/L
     - inappropriate response: inability to stimulate increased plasma cortisol
   - insulin tolerance is the gold standard test used to diagnose adrenal insufficiency (see **Pituitary Gland**, E15)

**SUPPRESSION TESTS**

- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

1. **Tests of Pituitary-Adrenal Suppressibility**

   Dexamethasone (DXM) Suppression Test
   - principle: DXM suppresses pituitary ACTH, plasma cortisol should be lowered if HPA axis is normal
   - **Screening Test**: Overnight DXM Suppression Test
     - oral administration of 1 mg DXM at midnight measure plasma cortisol levels the following day at 8 am
     - physiologic response: plasma cortisol <50 nmol/L, with 50-140 nmol/L being a “grey zone” (cannot be certain if normal or not)
     - inappropriate response: failure to suppress plasma cortisol
     - <20% false positive results due to obesity, depression, alcohol, other medications
   - **Confirmatory Test**: other testing is used to confirm the diagnosis, such as:
     - 24 h urine free cortisol (shows overproduction of cortisol)
     - midnight salivary cortisol (if available), shows lack of diurnal variation
     - inappropriate response: remains high (normally will be low at midnight)

2. **Tests of Mineralocorticoid Suppressibility**

   - principle: expansion of extracellular fluid volume (ECFV); plasma aldosterone should be lowered if HPA axis is normal
   - ECFV Expansion with Normal Saline (NS)
     - IV infusion of 500 mL/h of NS for 4 h, then measure plasma aldosterone levels
     - plasma aldosterone >277 pmol/L is consistent with primary hyperaldosteronism, <140 pmol/L is normal
     - inappropriate response: failure to suppress plasma aldosterone
**Mineralocorticoid Excess Syndromes**

**Figure 13. Approach to mineralocorticoid excess syndromes**

**Definition**
- primary hyperaldosteronism (PH): excess aldosterone production (intra-adrenal cause)
- secondary hyperaldosteronism (SH): aldosterone production in response to excess RAAS (extra-adrenal cause)

**Etiology**
- primary hyperaldosteronism
  - aldosterone-producing adrenal adenoma (Conn's syndrome)
  - bilateral or idiopathic adrenal hyperplasia
  - glucocorticoid-remediable aldosteronism
  - aldosterone-producing adrenocortical carcinoma
  - unilateral adrenal hyperplasia
- secondary hyperaldosteronism

**Clinical Features**
- HTN
- hypokalemia (may have mild hypernatremia), metabolic alkalosis
- normal K⁺, low Na⁺ in SH (low effective circulating volume leads to ADH release) edema
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, MI
- fatigue, weakness, paresthesia, headache; severe cases with tetany, intermittent paralysis

**Diagnosis**
- investigate plasma aldosterone to renin ratio in patients with HTN and hypokalemia
- confirmatory testing for PH: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECF volume expansion)
- imaging: CT adrenal glands

**Table 22. Diagnostic Tests in Hyperaldosteronism**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary Hyperaldosteronism</th>
<th>Secondary Hyperaldosteronism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma aldosterone to renin ratio (PAC/PRA)</td>
<td>Elevated (↑ ald, ↓ renin)</td>
<td>Normal (↑ ald, ↑ renin)</td>
</tr>
<tr>
<td>Salt loading test</td>
<td>↑ urine aldosterone</td>
<td>Not performed if normal PAC/PRA</td>
</tr>
<tr>
<td>A) Oral test</td>
<td>↑ plasma aldosterone</td>
<td></td>
</tr>
<tr>
<td>B) IV saline test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**
- inhibit action of aldosterone: spironolactone, eplerenone, triam erene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause
Cushing’s Syndrome

Definition
- results from chronic glucocorticoid excess (endogenous or exogenous sources)

Etiology
- ACTH-dependent (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
  - ACTH-secreting pituitary adenoma (Cushing’s disease; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma, or medullary thyroid tumours)
- ACTH-independent (15%)
  - long-term use of exogenous glucocorticoids
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia

Clinical Features
- symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism, and acne (ACTH dependent)
- signs: central obesity, round face, supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, HTN, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism if ACTH-dependent

Diagnosis
- complete a drug history to exclude iatrogenic Cushing’s
- perform one of: 1) 24 h urine free cortisol, 2) dexamethasone suppression test, or 3) late night salivary cortisol
- consider reasons for a false positive (e.g. pregnancy, depression, alcoholism, morbid obesity, poorly controlled DM)
- confirm with one of the remaining tests if necessary (do not rely on random cortisol, insulin tolerance, loperamide, or urinary 17-ketosteroid tests)

Treatment
- adrenal
  - adenoma: unilateral adrenalectomy (curative) with glucocorticoid supplementation post-operatively
  - carcinoma: adjunctive chemotherapy often not useful (frequent metastases, poor prognosis)
  - medical treatment: mitotane, ketoconazole to reduce cortisol
- pituitary
  - trans-sphenoidal resection, with glucocorticoid supplement post-operatively
  - if surgery delayed, contraindicated or unsuccessful consider medical management ex. adrenal enzyme inhibitors, glucocorticoid receptor antagonist
- ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis)
  - surgical resection, if possible; chemotherapy/radiation for primary tumour
  - medical treatment with mitotane or ketoconazole to reduce cortisol synthesis. Often required when surgery is delayed, contraindicated, or unsuccessful

Congenital Adrenal Hyperplasia
- see Pediatrics, P29

Hyperandrogenism

Definition
- state of having excessive secretion of androgens (DHEA, DHEA sulfate, testosterone)

Etiology and Pathophysiology

Table 23. Etiology of Hyperandrogenism

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional/Familial</td>
<td>Family history, predisposing ethnic background</td>
</tr>
<tr>
<td></td>
<td>Premature adrenarche</td>
</tr>
<tr>
<td>Medications Androgen-Mediated</td>
<td>Anabolic steroids, ACTH, androgens, progestational agents</td>
</tr>
<tr>
<td>Ovarian</td>
<td>PCOS</td>
</tr>
<tr>
<td></td>
<td>Ovarian hyperthecosis</td>
</tr>
<tr>
<td></td>
<td>Theca cell tumours</td>
</tr>
<tr>
<td></td>
<td>Pregnancy: placental sulfatase/aromatase deficiency</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Congenital adrenal hyperplasia (CAH, late-onset CAH)</td>
</tr>
<tr>
<td></td>
<td>Tumours (adenoma, carcinoma)</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Cushing’s disease – high ACTH</td>
</tr>
<tr>
<td></td>
<td>Hyperprolactinemia</td>
</tr>
</tbody>
</table>
Clinical Features

Females

- hirsutism
  - male pattern growth of androgen-dependent termina body hair in women: back, chest, upper abdomen, face, linea alba
  - Ferriman-Gallwey scoring system is used to quantify severity of hirsutism
- virilization
  - masculinization: hirsutism, temporal balding, clitoral enlargement, deepening of voice, acne
  - increase in musculature
- defeminization
  - loss of female secondary sex characteristics (i.e. amenorrhea, ↓ breast size, infertility)

Males

- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in: testicular size, testicular testosterone production, and spermatogenesis

Investigations

- testosterone, DHEA-S as a measure of adrenal androgen production
- LH/FSH (commonly in PCOS >2.5)
- 17-OH progesterone, elevated in CAH due to 21-OH deficiency; check on day 3 of menstrual cycle with a progesterone level
- for virilization: CT/MRI of adrenals and ovaries (identify tumours)
- if PCOS, check blood glucose, lipids, 75 g OGTT

Treatment

- discontinue causative medications
- antiandrogens, e.g. spironolactone
- oral contraceptives (increase sex hormone binding globulin, which binds androgens>estrogens; reduce ovarian production of androgens)
- surgical resection of tumour
- low dose glucocorticoid ± mineralocorticoid if CAH suspected
- treat specific causative disorders, e.g. tumours, Cushing’s, etc.
- cosmetic therapy (laser, electrolysis)

Adrenocortical Insufficiency

Definition

- state of inadequate cortisol and/or aldosterone production by the adrenal glands

Etiology

PRIMARY (ADDISON’S DISEASE)

Table 24. Etiology of Primary Adrenocortical Insufficiency

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Table 24. Etiology of Primary Adrenocortical Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune (70-90%)</td>
<td>Isolated adrenal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Polyglandular autoimmune syndrome type I and II</td>
</tr>
<tr>
<td></td>
<td>Antibodies often directed against adrenal enzymes and 3 cortical zones</td>
</tr>
<tr>
<td>Infection</td>
<td>TB (7-20%) (most common in developing world)</td>
</tr>
<tr>
<td></td>
<td>Fungal: histoplasmosis, paracoccidioidomycosis</td>
</tr>
<tr>
<td></td>
<td>HIV, CMV</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>African trypanosomiasian</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Metastatic cancer (lung&gt;stomach&gt;esophagus&gt;colon&gt;breast); lymphoma</td>
</tr>
<tr>
<td></td>
<td>Sarcoiosis, amyloidosis, hemochromatosis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Bilateral adrenal hemorrhage (risk increased by heparin and warfarin)</td>
</tr>
<tr>
<td></td>
<td>Sepsis (meningococcal Pseudomonas)</td>
</tr>
<tr>
<td></td>
<td>Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children</td>
</tr>
<tr>
<td></td>
<td>Thrombosis, embolism, adrenal infarction</td>
</tr>
<tr>
<td>Drugs</td>
<td>Inhibit cortisol: ketoconazole, etomideate, megestrol acetate</td>
</tr>
<tr>
<td></td>
<td>Increase cortisol metabolism: rifampin, phenytoin, barbiturates</td>
</tr>
<tr>
<td>Others</td>
<td>Adrenoleukodystrophy</td>
</tr>
<tr>
<td></td>
<td>Congenital adrenal hypoplasia (impaired steroidogenesis)</td>
</tr>
<tr>
<td></td>
<td>Familial glucocorticoid deficiency or resistance</td>
</tr>
</tbody>
</table>
SECONDARY ADRENOCORTICAL INSUFFICIENCY
- inadequate pituitary ACTH secretion
- multiple etiologies (see Hypopituitarism, E19), including withdrawal of exogenous steroids

Clinical Features

Table 25. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)

<table>
<thead>
<tr>
<th></th>
<th>Primary AI (Addison’s or Acute AI)</th>
<th>Secondary AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and Mucosa</td>
<td>Dark (palmar crease, extensor surface)</td>
<td>Pale</td>
</tr>
<tr>
<td>Potassium</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Sodium</td>
<td>Low</td>
<td>Normal or Low</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Associated Diseases</td>
<td>Primary hypothyroidy, type 1 DM, vitiligo, neurological deficits</td>
<td>Central hypogonadism or hypothyroidy, growth hormone deficiency, DI, headaches, visual abnormalities</td>
</tr>
<tr>
<td>Associated Symptoms</td>
<td>Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia, Gl: N/V, abdominal pain, diarrhea</td>
<td>Same except: No salt craving GI less common</td>
</tr>
<tr>
<td>Diagnostic Test</td>
<td>Insulin tolerance test Cosyntropin Stimulation Test High morning plasma ACTH</td>
<td>Insulin tolerance test Cosyntropin Stimulation Test Low morning plasma ACTH</td>
</tr>
</tbody>
</table>

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

Treatment
- acute condition – can be life-threatening
  - IV NS in large volumes (2-3 L); add D5W if hypoglycemic from adrenal insufficiency
  - hydrocortisone 50-100 mg IV q6-8h for 24h, then gradual tapering
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-20 mg total daily dose, in 2-3 divided doses, highest dose in the AM
  - Florinef (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
  - major stress (e.g. surgery, trauma) requires 150-300 hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection

Adrenal Medulla

Catecholamine Metabolism
- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine)
- broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine

Pheochromocytoma

Definition
- rare catecholamine secreting tumour derived from chromaffin cells of the sympathetic system

Epidemiology
- most commonly a single tumour of adrenal medulla
- rare cause of HTN (<0.2% of all hypertensives)

Etiology and Pathophysiology
- most cases sporadic (80%)
- familial: associated with multiple endocrine neoplasia II (MEN IIA and IIB 50% penetrance; i.e. 50% of people with the mutation get pheochromocytoma), von Hippel-Lindau (10-20% penetrance), paraganglioma (20% penetrance), or neurofibromatosis type 1 (0.1-5% penetrance)
- tumours, via unknown mechanism, able to synthesize and release excessive catecholamines
Clinical Features
• 50% suffer from paroxysmal HTN; the rest have sustained HTN
• classic triad (not found in most patients): episodic "pounding" headache, palpitations/tachycardia, diaphoresis
• other symptoms: tremor, anxiety, chest or abdominal pain, N/V, visual blurring, weight loss, polyuria, polydipsia
• other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
• symptoms may be triggered by stress, exertion anesthesia, abdominal pressure, certain foods (especially tyramine containing foods)

Investigations
• urine catecholamines
  ■ increased catecholamine metabolites (metanephrines) and free catecholamines
  ■ plasma metanephrines if available (most sensitive)
  • cut-off values will depend on assay used
• CT abdomen
  if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

Treatment
• surgical removal of tumour (curative) with careful pre- and post-operative ICU monitoring
• adequate pre-operative preparation
  • α-blockade for BP control: doxazosin or calcium channel blockers (10-21 d pre-operative), IV phentolamine (perioperative, if required)
  • β-blockade for HR control once α blocked for a few days
  • metyrosine (catecholamine synthesis inhibitor) + phenoxybenzamine or prazosin
  • volume restoration with vigorous salt-loading and fluids
• rescreen urine 1-3 mo post-operatively
• screen urine in first degree relatives; genetic testing in patients <50 yr old

Disorders of Multiple Endocrine Glands

Multiple Endocrine Neoplasm
• neoplastic syndromes involving multiple endocrine glands
• tumours of neuroectodermal origin
• autosomal dominant inheritance with variable penetrance
• genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit in MEN II
  • early cure and prevention of medullary thyroid cancer

Table 26. MEN Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissues Involved</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN I (chromosome 11)</td>
<td>Pituitary (15-42%) Anterior pituitary adenoma Parathyroid (&gt;95%) Primary hyperparathyroidism from hyperplasia Entero-pancreatic endocrine (30-80%) Pancreatic islet cell tumours Gastrinoma Insulinomas Vasoactive intestinal peptide (VIP)-omas Glucagonoma Carcinoid syndrome</td>
<td>Headache visual field defects, often non-secreting but may secrete GH (acromegaly) and PRL (galactorrhea, erectile dysfunction, decreased libido, amenorrhea) Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcemia Epigastric pain (peptic ulcers and esophagitis) Hypoglycemia Secretory diarrhea Rash, anorexia, anemia, diarrhea glossitis Flushing, diarrhea, bronchospasm</td>
</tr>
<tr>
<td>Wermer’s Syndrome</td>
<td>Thyroid (&gt;90%) Medullary thyroid cancer (MTC) Adrenal medulla (40-50%) Pheochromocytoma (40-50%) Parathyroid (10-20%) 1st parathyroid hyperplasia Skin Cutaneous lichen amyloidosis</td>
<td>Physical signs are variable and often subtle Neck mass or thyroid nodule; non-tender, anterior lymph nodes HTN, palpitations, headache, sweating Symptoms of hypercalcemia Scaly skin rash</td>
</tr>
<tr>
<td>MEN II (chromosome 10)</td>
<td>1. Ilia Sipple’s Syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Table 26. MEN Classification (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissues Involved</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Familial Medullary Thyroid Ca (a variant of IIa)</td>
<td>Thyroid MTC (≥95%)</td>
<td>MTC without other clinical manifestations of MEN IIa or IIb</td>
</tr>
<tr>
<td>3. IIb</td>
<td>Thyroid MTC Adrenal medulla Pheochromocytoma (≥50%) Neurons Mucosal neuroma, intestinal ganglioneuromas (100%) MSK (100%)</td>
<td>MTC: most common component, more aggressive and earlier onset than MEN IIa HTN, palpitations, headache, sweating Chronic constipation; megacolon Marfanoid habitus [no aortic abnormalities]</td>
</tr>
</tbody>
</table>

Investigations

- **MEN I**
  - laboratory
    - may consider genetic screening for MEN-1 mutation in index patients
    - if a mutation is identified, screen family members who are at risk
  - gastrinoma: elevated serum gastrin level (>200 ng/mL) after IV injection of secretin
  - insulinoma: reduced fasting blood glucose (hypoglycemia) with elevated insulin and C-peptide levels
  - glucagonoma: elevated blood glucose and glucagon levels
  - pituitary tumours: assess GH, IGF-1, and prolactin levels (for over-production), TSH, free T4, 8 AM cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)
  - hyperparathyroidism: serum Ca²⁺ and albumin, PTH levels; bone density scan (DEXA)
  - imaging
    - MRI for pituitary tumours, gastrinoma, insulinoma

- **MEN II**
  - laboratory
    - genetic screening for RET mutations in all index patients
    - if a mutation is identified, screen family members who are at risk
  - calcitonin levels (MTC); urine catecholamines and metanephrines (pheochromocytoma); serum Ca²⁺, albumin, and PTH levels (hyperparathyroidism)
  - pentagastrin ± calcium stimulation test if calcitonin level is within reference range
  - FNA for thyroid nodules-cytology
  - imaging
    - CT or MRI of adrenal glands, metaiodobenzylguanidine (MIBG) scan for pheochromocytoma
    - octreoscan and/or radionuclide scanning for determining the extent of metastasis

Treatment

- **MEN I**
  - medical
    - proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - cabergoline or other dopamine agonists to suppress prolactin secretion
    - somatostatin for symptomatic carcinoid tumours
  - surgery for hyperparathyroidism, insulinoma, glucagonoma, pituitary tumours (if medical treatment fails for the latter)
    - trans-sphenoidal approach with prn external radiation

- **MEN II**
  - surgery for MEN IIa with pre-operative medical therapy
    - prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
    - α blocker for at least 10-21 d for pheochromocytoma pre-operatively
    - hydration, calcitonin, IV bisphosphonates for hypercalcemia

**Calcium Homeostasis**

- normal total serum Ca²⁺: 2.2-2.6 mmol/L
- ionic/free Ca²⁺ levels: 1.15-1.31 mmol/L
- serum Ca²⁺ is about 40% protein bound (mostly albumin), 50% ionized, and 10% complexed with PO₄³⁻ and citrate
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D
- actions mainly on three organs: GI tract, bone, and kidney
Table 27. Major Regulators in Calcium Homeostasis

<table>
<thead>
<tr>
<th>Major Regulators</th>
<th>Source</th>
<th>Regulation</th>
<th>Net Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>Parathyroid glands</td>
<td>Stimulated by low serum Ca(^ {2+} ) and high serum PO(_ {4}^{3-} ); inhibited by chronic low serum Mg(_ {2}^{+} ), high serum Ca(^ {2+} ), and calcitriol</td>
<td>↑ Ca(^ {2+} ), ↑ Cacitriol, ↓ PO(_ {4}^{3-} )</td>
</tr>
<tr>
<td>Calcitriol (1,25-(OH)(_ {2} )D(_ {3} ))</td>
<td>Dietary intake</td>
<td>Synthesized from cholesterol: UV on skin makes cholecalciferol (vitD3) liver makes calcidol (25-(OH)D3) kidneys make calcitriol</td>
<td>Renal calcitriol production is stimulated by low serum PO(_ {4}^{3-} ) and PTH; inhibited by high serum PO(_ {4}^{3-} ) and calcitriol in negative feedback</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Thyroid C cells</td>
<td>Stimulated by pentagastrin (GI hormone) and high serum Ca(^ {2+} ); inhibited by low serum Ca(^ {2+} ) (in pharmacologic doses)</td>
<td>↓ Ca(^ {2+} )</td>
</tr>
<tr>
<td>Mg(_ {2}^{+} )</td>
<td>Major intracellular divalent cation</td>
<td>See Magnesium, NP15</td>
<td>Cofactor for PTH secretion</td>
</tr>
<tr>
<td>PO(_ {3}^{3-} )</td>
<td>Intracellular anion found in all tissues</td>
<td>See Phosphate, NP14</td>
<td>↓ Ca(^ {2+} )</td>
</tr>
</tbody>
</table>

Figure 15 Parathyroid hormone (PTH) regulation

**Hypercalcemia**

**Definition**
- total corrected serum Ca\(^ {2+} \) >2.6 mmol/L OR ionized Ca\(^ {2+} \) >1.35 mmol/L.

**Approach to Hypercalcemia**
1. Is the patient hypercalcemic? (correct for albumin – see sidebar)
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low? If phosphate is high/normal is the level of vitamin D metabolites high or low?
Clinical Features
• symptoms depend on the absolute Ca\(^{2+}\) value and the rate of its rise (may be asymptomatic)

Table 28. Symptoms of Hypercalcemia

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>GI</th>
<th>Renal</th>
<th>Rheumatological</th>
<th>MSK</th>
<th>Psychiatric</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN Ankylosing</td>
<td>Constipation</td>
<td>Polyuria</td>
<td>Gout</td>
<td>Weakness</td>
<td>&gt;3 mmol/L (12 mg/dL)</td>
<td>Hypotonia</td>
</tr>
<tr>
<td>Short QT</td>
<td>Anorexia</td>
<td>(Nephrogenic DI)</td>
<td>Pseudoarthrosis</td>
<td>Bone pain</td>
<td>Hyporeflexia</td>
<td>Myopathy</td>
</tr>
<tr>
<td>Deposition of</td>
<td>Nausea</td>
<td>Polydipsia</td>
<td>Chondrocalcinosis</td>
<td>&gt;3 mmol/L (12 mg/dL)</td>
<td>Dysesthesia</td>
<td>Paresis</td>
</tr>
<tr>
<td>Ca(^{2+}) on valves, coronary arteries, myocardial fibres</td>
<td>Vomiting (groans)</td>
<td>Nephrolithiasis (stones)</td>
<td>Renal failure (irreversible)</td>
<td>Cognitive dysfunction</td>
<td>Organic brain syndromes</td>
<td>Psychosis (moans)</td>
</tr>
</tbody>
</table>

** Hypercalcemic crisis usually >4 mmol/L or 16 mg/dL: primary symptoms include oliguria/anuria and mental status changes including somnolence and eventually coma → this is a medical emergency and should be treated immediately!

Treatment
• treatment depends on the Ca\(^{2+}\) level and the symptoms
• treat the underlying cause of the hypercalcemia
• treat acute, symptomatic hypercalcemia aggressively
• mild asymptomatic hypercalcemia; monitor, avoid: thiazide, volume depletion, high Ca\(^{2+}\) diet, lithium, bed rest

**The symptoms and signs of hypercalcemia include:**
"Bones, stones, groans, and psychiatric overtones"

**The most common cause of hypercalcemia in hospital is malignancy-associated hypercalcemia:**
• Usually occurs in the later stages of disease
• Most commonly seen in lung, renal, breast, ovarian, and squamous tumours, as well as lymphoma and multiple myeloma

Mechanisms:
• Secretion of parathyroid hormone-related protein (PThRPe) which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption
• Cytokines in multiple myeloma
• Calcitriol production by lymphoma
• Osteolytic bone metastases direct effect
• Excess PTH in parathyroid cancer
Approach to Hypocalcemia
1. Is the patient hypocalcemic?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?
4. Is the Mg\(^{2+}\) level low?

Approach to Treatment
- correct underlying disorder
- treat concurrent hypomagnesemia
- mild and symptomatic (ionized Ca\(^{2+}\) >0.8 mmol/L)
  - treat by increasing dietary Ca\(^{2+}\) by 1000 mg/d
  - calcitriol 0.25 \(\mu\)g/d (especially in renal failure)
- acute or symptomatic hypocalcemia (ionized Ca\(^{2+}\) <0.7 mmol/L)
  - immediate treatment required
  - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion if necessary
  - goal is to raise Ca\(^{2+}\) to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH secretion
  - if PTH recovery not expected requires long-term therapy with calcitriol and calcium
- do not correct hypocalcemia if asymptomatic and suspected to be transient

**Table 29. Treatment of Acute Hypercalcemia/Hypercalcemic Crisis**

<table>
<thead>
<tr>
<th>Increase Urinary Ca(^{2+}) Excretion</th>
<th>Isotonic saline (4-5 L) over 24 h ± loop diuretic (e.g. furosemide) but only if hypervolemic (urine output &gt;200mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium:</td>
</tr>
<tr>
<td></td>
<td>4 IU/kg IM/SC q12h</td>
</tr>
<tr>
<td></td>
<td>8 IU/kg IM/SC q6h</td>
</tr>
<tr>
<td></td>
<td>Only works for 48 h</td>
</tr>
<tr>
<td></td>
<td>Rapid onset within 4 6 h</td>
</tr>
<tr>
<td>Diminish Bone Resorption</td>
<td>Bisphosphonates (treatment of choice)</td>
</tr>
<tr>
<td></td>
<td>Inhibits osteoclastic bone resorption and promotes renal excretion of calcium</td>
</tr>
<tr>
<td></td>
<td>Acts rapidly but often transient response (decreased by 0.3-0.5 mmol/L beginning within 4-6 h max effect usually in 7 d)</td>
</tr>
<tr>
<td></td>
<td>Combination of calcitonin and steroids may prolong reduction in calcium</td>
</tr>
<tr>
<td></td>
<td>Tachyphylaxis may occur</td>
</tr>
<tr>
<td></td>
<td>Indicated in malignancy-related hypercalcemia (IV pamidronate or zoledronic acid used)</td>
</tr>
<tr>
<td></td>
<td>Mithramycin (rarely used) – effective when patient cannot tolerate large fluid load</td>
</tr>
<tr>
<td></td>
<td>Dangerous – hematotoxic and hepatotoxic</td>
</tr>
<tr>
<td>Decrease GI Ca(^{2+}) Absorption</td>
<td>Corticosteroids in hypervitaminosis D and hematologic malignancies</td>
</tr>
<tr>
<td></td>
<td>Anti-tumour effects → decreased calcitriol production by the activated mononuclear cells in lung and lymph node</td>
</tr>
<tr>
<td></td>
<td>Slow to act (5-10 d); need high dose</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Treatment of last resort</td>
</tr>
<tr>
<td></td>
<td>Indication: severe malignancy-associated hypercalcemia and renal insufficiency or heart failure</td>
</tr>
</tbody>
</table>

**Table 30. Clinical Features of Hypocalcemia**

<table>
<thead>
<tr>
<th>Acute Hypocalcemia</th>
<th>Chronic Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>CNS: lathargy seizures, psychosis, basal ganglia calcification, Parkinson’s, dystonia, hemiballismus, papilledema, pseudotumour cerebi</td>
</tr>
<tr>
<td>Laryngospasm (with stridor)</td>
<td>CVS: prolonged QT interval → Torsades de pointes (ventricular tachycardia)</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>GI: steatorrhea</td>
</tr>
<tr>
<td>Tetany</td>
<td>ENDO: impaired insulin release</td>
</tr>
<tr>
<td>Chvostek’s sign (tap CN VII)</td>
<td>SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition</td>
</tr>
<tr>
<td>Trousseau’s sign (carpal spasm)</td>
<td>OCULAR: cataracts</td>
</tr>
<tr>
<td>ECG changes</td>
<td>MSK: generalized muscle weakness and wasting</td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Sx: emotional instability, anxiety, and depression</td>
<td></td>
</tr>
</tbody>
</table>

**Hypomagnesemia**

**Definition**
- total corrected serum Ca\(^{2+}\) <2.2 mmol/L

**Table 30. Clinical Features of Hypocalcemia**

<table>
<thead>
<tr>
<th>Acute Hypocalcemia</th>
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<tbody>
<tr>
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<tr>
<td>Psychiatric Sx: emotional instability, anxiety, and depression</td>
<td></td>
</tr>
</tbody>
</table>
Metabolic Bone Disease

Osteoporosis

Definition
- a condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture
- bone mineral density (BMD) ≥2.5 standard deviations below the peak bone mass for young adults (i.e. T-score ≤–2.5)
- osteopenia: BMD with T-score between –1.0 and –2.5

ETIOLOGY AND PATHOPHYSIOLOGY

Primary Osteoporosis (95% of osteoporosis in women and 80% in men)
- primary type 1: most common in post-menopausal women, due to decline in estrogen, worsens with age
- primary type 2: occurs after age 75, seen in females and males at 2:1 ratio, possibly due to zinc deficiency

Secondary Osteoporosis
- gastrointestinal diseases
  - gastrectomy
  - malabsorption (e.g. celiac disease)
  - chronic liver disease
- bone marrow disorders
  - multiple myeloma
  - lymphoma
  - leukemia
- endocrinopathies
  - Cushing's syndrome
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - DM
  - hypogonadism
- malignancy
  - secondary to chemotherapy
  - myeloma
- drugs
  - corticosteroid therapy
  - phenytoin
  - chronic hepatic therapy
  - androgen deprivation therapy
  - aromatase inhibitors
- other
  - rheumatologic disorders
  - rheumatoid arthritis
  - SLE
  - ankylosing spondylitis
  - renal disease
  - poor nutrition
  - immobilization
  - COPD (due to disease, tobacco, and glucocorticoid use)

ECHOBOOK
Clinical Features
- commonly asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus, and wrist
  - fragility fractures: fracture with fall from standing height
  - Dowager's hump: collapse fracture of vertebral bodies in mid-dorsal region
  - x-ray: vertebral compression and crush fractures, wedge fractures, "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
- pain, especially backache, associated with fractures

Approach to Osteoporosis
1. assess risk factors for osteoporosis on history and physical
2. decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women ≥65 yr or younger if presence of risk factors
3. initial investigations
   - all patients with osteoporosis: calcium corrected for albumin, CBG, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis, celiac workup, and 24 h urinary Ca²⁺ excretion to rule out additional secondary causes
   - 25-OH-Vitamin D level should only be measured after 3–4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture
4. assess 10-yr fracture risk by combining BMD result and risk factors (only if ≥50 yr)
   1) WHO Fracture Risk Assessment Tool (FRAX)
   2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
   - approach to management guided by 10-yr risk stratification into low, medium, high risk
5. for all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see Table 33)

<table>
<thead>
<tr>
<th>Table 31. Indications for BMD Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Older Adults (age ≥ 50 yr)</strong></td>
</tr>
<tr>
<td>All women and men age ≥ 65 yr</td>
</tr>
<tr>
<td>Menopausal women, and men aged 50–64 yr with clinical risk factors for fracture:</td>
</tr>
<tr>
<td>Prolonged glucocorticoid use</td>
</tr>
<tr>
<td>Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy)</td>
</tr>
<tr>
<td>Parental hip fracture</td>
</tr>
<tr>
<td>Vertebral fracture or osteopenia</td>
</tr>
<tr>
<td>assessed on x-ray</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>High alcohol intake</td>
</tr>
<tr>
<td>Low body weight (&lt; 60 kg) or major weight loss (&gt; 10% of weight at age 25 yr)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, type 1 DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (&lt; 45 yr), Cushing’s disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g., inflammatory bowel disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 32. Osteoporosis Risk Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
</tr>
<tr>
<td>10 yr fracture risk &lt; 10%</td>
</tr>
<tr>
<td><strong>Medium Risk</strong></td>
</tr>
<tr>
<td>10 yr fracture risk 10–20%</td>
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<td></td>
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<tr>
<td>Repeat BMD and reassess risk every 1–3 yr initially</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
</tr>
<tr>
<td>10 yr fracture risk &gt; 20%; OR</td>
</tr>
<tr>
<td>Prior fragility fracture of hip or spine; OR</td>
</tr>
<tr>
<td>More than one fragility fracture</td>
</tr>
</tbody>
</table>
Treatment of Osteoporosis

Table 33. Treatment of Osteoporosis in Women and Men

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Diet: Elemental calcium 1000-1200 mg/d; Vit D 1000 IU/d, Exercise: 3x30 min weight-bearing exercises/wk, Cessation of smoking, Reduce caffeine intake, Stop/avoid osteoporosis-inducing medications</td>
</tr>
<tr>
<td><strong>Drug Therapy</strong></td>
<td>Bisphosphonate: inhibitors of osteoclast binding 1st line in prevention of hip, nonvertebral, and vertebral # (Grade A): alendronate, risedronate, zoledronic acid 2nd line (Grade B): etidronate RANKL Inhibitors Denosumab: 1st line in prevention of hip, nonvertebral, vertebral # (Grade A) Parathyroid Hormone YES fragility #: 18-24 mo duration Calcitonin (2nd line) osteoclast receptor binding YES fragility #: Calcitonin 200 IU nasally OD with Calcitriol 0.25 µg bid</td>
</tr>
<tr>
<td><strong>Treatment Specific to Post-Menopausal Women</strong></td>
<td>SERM (selective estrogen-receptor modulator): agonistic effect on uterus and breast 1st line in prevention of vertebra # (Grade A) +ve: prevents osteoporotic # [Gr de A to B evidence], improves lipid profile, decreased breast cancer risk -ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps HRT: combined estrogen + progestrone (see Gynecology, GY34) 1st line in prevention of hip, nonvertebral, and vertebral # (Grade A) For most women, risks &gt; benefits Combined estrogen/progestin prevents hip, vertebral, total # Increased risks of breast cancer, cardiovascular events, and DVT/PE</td>
</tr>
</tbody>
</table>

**Osteomalacia and Rickets**

- rickets: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue prior to epiphyseal closure (in childhood)
- osteomalacia: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue after epiphyseal closure (in adulthood)

**Etiology and Pathophysiology**

**Vitamin D Deficiency**

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency

**Osteomalacia and Rickets**

- malabsorption: p
gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency

**Factors Necessary for Mineralization**

- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

**Osteoporosis in Women and Men**

- Vitamin D Deficiency
- Etiology and Pathophysiology
- Figure 18. Physical examination test
- Table 33. Treatment of Osteoporosis in Women and Men
- Osteomalacia and Rickets
• defective 25-hydroxylation
  ■ liver disease
  ■ anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)
• loss of vitamin D binding protein
• nephrotic syndrome
• deficient 1-a-25 hydroxylation
• hypoparathyroidism
• renal failure
• pathophysiology: leads to secondary hyperparathyroidism and hypophosphatemia

MINERALIZATION DEFECT
• abnormal matrix
  ■ osteogenesis imperfecta
  ■ fibrogenesis imperfecta
  ■ axial osteomalacia
• enzyme deficiency
  ■ hypophosphatasia (inadequate ALP bioactivity)
• presence of calcification inhibitors
  ■ bisphosphonates, aluminum, high dose fluoride, anticonvulsants

Table 34. Clinical Presentations of Rickets and Osteomalacia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rickets</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal pain and deformities, bow legged</td>
<td>Not as dramatic</td>
<td></td>
</tr>
<tr>
<td>Fracture susceptibility</td>
<td>Diffuse skeletal pain</td>
<td></td>
</tr>
<tr>
<td>Weakness and hypotonia</td>
<td>Bone tenderness</td>
<td></td>
</tr>
<tr>
<td>Disturbed growth</td>
<td>Fractures</td>
<td></td>
</tr>
<tr>
<td>Rickett’s rosy (prominent costochondral junctions)</td>
<td>Gait disturbances (waddling)</td>
<td></td>
</tr>
<tr>
<td>Harrison’s groove (indentation of lower ribs)</td>
<td>Proximal muscle weakness</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Hypotonia</td>
<td></td>
</tr>
</tbody>
</table>

Investigations

Table 35. Laboratory Findings in Osteomalacia and Rickets

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Serum Phosphate</th>
<th>Serum Calcium</th>
<th>Serum ALP</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>Decreased</td>
<td>Decreased to normal</td>
<td>Increased</td>
<td>Decreased calcitriol</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Decreased</td>
<td>Normal</td>
<td>Decreased to normal</td>
<td></td>
</tr>
<tr>
<td>Proximal RTA</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Associated with hyperchloremic metabolic acidosis</td>
</tr>
<tr>
<td>Conditions associated with abnormal matrix formation</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

• radiologic findings
  ■ pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  ■ loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  ■ changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  ■ others: bowing of tibia, coxa profunda deformity
• bone biopsy: usually not necessary but considered the gold standard for diagnosis

Treatment
• definitive treatment depends on the underlying cause
• vitamin D supplementation
• PO₄³⁻ supplements if low serum PO₄³⁻, Ca²⁺ supplements for isolated calcium deficiency
• bicarbonate if chronic metabolic acidosis

Renal Osteodystrophy

• changes to mineral metabolism and bone structure secondary to chronic kidney disease
• represents a mixture of four types of bone disease:
  ■ osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  ■ adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  ■ osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  ■ mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoid
• metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology
• metabolic bone disease secondary to chronic renal failure
• combination of hyperphosphatemia (inhibits 1,25(OH)₂-Vit D synthesis) and loss of renal mass (reduced 1-a-hydroxylase)
Clinical Features
- soft tissue calcifications, necrotic skin lesions if vessels involved
- osteodystrophy, generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations
- serum Ca²⁺-corrected for albumin, PO₄³⁻, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy

Treatment
- prevention
- maintenance of normal serum Ca²⁺ and PO₄³⁻ by restricting PO₄³⁻ intake to 1 g OD
- Ca²⁺ supplements; PO₄³⁻ binding agents (calcium carbonate, aluminum hydroxide)
- vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

Paget’s Disease of Bone

Definition
- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology
- a common disease: 5% of the population, 10% of population >80 yr old
- consider Paget’s disease of bone in older adults with ↑ ALP but normal GGT

Etiology and Pathophysiology
- postulated to be related to a slowly progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis
- primary bone lesions
  - osteogenic sarcoma
  - multiple myeloma
  - fibrous dysplasia
- secondary bone lesions
  - osteitis fibrosa cystica
  - metastases

Clinical Features
- usually asymptomatic (routine x-ray finding or elevated ALP)
- severe bone pain (e.g. pelvis, femur, tibia) is often the presenting complaint
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- skull involvement: headaches, increased hat size, deafness
- increased warmth over involved bones due to increased vascularity
- high output CHF
- hypercalcemia with immobilization
- osteosarcoma

Investigations
- laboratory
  - ↑↑ serum ALP (unless burnt out), Ca²⁺ normal or ↑, PO₄³⁻ normal
  - urinary hydroxyproline ↑ (indicates resorption)
  - imaging
    - confirmation on x-ray required to establish the diagnosis
    - bone scan to evaluate the extent of disease and identify asymptomatic sites
    - skeletal survey: involved bones are denser and expanded with cortical thickening
      - initial lesion may be destructive and radiolucent
      - multiple fissure fractures in long bones

Complications
- local
  - fractures; osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
  - indicated by marked bone pain, new lytic lesions and suddenly increased ALP
- systemic
  - hypercalcemia and nephro lithiasis
  - high output CHF due to increased vascularity

Treatment
- goals: decrease pain, decrease rate of remodelling
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism

<table>
<thead>
<tr>
<th>Bones Most Often Affected in Paget’s Disease (in decreasing order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study: Two identical, randomized, double-blind, actively controlled trials (combined for analysis).</td>
</tr>
<tr>
<td>Patients: 397 men and women who were older than 30 yr of age and had radiologically confirmed Paget’s disease. All but 4 patients had alkaline phosphate levels that were more than twice the upper limit of normal.</td>
</tr>
<tr>
<td>Intervention: One 15-min infusion of 5 mg of zoledronic acid compared with 60 d of oral risedronate (30 mg/d) with follow-up at 6 mo.</td>
</tr>
<tr>
<td>Primary Outcome: Rate of therapeutic response at 6 mo, defined as a normalization of alkaline phosphate levels or a reduction of at least 75% in the total alkaline phosphate excess.</td>
</tr>
<tr>
<td>Results: At 6 mo, 96% of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3% of patients receiving risedronate (127 of 171, p&lt;0.001). Alkaline phosphate levels normalized in 88.6% of patients in the zoledronic acid group and 57.9% of patients in the risedronate group (p&lt;0.001). Zoledronic acid was associated with a shorter median time to a first therapeutic response (84 vs. 89 d, p&lt;0.001). Quality of life increased significantly from baseline at both 3 and 6 mo in the zoledronic acid group and differed significantly from those in the risedronate group at 3 mo. Pain scores improved in both groups. During post trial follow-up (median, 196 d), 21 of 62 patients in the risedronate group had a loss of therapeutic response, as compared with 1 of 113 patients in the zoledronic acid group (p=0.001).</td>
</tr>
<tr>
<td>Conclusions: A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget’s disease than does daily treatment with risedronate.</td>
</tr>
</tbody>
</table>
Male Reproductive Endocrinology

Androgen Regulation

- negative feedback may occur by androgens directly or after conversion to estrogen
- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm)
- LH, FSH, total, bioavailable, and/or free testosterone
- human chorionic gonadotropin (hCG) stimulation test
- semen analysis
- semen volume, sperm concentration, morphology, and motility are the most commonly used parameters
- testicular biopsy
- indicated with normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility

- see Urology, U34
- deficiency in gametogenesis or testosterone production

Etiology

- causes include primary (testicular failure), secondary (hypothalamo-pituitary failure), and idiopathic
- primary hypogonadism is more common than secondary

Diagnosis of Testosterone Deficiency Syndrome (aka adult onset primary hypogonadism)

- requires clinical manifestations of testosterone deficiency (see sidebar) AND documented testosterone levels below local lab ranges
- rule out secondary causes

Table 36. Classification and Features of Hypogonadism

<table>
<thead>
<tr>
<th>Hypogonadotropic Hypogonadism (Primary Hypogonadism)</th>
<th>Hypogonadotropic Hypogonadism (Secondary Hypogonadism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Hypothalamic-pituitary axis failure</td>
</tr>
<tr>
<td>Primary testicular failure</td>
<td>↓ LH + FSH (LH sometimes inappropriately normal)</td>
</tr>
<tr>
<td>↑ LH and FSH, ↑ FSH:LH ratio</td>
<td>↓ testosterone and sperm count</td>
</tr>
<tr>
<td>↓ testosterone and sperm count</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>Congenital</td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
</tr>
<tr>
<td>Chromosomal defects (Klinefelter’s, Noonan)</td>
<td>Kallman’s syndrome</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>D-syndrome of sexual development (DSD)</td>
<td>Abnormal subunit of LH or FSH</td>
</tr>
<tr>
<td>Bilateral anorchia (vanishing testicle syndrome)</td>
<td>Infection</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Tuberculosis, meningitis</td>
</tr>
<tr>
<td>Mutation of FSH or LH receptor gene</td>
<td>Endocrine</td>
</tr>
<tr>
<td>Disorders of androgen synthesis</td>
<td>Adrenal androgen excess</td>
</tr>
<tr>
<td>Germ cell defects</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Sertoli cell only syndrome</td>
<td>Hypo or hyperthyroidity</td>
</tr>
<tr>
<td>Leydig cell aplasia/failure</td>
<td>Hypogonadal-pituitary disease (tumor, hyperprolactinemia, hypopituitarism)</td>
</tr>
<tr>
<td>Infection/Inflammation</td>
<td>Drugs</td>
</tr>
<tr>
<td>Orchitis – TB, lymphoma, mumps, leprosy</td>
<td>Alcohol, marijuana, spironolactone, GnRH agonists, androgen/estrogen/progesterone use, chronic narcotic use</td>
</tr>
<tr>
<td>Physical factors</td>
<td>Chronic illness</td>
</tr>
<tr>
<td>Trauma, heat, irradiation, testicular torsion, varicocele</td>
<td>Cirrhosis, chronic renal failure, AIDS</td>
</tr>
<tr>
<td>Drugs</td>
<td>Sarcomatosis, Langerhan’s cell histiocytosis hemochromatosis</td>
</tr>
<tr>
<td>Marijuana, alcohol, chemotherapy, ketaonazole, gluocorticoid, spironolactone</td>
<td>Critical illness</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Surgery, MI, head trauma</td>
</tr>
<tr>
<td>Testicular size and consistency (soft/firm)</td>
<td>Obesity</td>
</tr>
<tr>
<td>Sperm count</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>LH, FSH, total, and/or bioavailable testosterone</td>
<td></td>
</tr>
<tr>
<td>hCG stimulation (mainly used in pediatrics)</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
</tr>
</tbody>
</table>

E45 Endocrinology

Male Reproductive Endocrinology

Toronto Notes 2018

• treat medically if symptomatic or asymptomatic with ALP >3x normal or planned surgery
  • new evidence indicates treatment may be warranted for all patients without contraindications
  • bisphosphonates, e.g. zoledronic acid 5 mg IV per yr (preferred) OR alendronate 40 mg PO OD x 6 mo OR risedronate 30 mg PO OD x 3 mo
  • calcitonin 50-100 U/d SC if unable to tolerate bisphosphonate
• surgery for fractures, deformity, degenerative changes

Figure 19. Hypothalomo-pituitary-gonadal axis

Two Distinct Features of Primary Hypogonadism

- The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level
- Likely to be associated with gynecomastia

Two Features of Secondary Hypogonadism

- Associated with an equivalent decrease in sperm count and serum testosterone
- Less likely to be associated with gynecomastia
Treatment
- goal: testosterone replacement (improve libido, muscle mass, strength, body hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
- side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy, uncertain effects on cardiac events/mortality in older men
- contraindicated if history of metastatic prostate cancer, breast cancer, severe LUTS associated with BPH, uncontrolled or poorly controlled CHF, PSA > 4, hematocrit > 50%
- testosterone therapy only to treat symptoms of hypogonadism, often results in decreased spermatogenesis by further suppression of hypothalamic-pituitary-gonad axis
  - goal: fertility
  - Treat underlying cause
  - GnRH agonist if hypothalamic dysfunction with intact pituitary, administered SC in pulsatile fashion using an external pump
  - hCG ± recombinant follicular stimulating hormone (rFSH) in cases of either hypothalamic or pituitary lesions
  - Dopamine agonist (eg. bromocriptine, cabergoline) if prolactinoma
  - testicular sperm extraction (TESE) or microscopic sperm extraction (MICROTESE) – only if testicular tissues are not functioning

Other Causes of Male Infertility
- hereditary disorders: Kartagener syndrome (primary ciliary dyskinesia), cystic fibrosis
- anatomy: hypospadias, retrograde ejaculation
- obstruction: vaginal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- surgery: TURP, radical prostatectomy, orchectomy

DEFECTS IN ANDROGEN ACTION

Etiology
- complete androgen insensitivity (CAIS)
- partial androgen insensitivity (PAIS)
- 5-a-reductase deficiency
- mixed gonadal dysgenesis
- defects in testosterone synthesis
- undervirilized fertile male syndrome

Clinical Features
- depends on age of onset

Table 37. Effects of Testosterone Deficiency

<table>
<thead>
<tr>
<th>First Trimester in Utero</th>
<th>Incomplete virilization of external genitalia (ambiguous genitalia)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphroditism)</td>
</tr>
<tr>
<td>Third Trimester in Utero</td>
<td>Micropenis</td>
</tr>
<tr>
<td></td>
<td>Cryptorchidism (failure of normal testicular descent)</td>
</tr>
<tr>
<td>Prepuberty</td>
<td>Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair)</td>
</tr>
<tr>
<td></td>
<td>Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones)</td>
</tr>
<tr>
<td></td>
<td>Poor muscle development, reduced peak bone mass</td>
</tr>
<tr>
<td>Postpuberty</td>
<td>Decrease in energy, mood, and libido</td>
</tr>
<tr>
<td></td>
<td>Fine wrinkles in corners of mouth and eyes</td>
</tr>
<tr>
<td></td>
<td>Decrease in pubic/axillary hair, hematocrit, muscle mass, strength, and BMD</td>
</tr>
</tbody>
</table>

Adapted from: UpToDate, 2010; Cecil’s Essentials of Medicine

Erectile Dysfunction

- see Urology, U30

Approach to Male Infertility

Infertility: failure of a couple to conceive after 12 mo of regular intercourse without use of contraception in women < 35 yr of age; after 6 mo of regular intercourse without use of contraception in women ≥ 35 yr

History
- Partner status re: infertility
- Length of time for attempt to conceive
- Prior successes with other partners
- Ejaculation problems
- Frequency of intercourse
- Prior Surg, Med Hx, STI Hx
- Hx orchitis? Cryptorchidism?
- Hx toxic exposure?
- Medications
- Alcohol and illicit drug use
- Heat exposure: bath, sauna, whirlpool
- Smoking

P/E
- General (height, weight, gynecomastia, masculine)
- Testicular size and consistency
- Varicocele?
- Pituitary disease?
- Thyroid disease?

Investigations
Should be considered for couples unable to conceive after 12 mo of unprotected and frequent intercourse. Consider earlier evaluation if suggestive medical Hx and physical, and in women ≥ 35 yr of age
- Semen analysis x 2 (sperm count, morphology, motility)
- Scrotal/testicular U/S (look for varicocele)
- Blood work: LH, FSH, testosterone, prolactin, thyroid function tests, DNA fragmentation of sperm, karyotype, Y chromosome deletion
- Test female partner (see Gynecology, GY23)

Treatment
- No specific therapy for majority of cases
- Treat specific causes
- Consider: intrauterine insemination, IVF, therapeutic donor insemination, testicular aspiration of sperm, adoption
**Gynecomastia**

**Definition**
- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals

**Etiology**

**Physiologic**
- puberty
- elderly (involutional)
- neonatal (maternal hormone)

**Pathologic**
- endocrinopathies: primary or secondary hypogonadism, hyperthyroidism, extreme hyperprolactinemia, adrenal disease
- tumours: pituitary, adrenal, testicular, breast, ectopic production of hCG
- chronic diseases: cirrhosis, renal, malnutrition (with refeeding)
- drugs: estrogens and estrogen agonists, spironolactone, ketoconazole, cimetidine, digoxin, chemotherapy, marijuana, alcohol
- congenital/genetic: Klinefelter’s syndrome, androgen insensitivity
- other: idiopathic (majority of gynecomastia is classified as idiopathic), familial

**Pathophysiology**
- hormonal imbalance due to increased estrogen activity (increased production, or increased availability of estrogen precursors for peripheral conversion to estrogen) or decreased androgen activity (decreased androgen production, binding of androgen to sex hormone binding globulin SHBG), or androgen receptor blockage

**History**
- recent change in breast characteristics
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction

**Physical Exam**
- signs of feminization
- breast
  - rule out red flags suggesting breast cancer: unilateral, eccentric, hard or fixed mass, skin dimpling or retraction, and nipple discharge or crusting
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue
- genito-urinary exam
- stigmata of liver or thyroid disease

**Investigations**
- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated need to locate the primary tumour)
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
- testicular U/S to rule out testicular mass
- MRI of hypothalamic-pituitary region if pituitary adenoma suspected

**Treatment**
- initial observation for most men with gynecomastia
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen has most evidence for benefit
  - aromatase inhibitors: less evidence of benefit as compared to anti-estrogens
- surgical
  - usually required for macromastia, gynecomastia present for >1 yr (fibrosis is unresponsive to medication), or failed medical treatment and for cosmetic purposes

**Pubertal Gynecomastia**
- This benign condition peaks between 13-14 years of age and spontaneously regresses in 90% of cases within 2yr
- Waiting is often the best approach

**Causes of Gynecomastia**
- Drugs
- Other
- Congenital
- Tumour
- Endocrine
- Chronic disease

**Occurrence of Gynecomastia**

<table>
<thead>
<tr>
<th>Peak</th>
<th>% Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy</td>
<td>60-90</td>
</tr>
<tr>
<td>Puberty</td>
<td>4-69</td>
</tr>
<tr>
<td>Ages 50-80</td>
<td>24-65</td>
</tr>
</tbody>
</table>
Female Reproductive Endocrinology

• see Gynecology, GY23

Paraneoplastic Syndrome

• clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
• triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
• commonly present with cancers of lung, breast, ovaries, or lymphatic system

Table 38. Clinical Presentation

<table>
<thead>
<tr>
<th>Syndrome Class</th>
<th>Symptom/Syndrome</th>
<th>Associated Malignancies</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Cushing’s syndrome</td>
<td>Small-cell lung cancer</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td>Pancreatic carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neural tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thymoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SIADH</td>
<td>Small-cell lung cancer, CNS malignancies</td>
<td>Antidiuretic hormone secretion</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>Lung cancer, Breast carcinoma, Renal cell carcinoma, Multiple myeloma, Ovarian carcinoma</td>
<td>PTH-related protein, TGF-α, TNF secretion</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>Hepatocellular carcinoma, Fibrosarcoma</td>
<td>Insulin or insulin-like substance secretion</td>
</tr>
<tr>
<td></td>
<td>Carcinoid</td>
<td>Pancreatic carcinoma, Gastric carcinoma</td>
<td>Serotonin, bradykinin secretion</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Lambert-Eaton myasthenic syndrome (LEMS), Muscle weakness in limbs</td>
<td>Small-cell lung cancer</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis, Fluctuating muscle weakness and fatigability</td>
<td>Thymoma</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic limbic encephalitis, Depression, seizures, short-term memory loss</td>
<td>Small-cell lung cancer</td>
<td>Unknown</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypokalemic nephropathy</td>
<td>Small-cell lung cancer</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td>Lymphoma, Melanomas</td>
<td>Immune complex sedimentation in nephrons</td>
</tr>
<tr>
<td>GI</td>
<td>Watery diarrhea</td>
<td>Medullary thyroid carcinomas</td>
<td>Prostaglandin secretion</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Erythrocytosis</td>
<td>Renal cell carcinoma, Hepatocellular carcinoma</td>
<td>EPO production</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>SLE, Antinuclear Ab production</td>
<td>Lymphomas, Lung cancer, Breast carcinoma, Gonadal carcinoma</td>
<td>Anti-nuclear Ab production</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
<td>Breast carcinoma, Lung cancer, Uterine cancer</td>
<td>Anti-nuclear Ab production</td>
</tr>
</tbody>
</table>

Investigations

- CBC, electrolytes, creatinine, LFTs, ALP, ESR, CRP, serum/urine electrophoresis
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, PET scan
- ± endoscopy

Treatment

- treat underlying tumour: surgery, radiation, chemotherapy
- treat immune-mediated disorder: IV Ig, steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)
# Diabetes Medications

| Drug Class          | Mechanism of Action                                                                 | Generic Drug Name     | Canada Name | US Name (if different) | Dosing                                      | Indications                                                                                     | Contraindications                                                                 | Side Effects                                                                                                                                                  | Comments        |
|---------------------|-------------------------------------------------------------------------------------|-----------------------|-------------|------------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Biguanide           | Sensitizes peripheral tissues to insulin → increases glucose uptake Decreases hepatic glucose production by stimulation of hepatic AMP-activated protein kinase (AMPK) | metformin             | Glucophage® | Glumetza®              | 500 mg OD titrated to 2000 mg/d maximum     | Useful in obese type 2 DM Improves both fasting and postprandial hyperglycemia Also ↓ TG           | ABSOLUTE: Moderate to severe liver dysfunction Moderate renal dysfunction GFR <30 mL/min Cardiac dysfunction | Gl upset (abdo discomfort, bloating, diaphoresis) Lactic acidosis Anorexia | ↓ HbA1c 1.0-1.5% |
| Insulin Secretogogue| Stimulates insulin release from β cells by causing K⁺ channel closure → depolarization → Ca²⁺ mediated insulin release Use in nonobese type 2 DM | sulfonylureas: glyburide | Diabeta®    | ExuGlicon®             | 2.5-5.0 mg/d titrated to >5 mg bd Max: 20 mg/d | Short t½ of 1 h: causes brief but rapid ↑ in insulin, therefore eff clove for post-prandial control | ABSOLUTE: Moderate to severe liver dysfunction RELATIVE (glyburide and gliclazide): Adjust dose in mild to moderate kidney dysfunction and avoid in severe kidney dysfunction Avoid glyburide in the elderly | Hypoglycemia Weight gain | ↓ HbA1c 0.8%     |
|                     |                                       | gliclazide            | Diametron®  | Glymase PreTab®        | 40-160 mg bd 30-120 mg OD                   |                                                                                               | INTERACTIONS: Do not combine with a non-sulfonylurea insulin secretagogue or preprandial insulin                                                      |                                                                              |                  |
|                     |                                       | glimepiride           | Amaryl®     |                        | 1-8 mg OD                                   |                                                                                               |                                                                              |                                                                              |                  |
| Insulin Sensitizers (thiazolidinedione) | Sensitizes peripheral tissues to insulin → increases glucose uptake Decreases FFA release from adipose Binds to nuclear receptor PPAR-γ | rosiglitazone         | Avandia®     |                        | 2-8 mg OD                                   | Rosiglitazone – indicated only in patients with type 2 DM for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance | ABSOLUTE: NYHA > class II CHF INTERACTIONS: Do not combine with a non-sulfonylurea or preprandial insulin | Peripheral edema CHF Anemia Fluid retention and CHF Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing) Increased risk of bladder cancer with pioglitazone Fractures | ↓ HbA1c 0.8%     |
|                     |                                       | pioglitazone          | Actos®      |                        | 15-45 mg OD                                 |                                                                                               |                                                                              |                                                                              |                  |
| Glucosidase Inhibitor | Decrease GI absorption by inhibiting brush border α-glucosidase | acarbose              | Glucobay®   |                        | 25 mg OD titrated to 100 mg tid            | ↓ postprandial hyperglycemia                                                                      | ABSOLUTE: Inflammatory bowel disease Severe liver dysfunction                  | Flatulence Abdominal cramps Diarrhea                                              | ↓ HbA1c 0.8%     |
| Dipeptidyl Peptidase IV (DPP-IV) Inhibitor | Inhibits degradation of endogenous antihyperglycemic incretin hormones Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emptying | sitagliptin           | Januvia®     |                        | 100 mg OD                                   |                                                                                               | ABSOLUTE: (sitagliptin): Type 1 DM DKA RELATIVE (sitagliptin and saxagliptin): Use with dose reduction in kidney dysfunction | Nasopharyngitis URTI Headache Pancytopenia Stevens-Johnson syndrome              | ↓ HbA1c 0.7%     |
## Diabetes Medications (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon-Like Peptide (GLP-1) Analogue</td>
<td>Binds to GLP-1 receptor to promote insulin release Insulinotropic effect suppressed as plasma glucose &lt; 4 mmol/L Slows gastric emptying, suppresses inappropriately elevated glucagon levels Causes β-cell regeneration and differentiation <em>in vitro</em></td>
<td>Exenatide</td>
<td>Ryetco®</td>
<td></td>
<td>5-10 µg SC bid 1 h before meals</td>
<td></td>
<td>1.0%</td>
<td>+ HbA1c 1.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liraglutide</td>
<td>Victara®</td>
<td></td>
<td>0.6-1.8 mg QD SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium–glucose linked transport 2 (SGLT2) Inhibitor</td>
<td>Enhances urinary glucose excretion by inhibiting glucose reabsorption in the proximal renal tubule</td>
<td>Canagliflozin</td>
<td>Innokana®</td>
<td></td>
<td>100 mg QD before first meal of the day</td>
<td></td>
<td></td>
<td>+ HbA1c 0.7-1.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapagliflozin</td>
<td>Fonsiga®</td>
<td></td>
<td>5 mg QD in the morning with or without food</td>
<td></td>
<td>+ HbA1c 0.7-1.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Empagliflozin</td>
<td>Jardiance®</td>
<td></td>
<td>10 mg QD in the morning with or without food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For insulin formulations see Table 9, E9

## Dyslipidemia Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA Reductase Inhibitor (statins)</td>
<td>Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↓ HDL, limited ↓ VLDL</td>
<td>Atorvastatin</td>
<td>Lipitor®</td>
<td></td>
<td>10-80 mg/d</td>
<td>1st line monotherapy</td>
<td>Active liver disease</td>
<td>GI symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluvastatin</td>
<td>Lescol®</td>
<td></td>
<td>20-80 mg/d</td>
<td>Used for ↑ LDL, ↑ TG</td>
<td>Persistent ↑ in AST, ALT unexplained</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lovastatin</td>
<td>Mevacor®</td>
<td></td>
<td>20-80 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pravastatin</td>
<td>Crestor®</td>
<td></td>
<td>10-40 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simvastatin</td>
<td>Zocor®</td>
<td></td>
<td>10-80 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bezafibrate</td>
<td>Bezalip®</td>
<td></td>
<td></td>
<td>400 mg/d</td>
<td>Used for ↑ TG, hypercholesterolemia</td>
<td>Hepatic disease</td>
<td>GI upset</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemfibrozil</td>
<td>Lipidil®</td>
<td></td>
<td>480-2000 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemfibrozil</td>
<td>Lopid®</td>
<td></td>
<td>600-1200 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>Upregulates lipoprotein lipase + apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↓ HDL</td>
<td>Bezafibrate</td>
<td>Bezalip®</td>
<td></td>
<td>400 mg/d</td>
<td>Used for ↑ TG, hypercholesterolemia</td>
<td>Hepatic disease</td>
<td>GI upset</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fenofibrate</td>
<td>Lipidil®</td>
<td></td>
<td>480-2000 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemfibrozil</td>
<td>Lopid®</td>
<td></td>
<td>600-1200 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL, and LDL; increased clearance of HDL</td>
<td>Nicotinic acid</td>
<td>Aspar®</td>
<td></td>
<td>0.5-2 g/d</td>
<td>Used for ↑ LDL, ↑ VLDL</td>
<td>Hypersensitivity</td>
<td>Generalized flushing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Generic niacin</td>
<td>Niacor®</td>
<td></td>
<td>1.5 g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>Resists that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL</td>
<td>Colestipol</td>
<td>Colestid®</td>
<td></td>
<td>5-30 g/d</td>
<td>Used for ↑ LDL, Use as adjunct with statins or fibrates</td>
<td>Complete biliary obstruction</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholestyramine</td>
<td>Questran®</td>
<td></td>
<td>2-24 g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol Absorption Inhibitors</td>
<td>Inhibits cholesterol absorption at the small intestine brush border</td>
<td>Ezetimibe</td>
<td>Zetia®</td>
<td></td>
<td>10 mg/d</td>
<td>Used for ↑ LDL, apo B</td>
<td>Hypersensitivity</td>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

For insulin formulations see Table 9, E9
## Thyroid Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid Agent (thionamides)</td>
<td>Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T&lt;sub&gt;4&lt;/sub&gt; and T&lt;sub&gt;3&lt;/sub&gt;. PTU also interferes with conversion of T&lt;sub&gt;4&lt;/sub&gt; to T&lt;sub&gt;3&lt;/sub&gt;.</td>
<td>propylthiouracil (PTU)</td>
<td>PropylThiouracil&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Start 100 mg PO tid, then adjust accordingly. Thyroid storm: start 200-300 PO qid, then adjust accordingly.</td>
<td>Hyperthyroidism</td>
<td>Hypersensitivity Relative: renal failure, liver disease. PTU recommended in 1st trimester, MMI during 2nd and 3rd trimester. Lactation: safe with PTU &lt; 300 mg/day and MMI &lt; 20-30 mg/d.</td>
<td>Cholestatic with MMI.</td>
</tr>
<tr>
<td></td>
<td>methimazole (MMI)</td>
<td>Tapazole&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Start 5-20 mg PO OD, then adjust accordingly. Up to 80 mg OD may be required.</td>
<td></td>
<td></td>
<td>N/V</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid Hormone</td>
<td>Synthetic form of thyroxine (T&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>levothyroxine</td>
<td>Synthroid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Eltroxin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.05-2.0 mg/d, usually 1.6x weight (kg) is dose in micrograms. In elderly patients start at 0.025 mg/d.</td>
<td>Hyperthyroidism</td>
<td>Recent MI, thyrotoxicosis. If wrong dosing: symptoms of hyperthyroidism or hypothyroidism. Skin rash from dye in pill.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithyroid Agent Radioisotopes</td>
<td>Radioactive isotope of iodine that is incorporated into the thyroid gland and irradiating the area and destroying local glandular tissue.</td>
<td>sodium iodide I-131</td>
<td>Iodotope&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Dose corrected for 24 h radioactive iodine uptake. Hyperthyroidism: 4-12 mCi. Thyroid Ca: 50-150 mCi.</td>
<td>Hyperthyroidism</td>
<td>Hypersensitivity. Concurrent antithyroid medication.</td>
<td>N/V</td>
</tr>
</tbody>
</table>

## Metabolic Bone Disease Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>risedronate</td>
<td>Actonel&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Osteoporosis: 5 mg OD, 35 mg once weekly. Pagets: 150 mg once monthly. Pagets: 30 mg OD for 2 mo.</td>
<td>Treatment and prevention of postmenopausal osteoporosis. Treatment and prevention of glucocorticoid-induced osteoporosis. Paget’s disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>etidronate</td>
<td>Didronel&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Pagets: 5-10 mg, 1 g OD x 6 mo.</td>
<td>Symptomatic Paget’s disease. Prevention and treatment of heterotopic ossification after total hip replacement or spinal cord injury.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ibandronate</td>
<td>Boniva&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>2.5 mg OD or 150 mg once monthly.</td>
<td>Treatment and prevention of postmenopausal osteoporosis (US only).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pamidronate</td>
<td>Aredia&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Hypercalcemia of malignancy. 60-90 mg IV over 2-24 h. Wait at least 7 d before considering retreatment.</td>
<td>Hypercalcemia of malignancy. Paget’s disease. Osteolytic bone metastases of breast cancer. Osteolytic lesions of multiple myeloma.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>zoledronate</td>
<td>Zometa&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Aclasta&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 mg IV once yearly IV.</td>
<td>Treatment of osteoporosis. Hypercalcemia of malignancy. Treatment and prevention of skeletal complications related to cancer.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Metabolic Bone Disease Medications (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective Estrogen Receptor Modulators</td>
<td>Decreases resorption of bone through binding to estrogen receptors</td>
<td>raloxifene</td>
<td>Evista®</td>
<td>60 mg OD</td>
<td>Treatment and prevention of postmenopausal osteoporosis (second line)</td>
<td>Lactation, Pregnancy, Active or past history of DVT, PE, or retinal vein thrombosis</td>
<td>Hot flashes, Leg cramps, Increased risk of fatal stroke, venous thromboembolism</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Inhibits osteoclast-mediated bone resorption</td>
<td>calcitonin</td>
<td>Micalcin®</td>
<td>One spray (200 IU) per d, alternating nostrils</td>
<td>Treatment of postmenopausal osteoporosis, greater than 5 yr postmenopause</td>
<td>Clinical allergy to salmon-calcitonin</td>
<td>Rhinitis, Epistaxis, Sinusitis, Nasal dryness</td>
</tr>
<tr>
<td>Anti-RANKL Monoclonal Ab</td>
<td>Inhibits RANKL (osteoclast differentiating factor) → inhibits osteoclast formation and decreases bone resorption</td>
<td>denosumab</td>
<td>Prolia®</td>
<td>60 mg SC q6m</td>
<td>Treatment of postmenopausal women at high risk of fracture</td>
<td>Hypocalcemia</td>
<td>Fatigue, headache, Dermatitis, rash, Hypophosphatemia/Hypocalcemia, Hypercholesterolemia, GI discomfort</td>
</tr>
<tr>
<td>PTH</td>
<td>Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclasts activity</td>
<td>teriparatide</td>
<td>Forteo®</td>
<td>20 µg SC OD x 16-24 mo</td>
<td>Treatment of postmenopausal women with osteoporosis who are at high risk for fracture</td>
<td>Paget’s disease, Prior external beam or implant radiation therapy involving the skeleton, Bone metastases, Metabolic bone diseases other than osteoporosis</td>
<td>Orthostatic hypotension, Hypercalcemia, Dizziness, Leg cramps</td>
</tr>
<tr>
<td>Calcium</td>
<td>Inhibits PTH secretion</td>
<td></td>
<td></td>
<td>1200 mg/d (including diet) Divided in 3 doses</td>
<td>Osteopenia, Osteoporosis, Prevention of metabolic bone disease</td>
<td>Caution with renal stones</td>
<td>Vomiting, Constipation, Dry mouth</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Regulation of calcium and phosphate homeostasis</td>
<td>cholecalciferol (vitamin D3)</td>
<td></td>
<td>800 - 2000 IU/d</td>
<td>Osteopenia, Osteoporosis, Prevention of metabolic bone disease</td>
<td>Cautio in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia)</td>
<td>Hypercalcemia, Headache, N/V, Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ergocalciferol (vitamin D2)</td>
<td>Drisdol®</td>
<td>50,000 IU/wk</td>
<td>Osteopenia in patients with liver dysfunction, refractory rickets, hypoparathyroidism</td>
<td>Hyperparathyroidism</td>
<td>Maldosorption syndrome, Decreased renal function, Hypercalcemia, Vitamin D toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>calcitriol (1,25(OH)2-D)</td>
<td>Recaltr®</td>
<td>Start 0.25 µg/d Titrate up by 0.25 µg/d at 4-8 wk intervals to 0.5-1 µg/d</td>
<td>Osteopenia and osteodystrophy in patients with chronic renal failure on dialysis</td>
<td>Hypocalcemia and osteodystrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calcijex®</td>
<td>Start 0.25 µg/d Titrate up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Adrenal Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mineralocorticoid Activity</th>
<th>Generic Drug Name</th>
<th>Potency Relative to Cortisol</th>
<th>Equivalent Dose (mg)</th>
<th>Duration of Action (h in h)</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>Cortef Solu-Cortef</td>
<td>1.0</td>
<td>20</td>
<td>8</td>
<td>Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q6h (continuous infusion x 24-48 h) PO once stable (50 mg q6h x 48 h, then taper over 14 d) Chronic Ad: 15-20 mg PO OD (2-3 AM, 1/2 PM)</td>
<td>In high doses, mineralocorticoid side effects may emerge (salt + water retention ECF volume expansion, HTN, low K+, metabolic alkalosis)</td>
</tr>
<tr>
<td>Cortisone Acetate</td>
<td>Yes</td>
<td>Cortisone Acetate</td>
<td>0.8</td>
<td>25</td>
<td>oral = 8 IM = 16</td>
<td>Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24h Chronic Ad: 25 mg/d</td>
<td>Pro-drug which is converted to active form as hydrocortisone. High doses can result in mineralocorticoid side effects (see above)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>No</td>
<td>Prednisone</td>
<td>4</td>
<td>5</td>
<td>16-06</td>
<td>Adrenal Crisis: 15-60 mg/d PO qid or divided bid/qid Chronic Ad: 5 mg daily</td>
<td>Pro-drug which is converted to active form as prednisolone</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>No</td>
<td>Dexamethasone</td>
<td>30</td>
<td>0.7</td>
<td>30-54</td>
<td>Adrenal Crisis: 4 mg IV; repeat q2-4h if necessary</td>
<td>Used for undiagnosed adrenal insufficiency (does not interfere with measurement of serum cortisol levels)</td>
</tr>
</tbody>
</table>
## Landmark Endocrinology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIABETES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>NEJM 2008;358:2560-72</td>
<td>Compared with standard therapy the use of intensive therapy to target normal HbA1c levels (&lt;6%) for 3.5 yr increased mortality and did not significantly reduce major cardiovascular events</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>NEJM 2008;358:2545-59</td>
<td>Intensive glucose control that lowered the HbA1c value to 6.5% reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events, or death from any cause; hypoglycemia was more common in the intensive control group</td>
</tr>
<tr>
<td>BARI-2D</td>
<td>NEJM 2009;360:2503-15</td>
<td>In patients with both type 2 DM and CAD no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin</td>
</tr>
<tr>
<td>DCCT</td>
<td>NEJM 1993;329:977-86</td>
<td>Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy, and neuropathy) in type 1 DM</td>
</tr>
<tr>
<td>EDIC</td>
<td>NEJM 2005;353:2644-53</td>
<td>Compared with conventional therapy intensive DM therapy early on without macrovascular disease (goal HbA1c &lt;6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with type 1 DM</td>
</tr>
<tr>
<td>Look AHEAD</td>
<td>NEJM 2013;369:145-54</td>
<td>Moderate weight loss (&lt;7% BW) and increased exercise are not associated with reduction in CVD and its complications among overweight or obese patients with type 2 DM</td>
</tr>
<tr>
<td>NAVIGATOR</td>
<td>NEJM 2010;362:1463-90</td>
<td>In patients with impaired glucose tolerance, nateglinide did not reduce progression to DM or risk of cardiovascular events while valsartan only reduced progression to DM</td>
</tr>
<tr>
<td>PREDIMED</td>
<td>NEJM 2013;368:1279-90</td>
<td>A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, CVA, or CV death in those at high risk for CV disease (outcome was driven by reduction in rates of CVA)</td>
</tr>
<tr>
<td>Steno-2</td>
<td>NEJM 2008;356:580-91</td>
<td>In at-risk patients with type 2 DM intensive intervention with multiple drug combinations and behaviour modification had sustained significant beneficial effects with respect to vascular complications and mortality; multifactorial intervention is critical in the management of type 2 DM</td>
</tr>
<tr>
<td>UKPDS</td>
<td>NEJM 2008;359:1577-89</td>
<td>Continued risk reduction in microvascular risk and emergent risk reductions for MI and death from any cause 10 yr post UKPDS trial follow-up in type 2 DM</td>
</tr>
<tr>
<td>VADT</td>
<td>NEJM 2009;360:1-11</td>
<td>In patients with longstanding poorly controlled type 2 DM intensive glucose control had no significant effect on the rates of major cardiovascular events, death, or microvascular complications; adverse events, predominantly hypoglycemia, were more common in the intensive control group</td>
</tr>
<tr>
<td><strong>LIPIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>Lancet 1994;344:1383-89</td>
<td>In patients with angina or previous MI and high total cholesterol simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty</td>
</tr>
<tr>
<td>FIELD</td>
<td>Lancet 2005;356:1849-61</td>
<td>In patients with type 2 DM not previously on statin therapy fenofibrate did not significantly reduce the risk of the primary outcome of coronary events; it did reduce non-fatal MI and revascularizations</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002;360:7-22</td>
<td>In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths, and major vascular events</td>
</tr>
<tr>
<td>Jupiter</td>
<td>NEJM 2008;359:2195</td>
<td>Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity CRP levels and no hyperlipidemia</td>
</tr>
<tr>
<td>TNT</td>
<td>NEJM 2005;352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d</td>
</tr>
</tbody>
</table>
### Four Principles of Family Medicine

- Health Promotion and Counselling
- Prostate Cancer Screening
- Cervical Cancer Screening
- Colorectal Cancer Screening Guidelines
- Lung Cancer Screening Guidelines
- Breast Cancer Screening Guidelines
- Classification of Recommendations (GRADE, 2011)

### Health Promotion and Counselling

- Motivational Strategies for Behavioural Change
- Nutrition
- Obesity
- Dyslipidemia
- Exercise
- Smoking Cessation
- Alcohol

### Common Presenting Problems

- Abdominal Pain
- Allergic Rhinitis
- Amenorrhea
- Anxiety
- Asthma/COPD
- Benign Prostatic Hyperplasia
- Bronchitis (Acute)
- Chest Pain
- Common Cold (Acute Rhinitis)
- Concussion/Mild Traumatic Brain Injury
- Contraception
- Cough
- Dementia (Major Neurocognitive Disorder)
- Depression
- Diabetes Mellitus
- Dizziness
- Domestic Violence/Elder Abuse
- Dyspepsia
- Dyspnea
- Dysuria
- Epistaxis
- Erectile Dysfunction
- Fatigue
- Fever
- Headache
- Hearing Impairment
- Hypertension
- Joint Pain
- Low Back Pain
- Menopause/Hormone Replacement Therapy
- Osteoarthritis
- Osteoporosis
- Palliative and End-of-Life Care
- Rash
- Sexually Transmitted Infections
- Sinusitis
- Sleep Disorders
- Sore Throat (Pharyngitis)

### Acronyms

- Periodic Health Examination
- Common Problems
- Acute Rhinitis
- Bronchitis
- Prostate Hyperplasia
- Acute Pain
- Anxiety
- Amenorrhea
- Asthma/COPD
- Benign Hyperplasia
- Bronchitis
- Chest Pain
- Common Cold
- Concussion
- Mild Traumatic Brain Injury
- Contraception
- Cough
- Dementia
- Major Neurocognitive Disorder
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- Diabetes Mellitus
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- Elder Abuse
- Dyspepsia
- Dyspnea
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- Erectile Dysfunction
- Fatigue
- Fever
- Headache
- Hearing Impairment
- Hypertension
- Joint Pain
- Low Back Pain
- Menopause
- Hormone Replacement Therapy
- Osteoarthritis
- Osteoporosis
- Palliative and End-of-Life Care
- Rash
- Sexually Transmitted Infections
- Sinusitis
- Sleep Disorders
- Sore Throat

### References
Acronyms

AAA: abdominal aortic aneurysm
ACR: albumin creatinine ratio
AIN: anal intraepithelial neoplasia
AMC: another medical condition
AHI: acute kidney injury
ARB: anagertinsin receptor blockers
BMI: body mass index
BPPV: benign paroxysmal positional vertigo
DRE: double rectal exam
DMPA: depot medroxyprogesterone acid
DHP: dihydropyridine
CRC: colorectal cancer
CHF: congestive heart failure
CF: cystic fibrosis
CCB: complete blood count
CCO: calcium channel blockers
DHEP: Canadian Hypertension Education Program
CHS: creatine kinase
CT: cognitive-behavioural therapy
CHO: congestive heart failure
CPAP: continuous positive airway pressure
CRC: colorectal cancer
CVD: cardiovascular disease
DHP: dihydropyridine
DM/PA: depot medroxyprogesterone
DRE: digital rectal exam
DS: double strength
ED: emergency department
ER: extended release
FRS: Framingham Risk Score
GAB: gastrectomy
GERD: gastroesophageal reflex disease
HC: high-grade squamous intraepithelial lesion
HPV: human papillomavirus
HRT: hormone replacement therapy
ICD: in-hospital death
IGT: impaired glucose tolerance
IU: insulin units
IVP: intravenous pyelogram
KUB: kidneys, ureter, bladder x-ray
LDL-C: low-density lipoprotein cholesterol
LSL: low-grade squamous intraepithelial lesion
LVH: left ventricle hypertrophy
MDI: metered dose inhaler
MAGI: monoamine oxidase inhibitor
MMSE: mini mental status examination
MOCA: Montreal cognitive assessment
MSM: men who have sex with men
MUA: monounsaturated fatty acids
NPH: neutralizing tube defects
NTD: nitroglycerin
OA: ogee and parasites
OCP: oral contraceptive pill
OPD: obsessive-compulsive personality disorder
PHE: periodic health examination
PSA: prostate-specific antigen
PTSD: post-traumatic stress disorder
PUD: peptic ulcer disease
PFA: polymersaturated fatty acids
PVD: peripheral vascular disease
RA: rheumatoid arthritis
RCT: randomized controlled trial
SAH: subarachnoid hemorrhage
SRI: serotonin dopamine reuptake inhibitor
SIDS: sudden infant death syndrome
SLE: systemic lupus erythematosus
SNRI: serotonin norepinephrine reuptake inhibitor
SOB: shortness of breath
SSRI: selective serotonin reuptake inhibitor
TC: total cholesterol
TCA: tricyclic antidepressant
TIA: transient ischaemic attack
TCA: total cholesterol
TCA: tricyclic antidepressant
TIC: triglyceride
TM: tympanic membrane
TMJ: temporomandibular joint
TPU: transurethral incision of the prostate
UC: urogenital colitis
UTI: urinary tract infection
VAIN: vaginal intraepithelial neoplasia
VBI: vulvar intraepithelial neoplasia
WSIB: Workplace Safety and Insurance Board

Four Principles of Family Medicine

College of Family Physicians of Canada Guidelines

1. The family physician is a skilled clinician
   - diagnoses and manages diseases common to the population served
   - recognizes importance of early diagnosis of serious life threatening illnesses

2. Family medicine is a community-based discipline
   - provides information and access to community services
   - responds/adapts to changing needs and circumstances of the community

3. The family physician is a resource to a defined practice population
   - serves as a health resource
   - advocates for public policy to promote health

4. The patient-physician relationship is central to the role of the family physician
   - commits to the person, not just the disease
   - promotes continuity of patient care

Periodic Health Examination

- Canadian Task Force on Preventive Health Care established in 1976, first published in 1979
- mandate: to develop and disseminate clinical practice guidelines for primary and preventive care
- recommendations are based on systematic analysis of scientific evidence
- most notable recommendation is the abolition of the annual physical exam; replaced by the PHE

Purpose of the Periodic Health Examination

- primary prevention: identify risk factors for common diseases; counsel patients to promote healthy behavior
- secondary prevention: presymptomatic detection of disease to allow early treatment and to prevent disease progression
- update clinical data
- enhance patient-physician relationship

Classification of Recommendations (GRADE, 2011)

Strength of Recommendation
- strong: high level of confidence that desirable effects outweigh undesirable effects (strong recommendation for an intervention) or that the undesirable effects outweigh desirable effects (strong recommendation against an intervention)
- implies that most individuals will be best served by the recommended course of action
• weak: desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention); uncertainty exists
• implies that most people would want the recommended course of action but that many would not
• different choices will be appropriate for different individuals, patients require support in reaching a management decision consistent with his/her values and preferences

Quality of Evidence
• high: high level of confidence that true effect lies close to the estimate of the effect
• moderate: true effect likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
• low or very low: true effect may be substantially different from the estimate of the effect

Table 1. Periodic Health Exam

<table>
<thead>
<tr>
<th>Table 1. Periodic Health Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Population</strong></td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
</tr>
<tr>
<td>Dental hygiene (community fluoridation, brushing, flossing) (A)</td>
</tr>
<tr>
<td>Noise control and hearing protection (A)</td>
</tr>
<tr>
<td>Screen for poverty</td>
</tr>
<tr>
<td>Smokers: counsel on smoking cessation, provide: Niacin replacement therapy (A)</td>
</tr>
<tr>
<td>Referral to smoking cessation program (B)</td>
</tr>
<tr>
<td>Dietary advice on leafy green vegetables and fruits (B)</td>
</tr>
<tr>
<td>Seat belt use (B)</td>
</tr>
<tr>
<td>Injury prevention (bicycle helmets, smoke detectors) (B)</td>
</tr>
<tr>
<td>Moderate physical activity (B)</td>
</tr>
<tr>
<td>Avoid sun exposure and wear protective clothing (B)</td>
</tr>
<tr>
<td>Problem drinking screening and counselling (B)</td>
</tr>
<tr>
<td>Counselling to protect against STIs (B)</td>
</tr>
<tr>
<td>Nutritional counselling and dietary advice on fat and cholesterol (B)</td>
</tr>
<tr>
<td>Dietary advice in calcium and vitamin D requirements (B)</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
</tr>
<tr>
<td>Blood pressure measurement, using techniques described in CHEP guidelines (strong recommendation; moderate quality evidence)</td>
</tr>
<tr>
<td>BMI measurement in obese adults (B)</td>
</tr>
<tr>
<td><strong>Tests</strong></td>
</tr>
<tr>
<td>See recommendations below for age and gender specific screening for diabetes, dyslipidemia, hypertension and cancer screening (colon, prostate, cervical, lung, and breast)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
</tr>
<tr>
<td>Folic acid supplementation to women of child-bearing age (A)</td>
</tr>
<tr>
<td>Pharmacologic treatment of HTN (Refer to CHEP Guidelines) (A)</td>
</tr>
<tr>
<td>Varicella vaccine for children age 1-12 and susceptible adolescents/adults (A)</td>
</tr>
<tr>
<td>Rubella vaccine for all non-pregnant women of child-bearing age unless there is proof of immunity via immunization records or serology (B)</td>
</tr>
<tr>
<td>Pertussis vaccine: adults ≥85 should receive one booster given as Tdap-Adacel® or Boostrix® (A)</td>
</tr>
<tr>
<td>Hepatitis A vaccine for adults ≥20</td>
</tr>
</tbody>
</table>

**Choosing Wisely Canada**
http://www.choosingwiselycanada.org/
A campaign to help clinicians and patients engage in conversations about unnecessary tests and treatments and make smart and effective choices to ensure high quality care

**Folic Acid Supplementation in Pregnancy**
(Joint SOGC-Motherisk Clinical Guideline)

- To prevent neural tube defects in all women capable of becoming pregnant
- Low risk women (no personal health risks, planned pregnancy): 0.4-1.0 mg daily folic acid supplementation for at least 2-3 months before conception and throughout pregnancy and postpartum period
- High risk women (health risks including epilepsy, insulin dependent diabetes, BMI >35, family history of NTD, high risk ethnic group): at least 3 mo prior to conception until 10-12 wk post conception: daily supplementation with multivitamins with 5 mg folic acid
- From wk 12 post-conception until postpartum period (4-6 wks or as long as breastfeeding continues): 0.4-1.0 mg of folic acid supplementation is sufficient
- Women with additional lifestyle issues (poor compliance with medications, no consistent birth control, taking possible teratogenic substances): higher folic acid dose of 5 mg and counselling about prevention of birth defects

**Breast Cancer Screening Guidelines**

2011 Canadian Task Force on Preventive Health Care

- average risk women: women age 40-74 with no personal history of breast cancer, history of breast cancer in 1st degree relatives, known mutations of the BRCA1/BRCA2 genes or previous exposures of the chest wall to radiation

Classification of recommendation in brackets. See sidebar on FM2 for classification details. See www.canadiantaskforce.ca – for up-to-date guidelines

Reference: Canadian Task Force on Preventive Health Care, 2014

Family Medicine FM3

Periodic Health Examination

Toronto Notes 2018
Mammography
- age 40-49: routine screening with mammography not recommended (weak recommendation - moderate quality evidence)
- age 50-74: routine screening q2-3yr (age 50-69: weak recommendation; moderate quality evidence, age 70-74: weak recommendation; low quality evidence)
- age 75+: screen if benefits outweigh harm, must take overall health into account

Magnetic Resonance Imaging
- no routine screening with MRI scans (weak recommendation - low quality evidence)

Clinical Breast Examination
- no routine CBE alone or in conjunction with mammography to screen for breast cancer (weak recommendation - low quality evidence)

Breast Self-Examination
- recommend not advising women to routinely practice breast self-examination
- for more information on benign breast lesions and breast cancer, see General Surgery, GS55

Lung Cancer Screening Guidelines
2016 Canadian Task Force on Preventative Health Care
- apply to adults aged 18 and older who are not suspected of having lung cancer
- annual screening with low dose CT for adults aged 55-74 with at least a 30 pack-year smoking history who currently smoke or quit less than 15 years ago, up to three consecutive times

Colorectal Cancer Screening Guidelines
- recommendations for average risk individuals (asymptomatic, no family history of UC, polyps, or CRC)
- average risk testing should begin at age 50, but assessment for risk factors should begin earlier to identify high-risk individuals
  - Canadian Task Force on Preventative Health Care (2016)
    - FOBT (either high sensitivity FOBT or FIT - fecal immunochemical testing) q2yr OR flexible sigmoidoscopy q10yr
    - no colonoscopy as a screening test
    - no screening after age 75 is recommended for average risk patients, but it may be assessed on an individual basis for ages 76-85
- for more information on colorectal neoplasms, see General Surgery, GS33

Figure 1. Approach to higher risk screening
AAPC = attenuated adenomatous polyposis; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; 1st degree relatives: parents, siblings, children, 2nd degree relatives: grandparents, aunts, uncles; 3rd degree relatives: great grandparents or cousins. Figure printed with permission from Can J Gastroenterol 2004;18:93-99. Also see: Colorectal Screening for Cancer Prevention in Asymptomatic Patients, March 2013. Available from http://www.bcguidelines.ca/pdf/colorectal_screening.pdf
Cervical Cancer Screening

- either conventional Papanicolaou (Pap) smear or liquid based cytology testing
  - endocervical and exocervical cell sampling (aim is to sample the transitional zone)
  - best identifies squamous cell abnormalities, less reliable for glandular abnormalities
    - false positives 5-10%, false negatives 10-40% (for single test)
    - false negative rate 50% for existing cervical cancer
- cervical cancer screening guidelines differ by provincial jurisdiction (see The Society of Obstetricians and Gynaecologists of Canada guidelines)

2013 Canadian Task Force for Preventative Care Guidelines

- screen all women age ≥ 25 q3yr (age 25-29: weak recommendation; moderate quality evidence, age 30-69: strong recommendation; high quality evidence)
- women age ≥ 70: if 3 normal tests in a row and no abnormal tests in last 10 yr, can discontinue screening (weak recommendation; low quality evidence)

Ontario guidelines

- screen all women age ≥ 21 who are or have ever been sexually active (includes intercourse or digital/oral activity with partner of either sex)
  - if cytology is normal, can screen every 3 yr
- women age ≥ 70: if 3 successive negative Pap tests in last 10 yr, can discontinue screening
- women who are not sexually active by age 21 should delay cervical cancer screening until sexually active

Pregnant women and women who have sex should follow the routine cervical screening regimen

- women who have had a hysterectomy
  - total: discontinue screening if hysterectomy was for benign disease and no history of cervical dysplasia or HPV infection, continue to swab vaginal vault if history of uterine malignancy/dysplasia
  - subtotal: continue screening according to guidelines

Exceptions to guidelines

- immunocompromised (transplant, steroids, diethylstilbestrol exposure, HIV)
- previously unscreened patients

For more information on cervical cancer (see Gynecology, GY44)

Figure 2. Decision making chart for cervical cancer screening not applicable to adolescents

AGUS = atypical glandular cells of unknown significance; ASCUS = abnormal squamous cells of unknown significance; ASC-H = abnormal squamous cells cannot rule out HSIL; HSIL = high-grade squamous intraepithelial lesion; LSL = low-grade squamous intraepithelial lesion; TZ = transitional zone

Adapted from: Ontario Cervical Screening Cytology Guidelines, May 2012

Prostate Cancer Screening

2014 Canadian Task Force for Preventative Care Guidelines

- screening for prostate cancer with the prostate specific antigen (PSA) test is not recommended for any age group (age < 55: strong recommendation; low quality evidence, age 55-69: weak recommendation; moderate quality evidence, age > 70: strong recommendation; low quality evidence)
Health Promotion and Counselling

- health promotion is the most effective preventive strategy
- there are several effective ways to promote healthy behavioural change, such as discussions appropriate to a patient's present stage of change
- for more information about motivational interviewing, see www.motivationalinterviewing.org

Motivational Strategies for Behavioural Change

<table>
<thead>
<tr>
<th>Patient’s Stage of Change</th>
<th>Physician’s Aim</th>
<th>Physician’s Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Contemplation</td>
<td>Encourage patient to consider the possibility of change</td>
<td>Raise issue in a sensitive manner</td>
</tr>
<tr>
<td></td>
<td>Assess readiness for change</td>
<td>Offer (not impose) a neutral exchange of information to avoid resistance</td>
</tr>
<tr>
<td></td>
<td>Increase patient’s awareness of the problem and its risks</td>
<td></td>
</tr>
<tr>
<td>Contemplation</td>
<td>Understand patient’s ambivalence and encourage change</td>
<td>Offer opportunity to discuss pros and cons of change using reflective listening</td>
</tr>
<tr>
<td></td>
<td>Build confidence and gain commitment to change</td>
<td></td>
</tr>
<tr>
<td>Preparation</td>
<td>Identify high-risk situations and develop strategies to prevent relapse</td>
<td>Offer realistic options for change and opportunity to discuss inevitable difficulties</td>
</tr>
<tr>
<td></td>
<td>Continue to strengthen confidence and commitment</td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>Help patients design rewards for success</td>
<td>Offer positive reinforcement and explore ways of coping with obstacles</td>
</tr>
<tr>
<td></td>
<td>Develop strategies to prevent relapse</td>
<td>Encourage self-rewards to positively reinforce change</td>
</tr>
<tr>
<td></td>
<td>Support and reinforce convictions towards long-term change</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>Help patient maintain motivation</td>
<td>Discuss progress and signs of impending relapse</td>
</tr>
<tr>
<td></td>
<td>Review identified high-risk situations and strategies for preventing relapse</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Help patient view relapse as a learning experience</td>
<td>Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future</td>
</tr>
<tr>
<td></td>
<td>Provide support appropriate to present level of readiness post-relapse</td>
<td>Reassess patient’s readiness to change</td>
</tr>
</tbody>
</table>


Nutrition

General Population

- Canada’s Food Guide is appropriate for individuals age ≥2
- counsel on variety, portion size, and plate layout

Table 3. Canada’s Food Guide 2011 Recommendations for Children >2 and Adults (# of servings/d)

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Children</th>
<th>Teens</th>
<th>Adults</th>
<th>Choose More From</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>2</td>
<td>3</td>
<td>4-8</td>
<td>9-13</td>
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<tr>
<td>14-18</td>
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<td>19-20</td>
<td>19-20</td>
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<tr>
<td>51+</td>
<td>51+</td>
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<tr>
<td>Grain Products</td>
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<td>4</td>
<td>6</td>
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<td>3-4</td>
<td>3-4</td>
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</tr>
<tr>
<td>Whole grain and enriched grain products</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables and Fruit</td>
<td>4</td>
<td>5</td>
<td>6</td>
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<tr>
<td>4-5</td>
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<td>F:7</td>
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<td>M:8</td>
<td>M:8</td>
<td>M:8</td>
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<td>M:8</td>
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<tr>
<td>Dark green vegetables, orange vegetables and fruit</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Milk and Alternatives</td>
<td>2</td>
<td>2</td>
<td>3-4</td>
<td>3-4</td>
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<td>2-3</td>
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<td>F:3</td>
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<td>M:4</td>
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<tr>
<td>Lower-fat dairy products</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat and Alternatives</td>
<td>1</td>
<td>1</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>1-2</td>
<td>1-2</td>
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<td>1-2</td>
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<tr>
<td>F:2</td>
<td>F:2</td>
<td>F:2</td>
<td>F:2</td>
<td>F:2</td>
</tr>
<tr>
<td>M:3</td>
<td>M:3</td>
<td>M:3</td>
<td>M:3</td>
<td>M:3</td>
</tr>
<tr>
<td>Lean meat, poultry, fish, peas, beans, lentils</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Motivational Strategies for Behavioural Change

Handy Serving Size Comparisons

- 3 oz meat, fish, poultry → palm of hand
- 1 cup dairy (milk/yogurt) → size of fist
- Bread/grains → one slice, palm of hand
- ½ cup rice/pasta → one hand cupped
- 1 cup of fruit/vegetables → two cupped hands
- 1 tsp oil/butter → tip of thumb
- Nuts/chips/snacks → palm covered

Energy Content of Food

- Carbohydrates 4 kcal/g
- Protein 4 kcal/g
- Fat 9 kcal/g
- Ethanol 7 kcal/g

Calculating Total Daily Energy Expenditure (TDEE)

- Roughly 35 kcal/kg/d
- Varies by age, weight, sex, and activity level
- Average 2000-2100 kcal/d for women, 2700-2900 kcal/d for men

Canadian Cancer Society (CCS) Recommendations for Vitamin D Use

- Based on CCS research on Vitamin D and the prevention of colorectal, breast and prostate cancer
- In consultation with their healthcare provider, the Society recommends that:
  - Adults living in Canada should consider taking Vitamin D supplementation of 1,000 international units (IU) a day during the fall and winter
  - Adults at higher risk of having lower Vitamin D levels should consider taking Vitamin D supplementation of 1,000 IU/d all year round. This includes people: who are older, with dark skin, who do not go outside often, and who wear clothing that covers most of their skin
  - Babies who are exclusively breast-fed: 400 IU/d
Cardiovascular Disease Prevention

Table 4. Dietary Guidelines for Reducing Risk of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat, Carbohydrates, Protein</td>
<td>Overall fat intake: 28-27% of total energy Saturated fat: 5-6% of total energy Trans fat: reduce intake, replace with MUFA or PUFA Carbohydrates: 55-55% of total energy Protein: 15-18% of total energy</td>
</tr>
<tr>
<td>Omega-3 Fatty Acid Rich Foods</td>
<td>≥2 servings/wk of fish (especially oily fish like salmon)</td>
</tr>
<tr>
<td>Salt</td>
<td>≤2,400 mg/d</td>
</tr>
<tr>
<td>Alcohol</td>
<td>≤3 drinks/d for men, max 15/wk ≤2 drink/d for women, max 10/wk</td>
</tr>
<tr>
<td>Dietary Approaches</td>
<td>DASH diet (Dietary Approaches to Stop Hypertension), recommended by the American Heart Association (AHA) Diet: high in vegetables/fruits, low-fat dairy, whole grains, poultry, fish, and nuts; Low in sweets, sugar-sweetened beverages, red meats Macronutrients: low in saturated total fat and cholesterol; high in potassium, magnesium, calcium, protein and fibre Mediterranean diet (fruits, vegetables, whole grains, legumes, nuts, olive oil, and herbs)</td>
</tr>
</tbody>
</table>

MUFAs = monounsaturated fatty acids; PUFAs = polyunsaturated fatty acids

Table 5. Classification of Weight by BMI, Waist Circumference, and Associated Disease Risks in Adults

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
<th>Men ≤102 cm (40 in)</th>
<th>Men &gt;102 cm (40 in)</th>
<th>Women ≤88 cm (35 in)</th>
<th>Women &gt;88 cm (35 in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity Class I</td>
<td>30.0-34.9</td>
<td>High</td>
<td>Very High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity Class II</td>
<td>35.0-39.9</td>
<td>Very High</td>
<td>Very High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity Class III (Extreme Obesity)</td>
<td>40.0 +</td>
<td>Extremely High</td>
<td>Extremely High</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Obesity

- see Canadian Task force on Preventive Health Care recommendations (CMAJ February 2015) at: canadiantaskforce.ca/cptphc-guidelines/2015/obesity-adults/
- body mass index (BMI) = weight (kg)/height (m)² = weight (lbs)/height (in)² x 703; BMI is a poor predictor of obesity
- waist circumference (WC) = flexible tape placed on horizontal plane at iliac crest, normal depends on ethnic background
- increased WC for BMI 25-35 increases the risk of cardiovascular disease and type 2 diabetes

Epidemiology

- 25.1% of Canadian adults over 18 (excluding pregnant females) were obese in 2008 and 36.8% were overweight (StatsCan, 2008)
- obesity rate in people of Aboriginal origin was 1.6 times higher than the national average
- proportion of children aged 6-11 who are overweight has more than doubled in the last 25 yr
- percentage of overweight adolescents has tripled
- overweight and obesity rates in children are directly proportional to screen time (see Exercise, FM10)
- only 10-15% of population consume <30% fat daily
- obese persons generally consume more energy-dense food which tends to be highly processed, micronutrient poor, and high in fats, sugars, or starch

Osteoporosis Canada Recommendations for Calcium and Vitamin D Daily Requirements

- Vitamin D: 800-1,000 IU for individuals age <50 yr, 800-2,000 IU for individuals ≥50 yr
- Calcium: 1,000 mg daily from all sources for individuals 19-50 yr and pregnant/lactating women; 1,200 mg daily for individuals >50 yr (recommended to obtain calcium from nutrition whenever possible vs. supplementation)

Effectiveness of Behavioral and Pharmacological Treatment for Overweight and Obesity in Adults

- Purpose: To evaluate the effectiveness of behavioral and pharmacological treatments for overweight and obese adults
- Methods: Review of RCTs of primary-care-relevant behavioral (diet, exercise, lifestyle) and pharmacological (phentermine, methyfentanyl) treatments with or without behavioral interventions in overweight or obese adults with 12 month follow-up from baseline for weight outcomes or harms. Secondary health outcomes (total cholesterol, LDL, fasting blood glucose, incidence of type 2 DM, systolic and diastolic BP) were also studied.
- Results: 50 RCTs were included, and showed that intervention participants had greater weight loss (3.02 kg, 95% CI 2.52-2.52), waist circumference reduction (2.78, 3.34 to 2.22) and body mass index reduction (-1.11, -1.39 to -0.84). Relative risk for weight loss of 5% or greater body weight was 1.77 (1.59 to 1.90), NNT 5, 95% CI (4-7). Incidence of type 2 DM was lower among pre-diabetic intervention participants.
- Conclusion: Behavioral and pharmacological treatments for overweight and obese adults may lead to clinically important reductions in weight and type 2 DM incidence in pre-diabetics.

Eating Disorders

- Anorexia Nervosa
- Bulimia Nervosa
- Binge Eating Disorder

Low BMI Associations

- Osteoporosis
- Gastrointestinal disturbances
- Pain
- Reproductive health

Adverse Medical Consequences of Obesity

- Type 2 DM
- Heart disease
- Stroke
- Sleep apnea
- Gastrointestinal disturbances
- Infections
- Heart failure
- Sleep apnea
- Reproductive health
- Pain
- Mental health
- Cognitive function
- Psychiatric disorders
- Physical activity
- Social function
- Employment status
- Economic productivity
- Quality of life

Obesity and Cardiovascular Disease

- Increased risk of heart disease, stroke, and diabetes
- Increased risk of hypertension, hypercholesterolemia, and hypertriglyceridemia
- Increased risk of cardiovascular disease and type 2 diabetes

Losing Weight

- Aim for caloric intake 500-1000 kcal/d less than total daily energy expenditure (TDEE)
- 3500 kcal energy expended of fat burned, results in 1-2 lb (0.5-1 kg) weight loss per week
- Achieved by combination of increased activity and/ or decreased caloric intake

Low BMI Associations

- Osteoporosis
- Gastrointestinal disturbances
- Pain
- Reproductive health

Pregnancy complications

- Pre-eclampsia
- Gestational diabetes
- Premature labor
- Low birth weight
- Perinatal mortality
- Postpartum depression
- Maternal mortality

Obesity and Pregnancy

- Increased risk of gestational diabetes
- Increased risk of pre-eclampsia
- Increased risk of cesarean delivery
- Increased risk of stillbirth
- Increased risk of infant mortality
- Increased risk of maternal mortality

Pregnancy and Weight

- Maternal weight gain
- Fetal weight gain
- Neonatal weight gain
- Maternal and fetal morbidity
- Maternal and fetal mortality

Hypertension

- Increased risk of hypertension
- Increased risk of stroke
- Increased risk of heart disease
- Increased risk of cardiovascular disease

Sleep Apnea

- Increased risk of sleep apnea
- Increased risk of cardiovascular disease
- Increased risk of stroke
- Increased risk of diabetes

Cancer Risk

- Increased risk of certain types of cancer
- Increased risk of breast cancer
- Increased risk of colon cancer
- Increased risk of prostate cancer
- Increased risk of endometrial cancer

Dyslipidemia

- Increased risk of dyslipidemia
- Increased risk of high cholesterol
- Increased risk of high triglycerides
- Increased risk of low HDL cholesterol

High Blood Pressure

- Increased risk of high blood pressure
- Increased risk of heart disease
- Increased risk of stroke
- Increased risk of kidney disease

Insulin Resistance

- Increased risk of insulin resistance
- Increased risk of type 2 diabetes
- Increased risk of gestational diabetes
- Increased risk of pre-eclampsia

Diabetes Mellitus

- Increased risk of type 2 diabetes
- Increased risk of gestational diabetes
- Increased risk of pre-eclampsia
- Increased risk of stillbirth
- Increased risk of infant mortality
- Increased risk of maternal mortality

Obstructive Sleep Apnea

- Increased risk of obstructive sleep apnea
- Increased risk of cardiovascular disease
- Increased risk of stroke
- Increased risk of diabetes

Osteoarthritis

- Increased risk of osteoarthritis
- Increased risk of knee osteoarthritis
- Increased risk of hip osteoarthritis
- Increased risk of shoulder osteoarthritis

Celiac Disease

- Increased risk of celiac disease
- Increased risk of gluten-sensitive enteropathy
- Increased risk of malabsorption syndrome

Reproductive Health

- Increased risk of infertility
- Increased risk of miscarriage
- Increased risk of preterm birth
- Increased risk of low birth weight
- Increased risk of stillbirth
- Increased risk of neonatal mortality

Cognitive Function

- Decreased cognitive function
- Decreased memory
- Decreased attention
- Decreased executive function

Dementia

- Increased risk of dementia
- Increased risk of Alzheimer’s disease
- Increased risk of vascular dementia
- Increased risk of mild cognitive impairment

Depression

- Increased risk of depression
- Increased risk of anxiety
- Increased risk of suicide
- Increased risk of postpartum depression

Anxiety

- Increased risk of anxiety
- Increased risk of panic disorder
- Increased risk of generalized anxiety disorder
- Increased risk of social anxiety disorder

Mental Health

- Increased risk of mental health problems
- Increased risk of mood disorders
- Increased risk of anxiety disorders
- Increased risk of substance use disorders

Social Function

- Decreased social function
- Decreased social interaction
- Decreased social support
- Decreased quality of life

Employment Status

- Decreased employment status
- Decreased job satisfaction
- Decreased income
- Decreased productivity

Economic Productivity

- Decreased economic productivity
- Decreased work productivity
- Decreased productivity at work
- Decreased income

Quality of Life

- Decreased quality of life
- Decreased physical health
- Decreased mental health
- Decreased overall health
Screening Recommendations
- the CANRISK or FINRISC scores can be used to assess the risk for type 2 DM in overweight and obese patients
- BMI risk assessment should be done every 3-5 yr in people at high risk of developing diabetes within 10 yr

Management

Behavioural/Lifestyle
- weight loss of >5% is clinically significant for reducing many cardiovascular risk factors (e.g., elevated blood pressure, glucose and lipids)
- efficacious behavioural interventions are greater than 12 months duration, include diet and/or exercise and/or lifestyle components, and include group and individual sessions
- structured behavioural and lifestyle interventions should be offered or arranged for overweight individuals BMI >25
- strong recommendation for those with increased risk of Type 2 DM
- BMI >35 and risk factors or BMI >40 are candidates for bariatric surgery failing behavioural modification

Pharmacologic
- the task force recommends against pharmacologic intervention to manage patients who are overweight and obese, although some patients may prefer medications and be good candidates for pharmacologic treatment
- high benefit of behavioural modification alone, NNH (number needed to harm) 10 (mostly GI side effects) for pharmacotherapy

Assess and screen for depression, eating and mood disorders
- Treat comorbidities and other health risks, if present
- Assess readiness to change behaviours and barriers to weight loss

Satisfactory progress or goal achieved?

Yes
- Regular monitoring
  - Assist with weight maintenance
  - Reinforce healthy eating and physical activity advice

No
- Weight maintenance and prevention of weight regain
  - Nutrition therapy
  - Physical activity
  - Cognitive behavioural therapy
  - Address other risk factors: periodic monitoring of weight, BMI and waist circumference q1-2yr
- Pharmacotherapy
  - BMI ≥27 kg/m² + risk factors or BMI ≥30 kg/m²
  - Adjust to lifestyle modifications: consider if patient has not lost 0.5-1 kg (1-2 lb) per wk vb 3-6 mo after lifestyle changes

No
- Bariatric surgery
  - BMI ≥35 kg/m² + risk factors or BMI ≥40 kg/m²
  - Consider if other weight loss attempts have failed. Requires lifelong medical monitoring

IMPORTANT MESSAGE
A modest weight loss of 5-10% of body weight is beneficial. Weight maintenance and prevention of weight regain should be considered as long-term goals

Figure 4. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children

Adapted from: CMAJ 2007;176:S1-S13

Pharmacotherapy for Obesity
- Orlistat: gastrointestinal lipase inhibitor, reduces fat absorption by 30% by inhibition of pancreatic lipase
- Orlistat is associated with several adverse effects and not approved for clinical use longer than 2 yr
- Orlistat should be avoided in people with inflammatory or chronic bowel disease

Hypertension Signs

Atheroma: plaques in blood vessel walls
- Xanthelasma: a sharply demarcated yellowish deposit of cholesterol underneath the skin, usually on or around the eyelid
- Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
- Eruptive xanthoma: hypertriglyceridemia induced reddish yellow, pruritic, and painful popular or nodular rash
- Lipemia retinalis: thin atheroma seen in the retinal blood vessels
- Corneal arcus (arcus senilis): lipid deposit in cornea

Hyperlipidemia Signs

Atheroma: plaques in blood vessel walls
- Xanthoma: a sharply demarcated yellowish deposit of cholesterol underneath the skin, usually on or around the eyelid
- Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
- Eruptive xanthoma: hypertriglyceridemia induced reddish yellow, pruritic, and painful popular or nodular rash
- Lipemia retinalis: thin atheroma seen in the retinal blood vessels
- Corneal arcus (arcus senilis): lipid deposit in cornea

Toronto Notes 2018
**Dyslipidemia**

- see Endocrinology F2

- defined as abnormal elevation of plasma cholesterol or triglyceride levels

### Assessment

**RISK ASSESSMENT, STRATIFICATION AND TREATMENT CONSIDERATION**

Calculate risk (unless statin-indicated condition) using the Framingham Risk Score (FRS) or Cardiovascular Life Expectancy Model (CLEM)

Repeat screening every 5 years for FRS <5% or every year for FRS ≥5%

**Low Risk**

- FRS <10%

**Intermediate Risk**

- FRS 10-19%
- LDL-C ≥3.5 mmol/L or Non-HDL-C ≥4.3 mmol/L or alternative method

**High Risk**

- FRS ≥20%
- LDL-C ≥5 mmol/L
- genetic dyslipidemia

**Clinical atherosclerosis**

- Abdominal aortic aneurysm
- Most diabetes including: Age ≤40yr
- Age ≥60yr and 25 yr duration (type 1 DM)
- Microvascular disease
- Chronic kidney disease

**Discuss Behavioural Modifications**

1. Smoking cessation
2. Diet: adopt a health dietary pattern
3. Exercise: for adults 150 min/wk of moderate-vigorous aerobic activity

Discuss add-on therapy with patient (evaluate reduction in CVD risk vs. additional cost & side effects)

**Monitor Response to statin Rx**

- 1st line: Ezetimibe (BAS as alternative)
- 2nd line: PCSK9 inhibitors (add-on to other drugs)

1. Target achieved on maximally tolerated dose?

   - YES
   - NO

   **ADD-ON**

- LDL-C <2.0 mmol/L or >50% reduction or apoB <0.8 g/L or non-HDL-C <2/6 mmol/L
- LDL-C >50% reduction

To calculate Framingham Risk Score, go to http://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#

### Risk Factors for Screening for Dyslipidemia

- First Nations or South Asian ancestry
- Current cigarette smoking
- Diabetes
- Arterial Hypertension
- Family history of premature CVD
- Family history of hyperlipidemia
- Erectile dysfunction
- Chronic kidney disease
- Inflammatory disease (lupus, rheumatoid arthritis, psoriatic arthritis, IBD)
- HIV infection
- Chronic obstructive pulmonary disease
- Clinical evidence of atherosclerosis or abdominal aneurysm
- Clinical manifestation of hyperlipidemia
- Obesity (BMI ⇒ 27)

### Non-fasting Lipids vs. Fasting Lipids

Non-fasting (TC and non-HDL cholesterol) can be used for Framingham Risk Assessment and hold same prognostic value as fasting lipids. In fasted vs. non-fasted samples, Non-HDL and TC varies by 2%, LDL-C by 10% and TG by 20%

Recently, non-fasting LDL-C has the same prognostic value as fasting LDL-C. Ontario Association of Medical Laboratories Guidelines for Lipid Testing in Adults (2013): http://www.oaml.com/documents/4kref/Adultlipidtest- ingFinal2013_000.pdf

**Safety of Statins: An Update**

Therapeutic Advances in Drug Safety 2012;3:133-144

Trials have shown that statin therapy slightly increases the incidence of diabetes; however, the absolute risk is small. Relative to the reduction in coronary events, the clinical significance is not great enough to recommend against their use.

Use with caution when prescribing combined statin and fibrate therapy as there has been concern regarding the safety of certain combinations (potential increased risk of myopathy and rhabdomyolysis).

### Figure 5. Target lipid values for primary prevention of CAD (2012 Canadian Cholesterol Guidelines)


- measure fasting serum TC, LDL-C, HDL-C, and TG
- screen with full fasting lipid profile q1-3yr in males >40 yr and females >50 yr or who are menopausal, or at any age for adults with additional dyslipidemia risk factors (see sidebar)
- screen for secondary causes: hypothyroidism, chronic kidney disease, DM, nephrotic syndrome, liver disease
- risk category
  - estimate using the model for 10 yr CAD risk developed from the Framingham data (Framingham Risk Score – FRS)
  - FRS calculated based on the following factors: gender, age, HDL-C, total cholesterol, sBP, smoking, DM
  - family history of CVD <55 male relative or <65 in female relative doubles FRS
  - to be completed for men age 40-75, and women age 50-75 q3-5yr
  - cardiovascular age calculated as patient’s age ± the difference between his or her estimated remaining life expectancy
  - used to increase adherence to therapy and reaffirm positive effect of following therapy
  - treatment decisions focus on LDL-C level and/or FRS risk; the alternate primary targets are apolipoprotein B (apo B) and non-HDL-C (not used widely yet)
  - if moderate risk and LDL-C <3.5, treatment decision thresholds shifted to apo B >1.2 g/L or non-HDL-C >4.3 mmol/L
  - other targets include: TCHDL-C ratio, apo B/apo A1 ratio, hs-CRP (used more for risk stratification of CAD), non-HDL-C, and serum TG levels
Management

- intensity and type of treatment is guided by “risk category” assigned (see Figure 5)
- 1. health behaviours (can decrease LDL-C by up to 10%)
  - smoking cessation: probably the most important for preventing CAD
  - dietary modification: reduce saturated fat, red meat, refined sugar, alcohol; consume nuts, fruits/vegetables, poultry, fish
  - physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per wk
  - employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high risk patients should start treatment immediately with concurrent health behaviour interventions
- for a comparison of dyslipidemia medications, see Endocrinology, E50
- 1st line monotherapy: statins (HMG-CoA reductase inhibitors)
  - risks: myopathy and hepatotoxicity
  - if severe side effects: ezetimibe (cholesterol absorption inhibitor) can be used for 19% reduction in LDL-C
  - post-acute coronary syndrome, cholesterol absorption inhibitors (e.g. ezetimibe) in addition to simvastatin reduced mortality, attained lipid targets <1.8, and improved outcomes in high risk individuals
  - lower evidence for other agents: bile acid sequestrants nicotinic acid, fibrates, psyllium
  - monitoring
    - ALT, CK, creatinine at baseline then 6 wk later for signs of transaminitis or myosit; tolerate rise in CK up to 10 times upper limit of normal vs 2-3 times if symptomatic, or serum creatinine rise of ≤25%
    - no routine repeated measures of ALT and CK necessary in asymptomatic patients using statin therapy
    - if adequate response is achieved, evaluate fasting lipids q6-12mo

Isolated Hypertriglyceridemia

- does not increase cardiovascular risk
- normal HDL-C and TC, elevated TG
- mild ≥2.2 mmol/L (≥200 mg/dL); marked ≥5.6 mmol/L (≥100 mg/dL)
- principal therapy is lifestyle modification
  - weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in diabetics, increased omega-3 fatty acid intake
  - severe hypertriglyceridemia (typically >10 mmol/L) is associated with an increased risk of acute pancreatitis
- drug therapy (used to prevent pancreatitis, NOT cardiovascular disease!)
  - nicotinic acid
  - fibrates

Exercise

Table 6. Canadian Physical Activity and Sedentary Behaviour Guidelines (2012 CSEP Guidelines)

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Physical Activity Guidelines</th>
<th>Example Activities</th>
<th>Sedentary Behaviour Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (&lt;1)</td>
<td>Active several times daily</td>
<td>Interactive floor-based play including tummy time, reaching for toys, crawling</td>
<td>Minimize time spent sedentary, including sitting and being restrained (stroller, etc.). Screen time not recommended for infants &lt;1 yr; limit to &lt;1 h/d ages 2-4</td>
</tr>
<tr>
<td>Toddler (1-2)</td>
<td>Accumulate 180 min of physical activity at any intensity spread throughout the day</td>
<td>Moving around the home (Climbing stairs, Exploring environment) Bink walking, running, dancing</td>
<td>Minimize time spent sedentary, including sitting and being restrained (stroller, etc.). Screen time limit to &lt;1 h/d</td>
</tr>
<tr>
<td>Preschool (2-4)</td>
<td>Same as Toddler above</td>
<td>Same as Toddler above</td>
<td>Same as Toddler above</td>
</tr>
<tr>
<td>Children (5-11)</td>
<td>Accumulate 60 min of moderate to vigorous intensity physical activity daily</td>
<td>Moderate: bike riding, playground Vigorous: running, swimming</td>
<td>Limit sedentary time to 2 h/d</td>
</tr>
<tr>
<td>Youth (12-17)</td>
<td>Same as Children above</td>
<td>Same as Children above</td>
<td>Same as Children Above</td>
</tr>
<tr>
<td>Adults (18-64)</td>
<td>Accumulate 150 min of moderate to vigorous intensity aerobic physical activity per wk, in bouts of 10 min or more. It is beneficial to add muscle and bone strengthening activities using major muscle groups, at least 2 d/wk</td>
<td>Moderate: brisk walking, bike riding Vigorous: jogging, cross country skiing</td>
<td>No specific guidelines</td>
</tr>
<tr>
<td>Older Adults (≥65)</td>
<td>Same as Adults above</td>
<td>Same as Adults above Those with poor mobility should perform physical activities to enhance balance and prevent falls</td>
<td>No specific guidelines</td>
</tr>
</tbody>
</table>
Epidemiology
- 25% of the population exercises regularly, 50% occasionally, 25% are sedentary

Management
- assess current level of fitness, motivation, and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, DM (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, type 2 DM, osteoporosis, and overweight/obesity
  - leads to improved fitness, strength, and mental health (morale and self-esteem)

Smoking Cessation

Epidemiology
- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2012 Canadian data from the Canadian Tobacco Use Monitoring Survey (CTUMS) on population age ≥15
  - 16% are current smokers (lowest since 1965)
  - highest prevalence in age group 20-24 (20%)
  - 11% of youth age 15-19 smoke (decreased from 25% in 2000): more males smoke than females; number of cigarettes consumed per day also decreasing

Management
- general approach
  - identify tobacco users; elicit smoking habits, previous quit attempts and results
  - CAN-ADAPPT 2012 guidelines
    - tobacco use status should be updated for all patients regularly (Grade 1A)
    - health care providers should clearly advise patients to quit (Grade 1C)
    - health care providers should also monitor the patient's mental health status/other addictions while quitting smoking. Medication dosage should be monitored and adjusted as necessary (Grade 1A)
  - every smoker should be offered treatment
    - combining counselling and smoking cessation medication is more effective than either alone (Grade 1A)
    - make patient aware of withdrawal symptoms
      - low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
    - ≥4 counselling sessions > 10 min each with 6-12 mo follow-up yields better results
    - 14% abstinent with counselling vs. 10% without counselling
    - approach depends on patient's stage of change (see Motivational Strategies for Behavioural Change, FM6)
  - willing to quit
    - provision of social support, community resources (self-help, group, helpline, web-based strategies)
    - pregnant patients: counselling is recommended as 1st line treatment (Grade 1A). Nicotine replacement therapy (NRT) should be made available to pregnant women who are unable to quit using non-pharmacologic methods; intermittent NRT use (lozenges, gum) is preferred over continuous dosing of the patch (Grade 1C).
    - Use bupropion (no evidence of fetal or reproductive harm) only if benefits > risks; consult Motherisk. Varenicline has not been studied in pregnancy and should no be used in pregnant women
    - pharmacologic therapy
      1. Nicotine Replacement Therapy
        - 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
        - no difference in achieving abstinence for different forms of NRT
        - reduces craving and withdrawal symptoms without other harmful substances that are contained in cigarettes
      - use with caution: immediately post-MI, serious/worsening angina, serious arrhythmia
      - advise NO smoking while using NRT
    2. Antidepressants (note: mode of action appears to be independent of antidepressant effect)
      - Bupropion SR (Zyban+)
        - 21% abstinent at 12 mo vs. 8% for placebo
        - no advantage for NRT vs. bupropion (similarly effective)
      - Varenicline (Champix)
        - partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce the response to smoked nicotine)
        - more effective than bupropion (23% abstinent from 9-52 wk with varenicline vs. 16% for bupropion vs. 9% with placebo)
        - significant side effects may lower patient compliance

Conclusion
- simple advice can increase cessation rates by 13%. More intensive advice and providing follow-up support may further increase quit rates.
Table 7. Types of Nicotine Replacement Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Dosage</th>
<th>Comment</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Gum (OTC)</td>
<td>2 mg if &lt; 25 cig/d</td>
<td>Chew until “peppy” taste then “park” between gum and cheek to facilitate absorption for 30 min</td>
<td>Mouth soreness, Hiccups, Dysepsia, Jaw ache, Most are transient</td>
</tr>
<tr>
<td></td>
<td>4 mg if &gt; 25 cig/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 piece q1-2h for 1-3 mo (max 24 pieces/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Patch (OTC)</td>
<td>Use for 8 wk</td>
<td>Start with lower dose if &lt; 10 cig/d Change patch q24h and alternate sides</td>
<td>Skin irritation, Insomnia, Palpitations, Anxiety</td>
</tr>
<tr>
<td></td>
<td>21 mg/d x 4 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 mg/d x 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 mg/d x 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Inhaler (OTC)</td>
<td>6-16 cartridges/d up to 12 wk</td>
<td>Nicotine inhaled through mouth, absorbed in mouth and throat not in lungs</td>
<td>Local irritation, Coughing</td>
</tr>
<tr>
<td>Nicotine Nasal Spray (Rx)</td>
<td>Newer form of NRT</td>
<td></td>
<td>Local irritation, Coughing</td>
</tr>
</tbody>
</table>

Table 8. Pharmacologic Treatments for Smoking Cessation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dosage</th>
<th>Prescribing*</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Inhibits re-uptake of dopamine and/or noradrenaline</td>
<td>1. 150 mg qAM x 3 d 2. Then 150 mg bid x 7-12 wk 3. For maintenance consider 150 mg bid for up to 8 mo</td>
<td>1. Decide on a quit date 2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk)</td>
<td>Seizure disorder, Eating disorder, Mood disorder use in past 14 d Simultaneous use of bupropion (Wellbutrin®) for depression</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Partial nicotinic receptor agonist, and partial nicotinic receptor competitive antagonist</td>
<td>1. 0.5 mg qAM x 3 d 2. Then 0.5 mg bid x 4 d 3. Continue 1 mg bid x 12 wk to additional 12 wk as maintenance</td>
<td>1. Decide on a quit date 2. Continue to smoke for first wk of treatment and then completely stop</td>
<td>Caution with pre-existing psychiatric condition</td>
</tr>
</tbody>
</table>

*Bupropion and Varenicline may be used in combination with nicotine replacement therapy

- unwilling to quit
  - motivational intervention (5 Rs)
    1. Relevance to patient
      - relevant to patient’s disease status or risk, family or social situation (e.g., having children in the home), health concerns, age, gender
    2. Risks of smoking
      - short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
      - long-term: MI, stroke, COPD, lung CA, other cancers
    3. Rewards: benefits
      - improved health, save money, food tastes better, good example to children
    4. Roadblocks: obstacles
      - fear of withdrawal, weight gain, failure, lack of support
    5. Repetition
      - reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)

- recent quitter
  - highest relapse rate within 3 mo of quitting
  - minimal practice: congratulate on success, encourage ongoing abstinence, review benefits and problems
  - prescriptive interventions: address problem of weight gain, negative mood, withdrawal, lack of support

Alcohol

- see Psychiatry, PS23

Definition

- diagnostic categories occur along a continuum

Epidemiology

- 10-15% of patients in family practice are problem drinkers
- 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
- more likely to miss diagnosis in women or elderly, patients with high socioeconomic status

- one standard drink = 14 g of pure alcohol
- Beer (5% alcohol) = 12 oz
- Wine (12-17% alcohol) = 5 oz
- Fortified wine = 3 oz
- Hard liquor (40%) = 1.5 oz
Assessment
- screen for alcohol dependence with CAGE questionnaire
  - if CAGE positive, explore with further questions for alcohol abuse/dependence
- assess drinking profile
  - setting, time, place, occasion, with whom
  - impact on: family, work, social
  - quantity-frequency history
    - how many drinks per day?
    - how many days per week?
    - maximum number of drinks on any one day in the past month?
- if identified positive for alcohol problem
  - screen for other drug use
  - identify medical/psychiatric complications
  - ask about drinking and driving
  - ask about past recovery attempts and current readiness for change

Investigations
- GGT and MCV for baseline and follow-up monitoring
- AST, ALT (usually AST:ALT approaches 2:1 in an alcoholic)
- CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by liver)

Management
- intervention should be consistent with patient’s motivation for change
- individualized counselling and regular follow-up is crucial
- 10% of patients in alcohol withdrawal will have seizures or delirium tremens
- Alcoholics Anonymous/12-step program
- outpatient/day programs for those with chronic, resistant problems
- family treatment (Al-Anon, Alateen, screen for spouse/child abuse)
- in-patient program if:
  - dangerous or highly unstable home environment
  - severe medical/psychiatric problem
  - addiction to drug that may require in-patient detoxification
  - refractory to other treatment programs
- pharmacologic
  - diazepam for withdrawal
  - disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, N/V, hypotension if alcohol is ingested (available in U.S., but no longer available in Canada)
  - naltrexone: competitive opioid antagonist that reduces craving and pleasurable effects of drinking
  - may trigger withdrawal in opioid-dependent patients
  - acamprosate: glutamate receptor modulator that also reduces craving
- see Psychiatry, PS23

Prognosis
- relapse is common and should not be viewed as failure
- monitor regularly for signs of relapse
- 25-30% of abusers exhibit spontaneous improvement over 1 yr
- 60-70% of individuals with jobs and families have an improved quality of life 1 yr post-treatment

Common Presenting Problems

Abdominal Pain
- see Gastroenterology, G11 and General Surgery, GS4

Epidemiology
- 20% of individuals have experienced abdominal pain within the last 6-12 mo
- 90% resolve in 2-3 wk
- only 10% are referred to specialists, of those <10% admitted to hospital

Etiology
- most common diagnosis in family medicine at 28% is “nonspecific abdominal pain,” which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticulitis, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: DKA, porphyria, hypercalcemia, medications (e.g. NSAIDs), alcohol, toxic ingestion, foreign body, psychogenic

Some Adverse Medical Consequences of Problem Drinking
- GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/ esophageal cancer
- Cardiac: HTN, alcoholic cardiomyopathy
- Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
- Hematologic: anemia, coagulopathies
- Other: trauma, insomnia family violence, anxiety/depression, social/ family dysfunction, sexual dysfunction, fetal damage

Figure 6. Continuum of alcohol use

Common Presenting Problems

Abdominal Pain

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Figure 6. Continuum of alcohol use
Pathophysiology

- type of pain
  - somatic pain: sharp, localized pain
  - visceral pain: dull, generalized pain

- location of pain
  - epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
  - RUQ: biliary, hepatic, colonic, pulmonary, renal
  - LUQ: cardiac, gastric, pancreatic, renal, vascular
  - periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon
  - hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region
  - any location: aneurism, dissection, ischemia, zoster, muscle strain, hernia, bowel obstruction, ischemia, peritonitis, porphyria, DKA

Investigations

- guided by findings on history and physical
- possible blood work: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, toxicology screen, β-hCG
- imaging
  - CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  - abdominal x-ray, KUB (consider: gas pattern, free air, kidney stones, constipation)
  - ultrasound (renal stones, gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  - CT scan (AAA, appendicitis), non-contrast helical CT-Scan (first choice for renal stones)
- other tests
  - urinalysis
  - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
  - H. pylori testing (urea breath test, serology, biopsy)

Allergic Rhinitis

- see Otolaryngology, OT23

Definition

- inflammation of the nasal mucosa that is triggered by an allergic reaction
- classification
  - seasonal
    - symptoms during a specific time of the year
    - common allergens: trees, grass and weed pollens, airborne moulds
  - perennial
    - symptoms throughout the year with variation in severity
    - common allergens: dust mites, animal dander, moulds
- persistent allergic rhinitis may lead to chronic rhinosinusitis

Etiology

- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

Epidemiology

- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, eczema, sinusitis, and otitis media

Assessment

- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

Management

- conservative
  - minimize exposure to allergens
  - most important aspect of management, often sufficient (may take months)
  - maintain hygiene, saline nasal rinses
- pharmacologic agents
  - oral antihistamines – first line therapy for mild symptoms
    - e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  - intranasal corticosteroids for moderate/severe or persistent symptoms (≥1 mo of consistent use to see results)
  - intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)

Abdominal Pain Red Flags

- Severe pain
- Signs of shock
- Peritoneal signs
- Abdominal distention
- Pain out of proportion to clinical findings
- New onset pain, change in pain, or altered bowel habits in elderly
- Weight loss
- Blood per rectum/melena
- Anemia
- Supraclavicular nodes
- Family history of serious bowel disease

In patients >50, keep a high index of suspicion for AAA – its presentation may mimic renal colic or diverticulitis

Differential Diagnosis

- Acute viral infection
- Vasomotor rhinitis
- Deviated septum
- Nasal polyps
- Acute/chronic sinusitis
- Drug-induced rhinitis

Rhinitis Medicamentosa

Rebound nasal congestion. Occurs with prolonged use (>5-7 d) of vasoconstrictive intranasal medications. Patient may become dependent, requiring more frequent dosing to achieve the same decongestant effect
Common Presenting Problems

- allergy skin testing
  - for patients with chronic rhinitis
  - symptoms not controlled by allergen avoidance, pharmacological therapy
  - may identify allergens to include in immunotherapy treatment
- immunotherapy (allergy shots)
  - reserved for severe cases unresponsive to pharmacologic agents
  - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

## Amenorrhea

- see Gynecology, GY10

## Anxiety

- see Psychiatry, PS13

### Epidemiology

- 25-30% of patients in primary care settings have psychiatric disorders
- many are undiagnosed or untreated; hence the need for good screening
- high rate of coexistence of anxiety disorders and depression

### Screening

- screening tools such as the GAD-7 tool
- screening questions
  - Do you tend to be an anxious or nervous person?
  - Have you felt unusually worried about things recently?
  - Has this worrying affected your life? How?

### Assessment

- associated symptoms
- risk factors
  - family history of anxiety or depression, past history of anxiety, stressful life event, social isolation, female, comorbid psychiatric diagnosis (e.g. depression)
  - assess substance abuse, comorbid depression, stressful life events, trauma, suicidal ideation/self-harm
- to differentiate anxiety disorders, consider symptoms (panic attacks, specific situations/stressors, excessive worry about common concerns, repetitive thoughts and/or behaviours to neutralize the anxiety) and their duration
- Generalized Anxiety Disorder 7–item (GAD – 7) scale to assess level of anxiety

![Symptoms of Anxiety](image)

**Symptoms of Anxiety**

Are the symptoms predominantly...

- In the form of panic with physical (autonomic) symptoms?
- Secondary to a specific experienced trauma?
- Recurrent anxious thoughts?

- Do the panic attacks come...
  - With a specific situation
  - "Out of the blue"

- Is patient avoiding situation?
  - Yes
  - No

- Patient afraid of another attack and its implications
- Are they accompanied by a repetitive behaviour meant to neutralize the anxiety?
- Are the thoughts intrusive, inappropriate and distressing?

- Specific trigger (e.g. flying, spiders, blood, etc.)
- Public setting where there might be negative evaluation
- Setting where it may be difficult to escape

**Specific Phobia**

**Social Phobia**

**Panic Disorder with Agoraphobia**

**Adjustment Disorder**

**GAD**

**PTSD**

**OCD**

**Rule Out**

- Cardiac (post MI, arrhythmias)
- Endocrine (hyperthyroidism, diabetes, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatofrom disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (OCPD)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/benzodiazepine withdrawal)

**Differential Diagnosis of Anxiety Disorders**

- Panic disorder
- GAD
- Social Anxiety Disorder (previously Social Phobia)
- Agoraphobia
- Specific phobia
- Selective Mutism
- Separation Anxiety Disorder
- Other: GMC, AMC, mood disorder, psychotic disorder, OCD

**Excessive worry and apprehension about social situations?**

Figure 7. Differentiating anxiety disorders

Management
- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- lifestyle advice: decrease caffeine and alcohol intake, exercise, relaxation techniques, mindfulness strategies
- self help materials, community resources (e.g. support groups)
- CBT, cognitive interventions, exposure therapy etc
- treat any underlying medical and/or comorbid conditions
- provide support to family and caregivers
- for pharmacotherapy, see Psychiatry, PS48

Asthma/COPD

Definition
- asthma
  - chronic, reversible airway inflammation characterized by periodic attacks of wheezing, SOB, chest tightness and coughing
  - airways hyper-responsive to triggers/antigens leading to acute obstructive symptoms by bronchoconstriction, mucus plugs and increased inflammation
  - cannot be diagnosed at first presentation; called reactive airway disease until recurrent presentations
  - pulmonary function tests (PFTs) can be done from age 6 or when child able to follow instructions to do PFTs
  - peak flow meters are useful in the office and at home for monitoring
- chronic obstructive pulmonary disease (COPD)
  - group of chronic, progressive, non-reversible diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
  - emphysema and chronic bronchitis are the most common forms

Table 9. Differentiating COPD from Asthma

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Usually in 6th decade</td>
</tr>
<tr>
<td><strong>Role of Smoking</strong></td>
<td>&gt;10 pack yr</td>
</tr>
<tr>
<td><strong>Reversibility of Airflow Obstruction</strong></td>
<td>Airflow obstruction is chronic and persistent</td>
</tr>
<tr>
<td><strong>Evolution</strong></td>
<td>Slow, progressive worsening (with periodic exacerbations)</td>
</tr>
<tr>
<td><strong>History of Allergy</strong></td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Precipitators</strong></td>
<td>Environmental irritants (air pollution), cigarette smoking, α-antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs)</td>
</tr>
<tr>
<td><strong>Symptoms/Signs</strong></td>
<td>Chronic cough, sputum, and/or dyspnea</td>
</tr>
<tr>
<td><strong>Diffusion Capacity</strong></td>
<td>Decreased (more so in pure emphysema)</td>
</tr>
<tr>
<td><strong>Hypoxemia</strong></td>
<td>Chronic in advanced stages</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td>May have improvement with bronchodilators but not universally seen</td>
</tr>
<tr>
<td><strong>Chest X-Ray</strong></td>
<td>Often normal</td>
</tr>
<tr>
<td></td>
<td>Increased bronchial markings (chronic bronchitis) and hyperinflation (emphysema) often co-exist, bullae</td>
</tr>
</tbody>
</table>

Management
- **Mild**
  - Step 1: SABA pm (salbutamol)
  - Step 2: SABA pm + LAAC (i.e. tiotropium) or LABA (e.g. salmeterol)
  - **Moderate**
    - Step 3: SABA pm + LAAC + low-dose combined ICS/LABA; consider inhaled vs. oral steroids
  - **Severe**
    - Step 4: 2-agonist + ICS
      - Pneumococcal vaccination, annual influenza immunization

**Advanced**
- Ongoing patient education, and environmental control SABA taken pm as rescue medication + maintenance meds
- Maintenance medications
  - Step 1: Low-dose ICS
  - Step 2: Medium/high dose ICS or low-dose ICS plus e ther LABA, LT modifier, or long-acting theophylline
  - Step 3: Medium/high dose ICS plus either LABA, LT modifier, or long-acting theophylline
  - Step 4: As above plus immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization

ICS = inhaled corticosteroids; LAAC = long-acting anticholinergic; LABA = long-acting β-agonist; LT modifier = leukotriene modifier; SABA = short-acting β-agonist

Figure 8. Expiratory flow volume curves (obstructive, normal, and restrictive disease)

See Respirology, R7
Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. With permission from Elsevier. ©2008

Signs of Poorly Controlled Asthma
- ≥3 β2 agonist use >4x/wk
- Asthma-related absence from work/school
- Exercise induced asthma
- Night-time symptoms >1x/wk.

What Colour is Your Inhaler?

<table>
<thead>
<tr>
<th>Name</th>
<th>Body/Cap Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol – Ventolin®</td>
<td>light blue/navy</td>
</tr>
<tr>
<td>Salmeterol – Serevent®</td>
<td>teal/light teal</td>
</tr>
<tr>
<td>Terbutaline – Bricanyl®</td>
<td>blue/white</td>
</tr>
<tr>
<td>Fluticasone – Flonase®</td>
<td>orange/peach</td>
</tr>
<tr>
<td>Budesonide – Pulmicort®</td>
<td>white/brown</td>
</tr>
<tr>
<td>Combined Long-Acting β2-Agonist + ICS</td>
<td></td>
</tr>
<tr>
<td>Fluticasone/Salmeterol – Advair®</td>
<td>purple discus</td>
</tr>
<tr>
<td>Budesonide/Formoterol – Symbicort®</td>
<td>red/white</td>
</tr>
<tr>
<td>Ipratropium/Albuterol – Combivent®</td>
<td>clear/orange</td>
</tr>
</tbody>
</table>

Anticholinergics
- Ipratropium – Atrovent®: clear/green
- Olodaterol – Alupent®: white/teal
- tiotropium – Spiriva®: white/turquoise

More About Inhalers
- • Aerosols (puffers = MDI, MDI + spacer) MDIs should be used with spacers to:
  - Reduce side effects
  - Improve amount inhaled
  - Improve efficiency of use
- • Dry Powder Inhalers (discus, turbuhaler, and diskhaler) require deep and fast breathing (may not be ideal for children)
- • Nebulizers can be used to convert liquid medications into a fine mist; recommended for use if contraindications to MDIs

Differential Diagnosis of Wheezing
- • Allergies, anaphylaxis
- • Asthma, reactive airway disease
- • GERD
- • Infections (bronchitis, pneumonia)
- • Obstructive Sleep Apnea
- • COPD
- • Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction

When prescribing salbutamol, watch out for signs of hypokalemia: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, N/V, polyuria

FM16 Family Medicine
Common Presenting Problems
Toronto Notes 2018
Benign Prostatic Hyperplasia

Definition
- hyperplasia of the stroma and epithelium in the periurethral transition zone

History and Physical
- include current/past health, surgeries, trauma, and current and OTC meds
- specific urinary symptoms
- physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth, and rubbery in BPH)

Investigations
- urinalysis to exclude UTI and for microscopic hematuria (common sign)
- serum PSA: protein produced by prostatic tissue
  - values
    - <4.0 ng/mL: normal, but must take into account patient's age and velocity of PSA increase
    - 4-10 ng/mL: consider measuring free/total PSA
    - >10 ng/mL: high likelihood of prostate pathology
- PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI
- increased PSA in a younger man is more often due to cancer than other causes
- abnormal DRE or PSA should trigger further assessment
- decision to test PSA in an asymptomatic man should involve discussion about the risks and possible benefits
- other tests
  - Cr, BUN
  - post-void residual volume by ultrasound
  - urodynamic studies, renal ultrasound
  - patient voiding diary
- tests NOT recommended as part of routine initial evaluation include:
  - cystoscopy
  - cytology
  - prostate ultrasound or biopsy
  - IVP
  - urodynamic studies

<table>
<thead>
<tr>
<th>Table 10. Symptoms and Complications of BPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive Symptoms</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Hesitancy (difficulty starting urine flow)</td>
</tr>
<tr>
<td>Diminution in size and force of urinary stream</td>
</tr>
<tr>
<td>Stream interruption (double voiding)</td>
</tr>
<tr>
<td>Urinary retention (bladder does not feel completely empty)</td>
</tr>
<tr>
<td>Post-void dribbling</td>
</tr>
<tr>
<td>Overflow incontinence</td>
</tr>
<tr>
<td>Nocturia</td>
</tr>
</tbody>
</table>

Management
- referral to urologist if moderate/severe symptoms
- conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
  - fluid restriction (avoid alcohol and caffeine)
  - avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
  - pelvic floor/Kegel exercises
  - bladder retraining (scheduled voiding)
- pharmacological: for moderate/severe symptoms
  - α-receptor antagonists (e.g. terazosin [Hytrin®], doxazosin [Cardura®], tamsulosin [Flomax®], alfuzosin [Xatral®])
  - relaxation of smooth muscle around the prostate and bladder neck
  - 5α reductase inhibitor (e.g. finasteride [Proscar®])
  - only for patients with demonstrated prostatic enlargement due to BPH
  - inhibits enzyme responsible for conversion of testosterone into dihydrotestosterone (DHT) thus reducing growth of prostate
  - phytotherapy (e.g. saw palmetto berry extract, Pygeum africanum)
  - more studies required before this can be recommended as standard therapy (considered safe)
- surgical
  - TURP (transurethral resection of the prostate), TUIP (transurethral incision of the prostate, for prostates <30 g)
  - absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
  - complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido

Differential Diagnosis
- Prostate cancer
- Urethral obstruction
- Bladder neck obstruction
- Neurogenic bladder
- Overactive bladder
- Cystitis
- Prostatitis

Self-Management Asthma and COPD
Education and Written Action Plan
- Education is a key component in management of asthma and COPD
- Guided self-management combining education, regular medical review, self-assessment, and written action plan have been shown to reduce hospitalizations, ER visits, and missed days at work or school.
- Sample action plans available online: http://www.respiratoryguidelines.ca
### Bronchitis (Acute)

**Definition**
- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

**Epidemiology**
- 5th most common diagnosis in family medicine, most common is URTI

**Etiology**
- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV)
- 20% bacterial: *M. pneumoniiae, C. pneumoniiae, S. pneumoniiae*

**Investigations**
- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not useful
- CXR if suspect pneumonia (cough >3 wk, abnormal vital signs, localized chest findings) or CHF
- PFT with methacholine challenge if suspect asthma

**Management**
- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/d when febrile), humidity, analgesics and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
  - antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic
  - (see Antimicrobial Quick Reference, FM49)
  - antibiotics in children show no benefit

### Chest Pain

- see Cardiology and Cardiac Surgery, C4 and Emergency Medicine, ER11

**Differential Diagnosis**

**Table 11. Differential Diagnosis of Chest Pain**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Findings</th>
<th>LR+</th>
<th>LR–</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myocardial Infarction</td>
<td>Chest pain radiates to both arms</td>
<td>7.1</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>Third heart sound on auscultation</td>
<td>3.2</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>3.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Chest Wall Pain</td>
<td>At least two of the following findings: localized muscle tension; stinging pain; pain reproducible by palpation; absence of cough</td>
<td>3.0</td>
<td>0.47</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Disease</td>
<td>ACEI, ARB, thiazide, or long-acting CCB</td>
<td>3.1</td>
<td>0.30</td>
</tr>
<tr>
<td>Panic Disorder/Anxiety State</td>
<td>Single question: In the past four weeks, have you had an anxiety attack</td>
<td>4.2</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>(suddenly feeling fear or panic?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Clinical triad of pleuritic chest pain (increases with inspiration or when</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>reclining, and is lessened by leaning forward), pericardial friction rub, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>electrocardiographic changes (diffuse ST segment elevation and PR interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>depression without T wave inversion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Egophony</td>
<td>8.6</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Dullness to percussion</td>
<td>4.3</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>2.1</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>Clinical impression</td>
<td>2.0</td>
<td>0.24</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Pulmonary edema on chest radiography</td>
<td>11.0</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Clinical impression/judgment</td>
<td>9.9</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>History of heart failure</td>
<td>5.8</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>History of acute myocardial infarction</td>
<td>3.1</td>
<td>0.69</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>High pretest probability based on Wells criteria</td>
<td>6.8</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Moderate pretest probability based on Wells criteria</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Low pretest probability based on Wells criteria</td>
<td>0.1</td>
<td>7.6</td>
</tr>
<tr>
<td>Acute Thoracic Aortic Dissection</td>
<td>Acute chest or back pain and a pulse differential in the upper extremities</td>
<td>5.3</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Adapted from: McClenachy J, Rupal S. Outpatient diagnosis of acute chest pain in adults. Am Fm Physicians. 2013 Feb 1; 87(3): 177-182*
Common Cold (Acute Rhinitis)

- Definition: viral URI with inflammation

Epidemiology
- most common diagnosis in family medicine, peaks in winter months
- incidence: adults = 2-4/yr, children = 6-10/yr
- organisms:
  - mainly rhinoviruses (30-35% of all colds)
  - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
- incubation: 1-5 d
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

Risk Factors
- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

Clinical Features
- symptoms:
  - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
  - general: malaise, headache, myalgias, mild fever
- signs:
  - erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam
- complications:
  - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
  - asthma/COPD exacerbation

Differential Diagnosis
- allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

Management
- patient education:
  - symptoms peak at 1-3 d and usually subside within 1 wk
  - cough may persist for days to weeks after other symptoms disappear
  - no antibiotics indicated because of viral etiology
  - secondary bacterial infection can present within 3-10 d after onset of cold symptoms
- prevention:
  - frequent hand washing, avoidance of hand to mucous membrane contact, use of surface disinfectant
  - yearly influenza vaccination
- symptomatic relief:
  - rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
  - analgesics and antipyretics: acetaminophen, ASA (not in children because risk of Reye's syndrome)
  - cough suppression: dextromethorphan or codeine if necessary (children under 6 yr of age should not use any cough/cold medications)
- decongestants, antihistamines
- patients with reactive airway disease will require increased use of bronchodilators and inhaled steroids

Infections
- ECG, CXR, and others if indicated (cardiac enzymes, d-dimers, liver function tests [LFTs], etc.)
- refer to ED if suspect serious etiology (e.g. aortic dissection, MI)

Management of Common Causes of Chest Pain
- angina/ischemic heart disease
  - nitroglycerin (NTG): wait 5 min between sprays and if no effect after 3 sprays, send to ED
  - myocardial infarction
    - ASA (160-325 mg, chewed stat), clopidogrel (Plavix®), LMWH (enoxaparin), morphine, oxygen, NTG
    - ± reperfusion therapy with fibrinolytics (e.g. tPA, RPA, TNK, or SK) if within 12 h (ideally <30 min)
  - percutaneous intervention (cath lab) if <90 min
  - start β-blocker (e.g. metoprolol starting dose 25 mg PO q6h or bid, titrating to HR goal of 55-60 bpm)
  - endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results
  - GERD: antacids, H2-blockers, PPIs, patient education
  - costochondritis: NSAIDs

Inflammation vs Colds: A Guide to Symptoms

<table>
<thead>
<tr>
<th>Feature</th>
<th>Flu</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Illness</td>
<td>Sudden</td>
<td>Slow</td>
</tr>
<tr>
<td>Fever</td>
<td>High fever</td>
<td>Mild</td>
</tr>
<tr>
<td>Exhaustion level</td>
<td>Severe</td>
<td>None</td>
</tr>
<tr>
<td>Cough</td>
<td>Dry severe</td>
<td>±</td>
</tr>
<tr>
<td>Throat</td>
<td>Fine</td>
<td>Sore</td>
</tr>
<tr>
<td>Nose</td>
<td>Dry and clear</td>
<td>Runny</td>
</tr>
<tr>
<td>Headache</td>
<td>Fine</td>
<td>Headache-free</td>
</tr>
<tr>
<td>Appetite</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Muscles</td>
<td>Achy</td>
<td>Fine</td>
</tr>
<tr>
<td>Chills</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Echinacea for Preventing and Treating the Common Cold
(Cochrane Database Syst Rev 2014;2:CD000530)

Purpose: To assess whether Echinacea preparations are effective and safe for the prevention and treatment of the common cold.

Methods: Meta-analysis of RCTs comparing mono-preparations of Echinacea with placebo. Primary efficacy outcome was number of individuals with at least one cold in prevention trials, and duration of colds in treatment trials. Primary safety and acceptability outcome was number of participants dropping out due to adverse events.

Results: 24 double-blind trials with 4,631 participants were included. No prevention study comparisons comparing Echinacea and placebo found a statistically significant difference in terms of number of patients with at least one cold episode, though a relative risk reduction of 10% to 25% was identified. Of treatment trials reporting on duration of colds, only 1 study of 7 showed a significant effect favouring Echinacea over placebo. No significant differences were found between Echinacea and placebo groups in number of drops due to adverse events, though prevention trials showed a trend towards higher drop-out numbers due to adverse events in treatment groups.

Conclusions: Echinacea products have not been shown to provide benefits for treating colds, although it is possible there is a weak benefit from some Echinacea products. Individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance.
Concussion/Mild Traumatic Brain Injury

- see Neurosurgery, NS30, and Emergency Medicine, ER9
- a useful tool for the assessment of individuals and athletes with concussion is the Sport Concussion Assessment Tool, 3rd edition (SCAT3), Br J Sports Med 2013 47: 259

Contraception

- see Gynecology, GY17

EMERGENCY CONTRACEPTION

- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 h apart) or post-coital copper IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
- copper IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
- pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
- advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
- pharmacists across Canada can dispense Plan B® OTC

Cough

History and Physical

- duration (chronic - 8 wk), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptysis, wheezing, chest pain, orthopnea, PND, rhinitis, reflux, post-nasal drip
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (e.g. ACEI, β-blockers), allergies
- PMH: lung (asthma, COPD, CF), heart (CHF, MI, arrhythmias), chronic illness, GI (reflux)
- vitals including O2 saturation, respiratory exam, HEENT and precordial exam

Investigations

- guided by findings on history and physical
  - consider throat swab, CXR, PFTs, upper GI series, sputum culture test for acid-fast bacilli (if TB is suspected)

Dementia (Major Neurocognitive Disorder)

- see Psychiatry, PS20

Epidemiology

- 15% of Canadians ≥65 yr are living with dementia; risk for dementia doubles every 5 years after age 65
- prevalence of depression in dementia is 20-60%; major depression decreases as dementia severity increases; vascular and mixed dementias have a higher prevalence of depression
- leading causes: Alzheimer’s dementia (40-50%), Mixed dementia (20-25%), Lewy-Body dementia (5-15%), Vascular dementia (5-10%), Frontotemporal dementia (5-10%)

Investigations

- history, physical exam, MMSE, MOCA (best screening test), dementia quick screen (see sidebar)
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin B12, folate, VDRL, HIV, head CT

Management

- treat and prevent reversible causes
  - provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
  - family education, counselling, and support (respite programs, group homes)
  - pharmacologic therapy: NMDA receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose neuroleptics and antidepressants can be used to treat behavioural and emotional symptoms
  - 20% of patients develop clinical depression, most commonly seen in vascular dementia

Dementia Quick Screen = Mini Cog + Animal Naming

- 3 simple tests, takes about 2 min
- Use when suspect mild cognitive impairment or when patient is at high risk
- Mini Cog = 3-word recall + clock drawing
- Clock Drawing – including numbers and hands so time shows 10 min past 11 (normal = correct number/hand placing or only minor spacing problems)
  - 0 word recall = impairment, 1-2 words and clock drawing abnormal = impairment, 3-word recall = normal
- Naming animals in 1 min (normal = >15 in one min)
- Interpretation: If all 3 results within normal range, cognitive impairment unlikely
- Return for further evaluation if:
  - <15 animals named
  - 0.1 words recalled
  - Clock Drawing Abnormal
**Depression**

- see Psychiatry, PS10

**Etiology**
- often presents as non-specific complaints (e.g. sleep disturbance, chronic fatigue, pain)
- depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of patients may not receive appropriate treatment for their depression
- early diagnosis and treatment improve outcomes

**Screening Questions**
- Canadian Task Force on Preventive Health Care (2103) recommends not routinely screening for depression
- high-yield screening questions are:
  - "Are you depressed?" (high specificity and sensitivity)
  - "Have you lost interest or pleasure in the things you usually like to do?" (anhedonia)
  - "Do you have problems sleeping?"
- PHQ9 tool is useful to screen, diagnose and monitor depression; use Geriatric Depression Scale (GDS) for the geriatric population

**Assessment**
- risk factors: see Psychiatry, PS10
- personal or family history of depression
- medications and potential substance abuse problems
- high risk for suicide/homicide
  - fill out Form 1 (in Ontario): application by physician to hospitalize a patient against his/her will for psychiatric assessment (up to 72 h)
- functional impairment (e.g. work, relationships)
- at least 5 out of 9 criteria including at least one of anhedonia or depressed mood ≥2 wk for actual diagnosis to be met (see sidebar)
- validated depression rating scales: Beck’s Depression Inventory, Zung’s self-rating depression scale, Children’s Depression Inventory, Geriatric Depression Scale, Personal Health Questionnaire Depression Scale (PHQ-9)
- routine medical workup (physical exam, CBC, TSH, ferritin, folate, B12, electrolytes, urinalysis, glucose, etc.)

**Treatment**
- goal: full remission of symptoms and return to baseline psychosocial function
- phases of treatment
  - acute phase (8-12 wk): relieve symptoms and improve quality of life
  - maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
  - treatment options are pharmacotherapy, psychotherapy, or a combination of both
  - combination therapy is synergistic and most effective (refer to EBM in sidebar)
  - treatment of youth (age 10-21)
  - for mild depression, a period of active support and monitoring before initiating treatment is recommended
  - fluoxetine is first line among SSRIs (most evidence)
  - monitor closely for adverse effects such as suicidal ideation and behaviour
  - psychotherapy
    - CBT or interpersonal therapy (IPT) alone can be used for mild depression
    - psychotherapy plus medication is recommended for moderate to severe depression
  - treatment should continue for at least 6 months
  - ongoing management should include assessment in key domains (school, home, social setting)
  - reassessment and referral recommended if no improvement after 6-8 wk of treatment
  - for adolescents with moderate/severe depression and coexisting psychosis and/or substance abuse, consider referral

**Table 12: Common Medications**

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Action</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>paroxetine (Paxil®), fluoxetine (Prozac®), sertraline (Zoloft®), citalopram (Celexa®), fluvoxamine (Luvox®), escitalopram (Cipralex®)</td>
<td>Block serotonin reuptake</td>
<td>Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase QT interval (baseline ECG is suggested)</td>
<td>First line therapy for youth is fluoxetine; paroxetine is not recommended for youth (controversial)</td>
</tr>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor®), duloxetine (Cymbalta®)</td>
<td>Block serotonin and NE reuptake</td>
<td>Insomnia, tremors, tachycardia, sweating</td>
<td>Often chosen for lack of sexual side effects, can be used for augmentation of anti-depressant effects with other classes of medication</td>
</tr>
<tr>
<td>SDRI</td>
<td>bupropion (Wellbutrin®)</td>
<td>Block dopamine and NE reuptake</td>
<td>Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs</td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>amitriptyline (Elavil®)</td>
<td>Block serotonin and NE reuptake</td>
<td>Sexual dysfunction, weight gain, tremors, tachycardia, sweating</td>
<td>Narrow therapeutic window, lethal in overdose</td>
</tr>
</tbody>
</table>

**Conclusion**

Combination pharmacotherapy and psychological treatment for depression: A systematic review

**Purpose:** To examine the relationship between adherence and efficacy of antidepressant medications plus psychological treatment versus medications alone in the management of depressive disorders.

**Methods:** Systematic review of RCTs comparing antidepressant medications alone versus combination therapy with psychological intervention included. Efficacy and adherence to therapy were the main outcomes.

**Results:** 16 trials with 3,182 patients were included.

Patients receiving combination therapy showed significantly greater improvements than those receiving medications alone (OR 1.86, 95% CI 1.30-2.64); dropout and non-responder proportions did not differ in distribution between the two groups (OR 0.36, 0.13-1.20).

A significant advantage with combination therapy was noted in studies with follow-up longer than 12 weeks (OR 2.11, 1.20-3.63), accompanied by significant reduction in dropout and non-responder proportions.

**Conclusions:** Combination therapy with psychological treatment and medication is associated with greater improvement rates than medication alone, and may decrease dropout rates with longer therapies.
Prognosis
- up to 40% resolve spontaneously within 6-12 mo
- risks of recurrence: 50% after 1 episode; 70% after 2 episodes; 90% after 3 episodes

Diabetes Mellitus

Definition
- metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both

Classification and Diagnosis
- see Endocrinology

Epidemiology
- major health concern, affecting up to 10% of Canadians
- incidence of type 2 DM is rising due to increasing obesity, sedentary lifestyle, and age of the population
- Canadian adults with DM are twice as likely to die prematurely, compared to persons without DM

Risk Factors
- type 1 DM
  - personal or family history of autoimmune disease
- type 2 DM
  - first degree relative with DM
  - age ≥40 yr
  - obesity (especially abdominal), HTN, hyperlipidemia, CAD, vascular disease
  - prior GDM, macrosomic baby (>4 kg)
  - PCOS
  - history of IGT or IFG
  - presence of complications associated with DM
  - presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  - medications: glucocorticoids, atypical antipsychotics, HAART
- both
  - member of a high risk population (e.g. Aboriginal, Hispanic, Asian, or African descent)

Screening
- type 2 DM
  - FBG in everyone ≥40 q3yr, or at high risk using the CANRISK calculator
  - more frequent and/or earlier testing if presence of ≥1 risk factor (see above)
- GDM (see Obstetrics, OB26)
  - all pregnant women between 24-28 wk gestation

Goals of Therapy
- see Endocrinology and side bar (SMART Goals)

DM Related Symptoms
- Hyperglycemia: polyphagia, polydipsia, polyuria, weight change, blurry vision, yeast infections
- Diabetic Ketoacidosis (DKA): fruity breath, anorexia, N/V, fatigue, abdominal pain, Kussmaul breathing, dehydration
- Hypoglycemia: hunger, anxiety, tremors, palpitations, sweating, headache, fatigue, confusion, seizures, coma

Long-Term Complications of DM
- Microvascular: nephropathy, retinopathy, neuropathy
- Macrovascular: CAD, CVD, PVD

Smart Goals
- Diabetes Quick Reference Guide
  - A1C: Optimal Glycemic Control (Usually <7%)
# Assessment and Monitoring

## Table 13. Assessment and Monitoring

<table>
<thead>
<tr>
<th>Category</th>
<th>Initial Assessment</th>
<th>q2-4mo</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Symptoms of hyperglycemia, ketoacidosis, hypoglycemia</td>
<td>DM directed history</td>
<td>DM-directed history</td>
</tr>
<tr>
<td></td>
<td>Past medical history</td>
<td>Screen for awareness and frequency of hypoglycemia and DKA</td>
<td>Screen for awareness and frequency of hypoglycemia and DKA</td>
</tr>
<tr>
<td></td>
<td>Functional inquiry</td>
<td>Glucose monitoring</td>
<td>Glucose monitoring</td>
</tr>
<tr>
<td></td>
<td>Family history</td>
<td>Use of insulin and oral agents</td>
<td>Use of insulin and oral agents</td>
</tr>
<tr>
<td></td>
<td>Risk factors</td>
<td>Smoking cessation</td>
<td>Sexual function</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td></td>
<td>Lifestyle counselling</td>
</tr>
<tr>
<td></td>
<td>Sexual function</td>
<td></td>
<td>Screen for depression</td>
</tr>
<tr>
<td></td>
<td>Lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td>General: Ht, Wt, BMI, BP, WC</td>
<td>Wt, BP, BMI, WC</td>
<td>Foot exam for sensation (using a 10 g monofilament), ulcers or infection</td>
</tr>
<tr>
<td></td>
<td>Head and neck: fundoscopy, thyroid exam</td>
<td></td>
<td>Remainder of exam as per PHE</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular exam: signs of PVD, pulses, bruits</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal exam (e.g. for organomegaly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand/foot/skin exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurological exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>FBG, HbA1c, fasting lipids, Cr, microalbumin:creatinine ratio</td>
<td>HbA1c q3mo</td>
<td>Fasting lipid profile</td>
</tr>
<tr>
<td></td>
<td>Baseline ECG; repeat testing q2yr for those at high risk</td>
<td>FBG as needed</td>
<td>Annual random ACR and eGFR</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Nutritional and physical education Consider referral to DM education program if available</td>
<td>Assess progress towards long-term complications</td>
<td>Calibrate home glucose monitor</td>
</tr>
<tr>
<td></td>
<td>Monitoring BG: explain methods and frequency</td>
<td>Adjust treatment plan if necessary</td>
<td>Arrange retinopathy screening</td>
</tr>
<tr>
<td></td>
<td>Medication counselling: oral hypoglycemics and/or insulin, method of administration, dosage adjustments</td>
<td></td>
<td>Influenza vaccination annually</td>
</tr>
<tr>
<td></td>
<td>Pneumococcal vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ophthalmology consult type 1 DM within 5 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>type 2 DM at diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Nonpharmacologic Management

- **diet**
  - all diabetics should see a registered dietician for nutrition counselling
  - can reduce HbA1c by 1-2%
  - moderate weight loss (5%) improves glycemic control and CVD risk factors
  - decrease combined saturated fats and trans-fatty acids to <10% of calories
  - avoid simple sugars, choose low glycemic-index foods, ensure regularity in timing and spacing of meals
- **physical activity and exercise**
  - at least 150 min of aerobic exercise per wk, plus 2 sessions per wk of resistance exercise is recommended
  - encourage 30-45 min of moderate exercise 4-7 d/wk
  - promote cardiovascular fitness: increases insulin sensitivity, lowers BP, and improves lipid profile
  - if insulin treated, may require alterations of diet, insulin regimen, injection sites, and self-monitoring

## Self-Monitoring of Blood Glucose

- **type 1 DM**: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
- **type 2 DM**: recommendations vary based on treatment regimen (e.g. insulin dependent requires more frequent monitoring – refer to 2013 Canadian Practice Guidelines)
- if FBG >14 mmol/L, perform ketone testing to rule out DKA
- if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia

## Calculate Total Insulin Required

- **type 1 DM**: 0.5-0.7 units/kg/d
- **type 2 DM**: 0.3 units/kg/d

## Dietary Advice for Treatment of Type 2 DM in Adults

- **Purpose**: To assess the effects of type and frequency of different dietary advice strategies for adults with type 2 diabetes.
- **Methods**: Systematic review of RCTs with follow-up of 6 mo or longer, where dietary advice was the main intervention.
- **Results**: 36 RCTs with 1,467 participants were included, all measuring weight and glycemic control measures, and some reporting mortality, blood pressure, serum cholesterol and triglycerides, maximal exercise capacity and compliance. No data was available for efficacy of dietary advice in terms of dietary changes. Adoption of regular exercise was found to promote HbA1C glycemic control in type 2 diabetic patients.
- **Conclusion**: No high-quality data is available for the efficacy of dietary treatment of type 2 diabetes, though exercise has been shown to improve HbA1C at 6 and 12 mo follow-up in patients.
Common Presenting Problems

**Figure 9. Types of insulin preparation**

<table>
<thead>
<tr>
<th>Plasma Insulin Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glulisine, aspart, lispro</td>
</tr>
<tr>
<td>Regular</td>
</tr>
<tr>
<td>NPH</td>
</tr>
<tr>
<td>Glargine, detemir</td>
</tr>
</tbody>
</table>

**Figure 10. Management of hyperglycemia in type 2 diabetes**

**At diagnosis of Type 2 DM**

- **Start lifestyle intervention (nutrition therapy and physical activity) ± Metformin**

  - **A1C < 8.5%**
  - **A1C ≥ 8.5%**
  - **Symptomatic hyperglycemia with metabolic decompensation**

  **If not at glycemic target (2-3 mo)**
  - **Start or increase metformin**

  **If not at glycemic targets**
  - **Initiate insulin ± metformin**

**Add another agent best suited by prioritizing patient characteristics:**

**PATIENT CHARACTERISTIC**

- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obesity
- Cardiovascular disease
- Comorbidities (renal, CHF, hepatic)
- Preferences and access to treatment

**CHOICE OF AGENT**

- SGLT2 inhibitor with demonstrated CV outcome benefit

**Add another class of agent best suited to the individual (classes listed in alphabetical order):**

<table>
<thead>
<tr>
<th>Class</th>
<th>Relative A1C Lowering</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Effect in Cardiovascular Outcome Trial</th>
<th>Other Therapeutic Considerations</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosidase inhibitor (acarbose)</td>
<td>↓</td>
<td>Rare</td>
<td>Neutral to ↓</td>
<td>Improved postprandial control, GI side-effects</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>↓↓</td>
<td>Rare</td>
<td>Neutral to ↓</td>
<td>Neutral (aio, sava, sita)</td>
<td>Cautions with saxagliptin in heart failure</td>
<td>$$$</td>
</tr>
<tr>
<td>GLP-1R agonists</td>
<td>↑↓ to ↓↓</td>
<td>Rare</td>
<td>↑</td>
<td>Neutral (lixi)</td>
<td>GI side effects</td>
<td>$$$$</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓↓</td>
<td>Yes</td>
<td>↑</td>
<td>Neutral (glar)</td>
<td>No dose ceiling, flexible regimens</td>
<td>$-$$$$</td>
</tr>
<tr>
<td>Insulin secretagogue; Meglitinide</td>
<td>↓↓</td>
<td>Yes</td>
<td>↑</td>
<td>Neutral (glar)</td>
<td>Less hypoglycemia in context of missed meals, but usually requires TID to QID dosing</td>
<td>$</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>↓↓</td>
<td>Yes</td>
<td>↑</td>
<td>Neutral (glar)</td>
<td>Glutamine and gliptin associated with less hypoglycemia than glyburide</td>
<td>$</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>↓↓ to ↓↓</td>
<td>Rare</td>
<td>↓</td>
<td>Superior (empa in T2DM patients with clinical CVD)</td>
<td>Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia)</td>
<td>$$$</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>↓↓</td>
<td>Rare</td>
<td>↑↑</td>
<td>Neutral</td>
<td>CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 wk required for max effect</td>
<td>$</td>
</tr>
<tr>
<td>Weight loss agent (orlistat)</td>
<td>↓</td>
<td>None</td>
<td>↓</td>
<td>Neutral</td>
<td>GI side-effects</td>
<td>$$$$</td>
</tr>
</tbody>
</table>

**Note:** Physicians should refer to the most recent edition of the Compendium of Pharmaceuticals and Specialties (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information.

**Add another agent from a different class; add or intensify insulin regimen**

**Make timely adjustments to attain target A1C within 3-6 mo**

**Figure 11. Management of hyperglycemia in type 2 diabetes**

With permission of: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee Pharmacologic Management of Type 2 Diabetes. Can J Diabetes 2013;37(S61-S68)
Hypoglycemic Agents (Type 2 DM)

- **oral**
  - biguanide: metformin (GlucoPhage®)
  - thiazolidinedione: troglitazone (Rezulin®), rosiglitazone (Avandia®)
  - α-glucosidase inhibitor: acarbose (Precose®)
  - nonsulfonylureas: nateglinide (Starlix®), repaglinide (Gluconorm®)
  - sulfonylureas: glyburide (DiaBeta®), glimepiride (Amaryl®), gliclazide (Diamicron®)
  - DPP-4 inhibitor: sitagliptin (Januvia®)
- **injectable**
  - GLP-1 analogue: liraglutide (Victoza®)

Other Medications Used in DM

- ACEI or ARB in those with any of:
  - clinical macrovascular disease
  - age ≥55
  - age <55 and microvascular complications
- statin in those with any of:
  - clinical macrovascular disease
  - age ≥40
  - age <40 and any of the following:
    - diabetes duration >15 yr and age >30 yr
    - microvascular complications
    - other cardiovascular risk factors
- low dose ASA (81-325 mg)
  - for secondary prevention in people with established CVD (NOT to be used routinely for primary prevention)

**Dizziness**

- see **Otolaryngology, OT6**

**Epidemiology**

- 70% see general practitioners initially; 4% referred to specialists
- frequency proportional to age; commonest complaint of ambulatory patients age >75

**Differential Diagnosis**

- **Vertigo (vestibular)**
  - Objective (external world seems to revolve around individual) or subjective (individual revolves in space)
  - **Central (15%)**
    - Brainstem
    - Cerebellar
    - Tumour
    - Stroke
    - Drugs
    - Multiple sclerosis
  - **Peripheral (85%)**
    - Inner ear
    - Vestibular nerve
    - Idiopathic Menière’s
    - BPPV
    - Acoustic neuroma
    - Trauma
    - Drugs
    - Labyrinthitis
- **Psychogenic**
  - Diagnosis of exclusion
  - Feeling “light-headed,” “giddy,” “dazed,” “mentally confused,” or “disoriented”
  - **Vascular**
    - Etiology
    - Basilar migraine
    - TIA
    - Orthostatic hypotension
    - Stokes-Adams syndrome
    - Atrial fibrillation
    - CHF
    - Aortic stenosis
    - Vasovagal episodes
    - Metabolic causes
  - **Ocular**
    - Etiology
    - Decreased visual acuity

**Figure 11. Differential diagnosis of dizziness**

**History**

- clarify type of dizziness: vertigo, pre-syncope, disequilibrium, light-headedness
- duration
- exacerbations
  - worse with head movement or eye closure (vestibular)
  - no change with head movement and eye closure (nonvestibular)
  - worse with exercise (cardiac/pulmonary causes)
Common Presenting Problems

associated symptoms
- neurologic (central)
  - transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
  - persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)
- audiologic (peripheral)
  - hearing loss, tinnitus, otalgia, aural fullness
- others
  - N/V (peripheral vestibular disorders)
  - SOB, palpitations (hyperventilation, cardiac problem)
- general medical history
  - HTN, DM, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
  - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - hypotension (secondary to diuresis): furosemide, caffeine, alcohol
  - depression/anxiety: can present with light-headedness

Physical Exam/Investigations
- syncopal
  - cardiac (orthostatic changes in vitals), peripheral vascular, and neurologic exams
  - blood work, ECG, 24 h Holter, treadmill stress test, loop ECG, tilt table testing, carotid, and vertebral doppler, EEG
- vertiginous
  - ENT and neurologic exams
  - Dix-Hallpike, consider audiometry and MRI if indicated
- non-syncopal, non-vertiginous
  - assess gait, vision and test for neuropathy
  - cardiac and neurologic exams
  - 3 min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG
  - Romberg test: test for disequilibrium (patient sways towards the side of vestibular dysfunction)

Treatment
- guided by history, physical exam, and investigations
- include education, lifestyle modification, physical maneuvers (e.g. Epley for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy, and surgery
- refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or if atypical presentation

Domestic Violence/Elder Abuse

INTIMATE PARTNER VIOLENCE

Definition
- includes physical, sexual, emotional, psychological, and financial abuse (see Emergency Medicine, ER27)

Epidemiology
- lifetime prevalence of intimate partner violence against women is between 25-30%
- women who experience abuse have increased rates of injury, death, and health consequences including 50-70% increase in gynecological, central nervous system, stress-related problems
- occurs in all socioeconomic, educational, and cultural groups with increased incidence in pregnancy, disabled women, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where partner abuse occurs
- physician recognition rates as low as 5%

Presentation
- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

Management
- screen ALL patients
  - always have a high index of suspicion
  - asking about abuse is the strongest predictor of disclosure
  - several screening tools (see sidebar) exist to identify victims of partner violence
  - make sure to determine the victim's level of immediate and long-term danger and ask if there are weapons in the house
  - ensure patient safety
  - victim most at risk for homicide when attempting to leave home or following separation

Screening Instruments for Domestic Violence
A) Woman Abuse Screening Tool (WAST)-SHORT
1. In general how would you describe your relationship?
   a. A lot of tension
   b. Some tension
   c. No tension
2. Do you and your partner work out arguments with . . . ?
   a. Great difficulty
   b. Some difficulty
   c. No difficulty
Endorsing either question 1 (“a lot of tension”) or question 2 (“great difficulty”) makes intimate partner violence exposure likely

B) HITS
How often does your partner:
1. Physically hurt you?
2. Insult you?
3. Threaten you with harm?
4. Scream or curse at you?
Each question on HITS to be answered on a 5 point scale ranging from 1 (= never) to 5 (= frequently)
A total score of 10.5 is significant
Dyspepsia

- see Gastroenterology, G10

**Definition and Clinical Features**
- defined as epigastric pain or discomfort
- can be associated with fullness, belching, bloating, heartburn, food intolerance, N/V

**Epidemiology**
- annual incidence 1-2%, prevalence 20-40%

**Etiology**
- common: functional, PUD, GERD, gastritis
- others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

**History**
- symptoms may not be useful in finding cause
- associated with eating, anorexia, N/V, alcohol, NSAID use
- red flags: vomiting, bleeding/anemia, abdominal mass, dysphagia (VBAD)

**Investigations and Management**
- for new onset dyspepsia, test for *H. pylori* using the urea breath test or serology
- upper endoscopy (preferred), upper GI series (not in patients with alarm symptoms)
- lifestyle modifications: decreased caffeine and alcohol intake, avoid citrus food, avoid supine position right after meals, smoking cessation
- pharmacologic treatment
  - gastric acid suppression: H₂ blockers, PPIs; both are effective for PUD and GERD
  - prokinetics: e.g. Metoclopramide; effective for functional dyspepsia
  - *H. pylori* eradication
- do not keep patients on PPI without at least 1 trial off the medication per year (http://www.choosingwiselycanada.org/in-action/toolkits/bye-bye-ppi/)
- for non-responders, gastroscopy should be considered

**Dyspnea**

- see Respiratory, R3 and Emergency Medicine, ER26

**Definition**
- uncomfortable, abnormal awareness of breathing

**History and Physical Exam**
- history
  - cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema, SOB
  - asthma, allergy, eczema, ASA/NSAID sensitivity, nasal polyps
  - constitutional symptoms
  - smoking, recreational drugs, medications
  - occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  - travel and birth place
  - FHx of atopy
  - previous CXR or PFTs
- physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

**Dyspnea Bed Flags**
- Weight Loss
- Dysphagia
- Persistent vomiting
- GI bleeding (hematemesis, hematochezia, melena)
- Onset age >50

**H. pylori Eradication**
- Take the following 10 day treatment
  1) PPI 1 tablet 2x/d for 10 d and
  2) Amoxicillin 1 g twice a day for 5 d (day 1-5)
  Followed by
  3) Clarithromycin 500 mg 2x/d (day 6-10) and
  4) Metronidazole 500 mg 2x/d (day 6-10)

**Differential Diagnosis of Dyspnea**
- Pulmonary
  - COPD
  - Asthma
  - Restrictive lung disease
  - Pneumothorax
  - Congenital lung disease
  - PE
- Cardiac
  - CHF
  - CAD
  - MI (recent or past)
  - Cardiomyopathy
  - Valve dysfunction
  - Pericarditis
  - Arrhythmia
  - Hypertrophy
- Mixed/Other
  - Deconditioning
  - Trauma
  - Pain
  - Neuromuscular
  - Metabolic condition
  - Functional: anxiety, panic attack, hyperventilation

**ELDER ABUSE**
- see Geriatric Medicine, GM10

**How to Document Abuse**
- Take photographs (with permission) of proven or suspected injuries
- Use an injury location chart or “body map” when documenting physical findings
- Document any investigations ordered (e.g. x-ray)
- Write legibly or use a computer
- Record the patient’s own words in quotation marks
- Avoid phrases that imply doubt about the patient’s reliability (e.g. “patient claims that…”)
- Record the patient’s demeanor (e.g. upset, agitated)
- Record the time of day the patient is examined and how much time has elapsed since the abuse occurred

**RED FLAGS**
- vomiting, bleeding/anemia, abdominal mass, dysphagia (VBAD)

**Common Presenting Problems**
- see Geriatric Medicine, GM10

**How to Document Abuse**
- Take photographs (with permission) of proven or suspected injuries
- Use an injury location chart or “body map” when documenting physical findings
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**Dyspepsia Red Flags**
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- Dysphagia
- Persistent vomiting
- GI bleeding (hematemesis, hematochezia, melena)
- Onset age >50

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- Take the following 10 day treatment
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**Differential Diagnosis of Dyspnea**
- Pulmonary
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  - Congenital lung disease
  - PE
- Cardiac
  - CHF
  - CAD
  - MI (recent or past)
  - Cardiomyopathy
  - Valve dysfunction
  - Pericarditis
  - Arrhythmia
  - Hypertrophy
- Mixed/Other
  - Deconditioning
  - Trauma
  - Pain
  - Neuromuscular
  - Metabolic condition
  - Functional: anxiety, panic attack, hyperventilation
Investigations
- CXR, ECG
- FTTs, ABG acutely if indicated

Management
- ABCs: send to ED if in severe respiratory distress
- depends on cause

Dysuria
- see Urology, U10

Definition
- the sensation of pain, burning, or discomfort on urination

Epidemiology
- in adulthood, more common in women than men
- approximately 25% of women report one episode of acute dysuria per yr
- most common in women age 25-54 and in those who are sexually active
- in men, dysuria becomes more prevalent with increasing age

Etiology
- infectious
  - most common cause
  - presents as cystitis, urethritis, pyelonephritis, vaginitis, cervicitis, epididymo-orchitis, or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, radiation, drugs/chemicals, foreign bodies, trauma, neoplasm, kidney stones, inflammatory diseases, endometriosis, psychogenic

Table 14. Etiology, Signs and Symptoms of Common Causes of Dysuria

<table>
<thead>
<tr>
<th>Infection</th>
<th>Etiology</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI/Cystitis</td>
<td><em>KEEPs</em> bacteria (<em>Klebsiella, E. coli, Enterobacter, Proteus mirabilis, Pseudomonas, S. saprophyticus</em>)</td>
<td>Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)</td>
</tr>
<tr>
<td>Urethritis</td>
<td><em>C. trachomatis, N. gonorrhoeae, Trichomonas, Candida, herpes</em></td>
<td>Initial dysuria, urethral/vaginal discharge, history of STI</td>
</tr>
<tr>
<td>Vaginitis</td>
<td><em>Candida, Gardnerella, Trichomonas, C. trachomatis, atrophic, herpes, lichen sclerosis</em></td>
<td>External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding</td>
</tr>
<tr>
<td>Prostatitis</td>
<td><em>E. coli, C. trachomatis, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas</em></td>
<td>Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td><em>E. coli, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas</em></td>
<td>Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, N/V</td>
</tr>
</tbody>
</table>

Investigations
- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- urinalysis/dipstick: positive for nitrates and leukocytes
- urine R&M: pyuria, bacteriuria, hematuria
- urine C&S
- CBC and differential if suspecting pyelonephritis
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomonas, endocervical/urethral swab or urine PCR for N. gonorrhoeae and C. trachomatis
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P62 for UTI

Management
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic, due to increased risk of pyelonephritis, preterm labour, low birth weight and perinatal mortality; need to follow with monthly urine cultures and retreat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
  - urethritis
  - when swab or PCR is positive for chlamydia or gonorrhea must report to Public Health
  - all patients should return 4-7 d after completion of therapy for clinical evaluation

Cranberries for Preventing Urinary Tract Infections
Cochrane DB Syst Rev 2008;1:CD001321

Study: Meta-analysis of 10 RCTs (n=1,049).
Patients: All populations.
Intervention: Cranberry juice vs. placebo, juice or water was evaluated in seven studies, and cranberry tablets vs. placebo in four studies.
Main Outcome: UTIs – symptomatic and asymptomatic.
Results: Cranberry products significantly reduced the incidence of UTIs at 12 mo (OR 0.66, 95% CI 0.46-0.90) compared with placebo/control
Conclusion: There is some evidence that cranberry products may decrease the number of symptomatic UTIs over a 12 mo period, particularly for women with recurrent UTIs.

Prevention of UTIs
- Maintain good hydration (especially with cranberry juice) (recommendation level I)
- Wipe urethra from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse
Epistaxis

- see Otolaryngology, OT26

Erectile Dysfunction

- see Urology, U30

Definition

- consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance of ≥3 mo duration

Epidemiology

- ~20% of men age 40; ~50% of men age 70

Etiology

- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, DM), anatomic (structural abnormality, e.g. Peyronie’s), neurologic (post-operative, DM), medications (clonidine, antihypertensives, psychotropics)
- psychogenic (10%)

Table 15. Differentiation Between Organic and Psychogenic ED

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Organic</th>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Acute</td>
</tr>
<tr>
<td>Circumstances</td>
<td>Global</td>
<td>Situational</td>
</tr>
<tr>
<td>Course</td>
<td>Constant</td>
<td>Varying</td>
</tr>
<tr>
<td>Non-Coital Erection</td>
<td>Poor</td>
<td>Rigid</td>
</tr>
<tr>
<td>Morning Erection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Psychosexual Problem</td>
<td>Secondary</td>
<td>Long history</td>
</tr>
<tr>
<td>Partner Problem</td>
<td>Secondary</td>
<td>At onset</td>
</tr>
<tr>
<td>Anxiety and Fear</td>
<td>Secondary</td>
<td>Primary</td>
</tr>
</tbody>
</table>

Walsh PC, Campbell MF, Retik AB. Campbell’s Urology, 8th ed. W.B. Saunders, 2002. Table 46-4

History

- comprehensive sexual, medical, and psychosocial history
- time course
  - last satisfactory erection
  - gradual or sudden onset
  - attempts at sexual activity
- quantify
  - presence of morning or night time erections
  - stiffness (scale of 1-10)
  - ability to initiate and maintain an erection with sexual stimulation
  - erection stiffness during sex (scale of 1-10)
- qualify
  - partner or situation specific
  - loss of erection before penetration or climax
  - degree of concentration required to maintain an erection
  - percentage of sexual attempts satisfactory to patient and/or his partner
  - significant bends in penis or pain with erection
  - difficulty with specific positions
  - impact on quality of life and relationship

Investigations

- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: fasting glucose, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
  - psychological and/or psychiatric consultation
  - in-depth psychosexual and relationship evaluation
  - nocturnal penile tumescence and rigidity (NPTR) assessment
  - vascular diagnostics (e.g. doppler studies, angiography)

The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction

Arch Intern Med 2011;171:1797-1803

Purpose: To evaluate the effectiveness of lifestyle interventions and pharmacotherapy for cardiovascular (CV) risk factors on severity of erectile dysfunction (ED).

Methods: Meta-analysis of RCTs with a follow-up of a minimum of 6 weeks, evaluating lifestyle intervention versus pharmacotherapy for CV risk factor reduction. Main outcome measure was weighted mean differences in the International Index of Erectile Dysfunction (IIEF-5) score.

Results: 6 RCTs with a total of 740 participants were included. Lifestyle modifications and pharmacotherapy for CV risk factor reduction were both associated with significant improvements in sexual function based on IIEF-5 scores (weighted mean difference [WMD]: 2.98, 95% CI 1.86-4.10). Excluding trials with lifestyle interference and pharmacotherapy interventions were associated with a statistically significant improvement in sexual function (WMD: 2.04, 95% CI 1.19-2.87). Conclusions: Lifestyle modifications and pharmacotherapy for CV risk reduction are effective in improving male sexual function.
Management

### Table 16. Management of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
<th>Pharmacologic</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes (alcohol, smoking, exercise)</td>
<td>Oral agents</td>
<td>Implants</td>
</tr>
<tr>
<td>Relationship/sexual counselling</td>
<td>Suppository</td>
<td>Vascular repair</td>
</tr>
<tr>
<td>Vacuum devices</td>
<td>Male urethral suppository for erection (MUSE)</td>
<td>Realignments</td>
</tr>
<tr>
<td></td>
<td>Injections</td>
<td></td>
</tr>
</tbody>
</table>

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors
  - α-adrenergic blockers (e.g. yohimbine)
  - serotonin antagonist and reuptake inhibitor (e.g. trazodone)
  - testosterone – currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications)

### Table 17. Phosphodiesterase Type 5 Inhibitors

<table>
<thead>
<tr>
<th>Examples</th>
<th>Dosing (1 dose/d)</th>
<th>Specifics</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil (Viagra®)</td>
<td>25-100 mg/dose</td>
<td>Take 0.5-4 h prior to intercourse</td>
<td>Flushing, headache, indigestion</td>
<td>Not to be used in patients taking nitrates</td>
</tr>
<tr>
<td>tadalafil (Cialis®)</td>
<td>5-20 mg/dose</td>
<td>Effects may last 36 h</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>vardenafil (Levitra®)</td>
<td>2.5-20 mg/dose</td>
<td>Take 1 h prior to intercourse</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>

Fatigue

### Epidemiology

- 25% of office visits to family physicians
  - peaks in ages 20-40
  - F:M = 3-4:1
- 50% have associated psychological complaints/problems, especially if <6 mo duration

### Differential Diagnosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>P Psychogenic</td>
<td>Depression, life stresses, anxiety disorder, chronic fatigue syndrome, fibromyalgia</td>
</tr>
<tr>
<td>S Sleep disturbance</td>
<td>Obstructive sleep apnea, sleep disorder, poor sleep hygiene, BPH, shift work, pain</td>
</tr>
<tr>
<td>V Vascular</td>
<td>Stroke</td>
</tr>
<tr>
<td>I Infectious</td>
<td>Viral (e.g. mononucleosis, hepatitis, HIV), bacterial (e.g. TB), fungal, parasitic</td>
</tr>
<tr>
<td>N Neoplastic</td>
<td>Any malignancy</td>
</tr>
<tr>
<td>D Drugs</td>
<td>β-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics, antidepressants</td>
</tr>
<tr>
<td>I Idiopathic</td>
<td></td>
</tr>
<tr>
<td>C Chronic illnesses</td>
<td>CHF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease</td>
</tr>
<tr>
<td>A Autoimmune</td>
<td>SLE, RA, mixed connective tissue disease, polymyalgia rheumatica</td>
</tr>
<tr>
<td>T Toxic</td>
<td>Substance abuse (e.g. alcohol), heavy metal</td>
</tr>
<tr>
<td>E Endocrine</td>
<td>Hypothyroidism, DM, Cushing’s syndrome, adrenal insufficiency, pregnancy</td>
</tr>
</tbody>
</table>

Common causes are in **bold**

### Investigations

- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical exam
- investigations should be guided by history and physical exam and may include:
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vitamin B₁₂, serum protein electrophoresis, Bence-Jones protein, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - urinalysis, CXR, ECG
  - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests
Common Presenting Problems

Treatment
- treat underlying cause
- if etiology cannot be identified (1/3 of patients)
  - reassurance and follow-up, especially with fatigue of psychogenic etiology
  - quick follow-up for reassurance
  - supportive counselling, behavioural, or group therapy
  - encourage patient to stay physically active to maximize function
  - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
- prognosis: after 1 yr, 40% are no longer fatigued

CHRONIC FATIGUE SYNDROME

Definition (CDC 2006) – must meet both criteria
1. new or definite onset of unexplained, clinically evaluated, persistent or relapsing chronic fatigue, not relieved by rest, which results in occupational, educational, social, or personal dysfunction
2. concurrent presence of ≥4 of the following symptoms for a minimum of 6 mo
   - impairment of short-term memory or concentration, severe enough to cause significant decline in function
   - sore throat
   - tender cervical or axillary lymph nodes
   - muscle pain
   - multi-joint pain with no swelling or redness
   - new headache
   - unrefreshing sleep
   - post-exertion malaise lasting >24 h
- exclusion criteria: medical conditions that may explain the fatigue, certain psychiatric disorders (depression with psychotic or melancholic features, schizophrenia, eating disorders), substance abuse, severe obesity (BMI >45)

Epidemiology
- F>M, Caucasians > other groups, majority in their 30s
- found in <5% of patients presenting with fatigue

Etiology
- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency

Investigations
- no specific diagnostic laboratory tests

Treatment
- promote sleep hygiene
- provide support and reassurance that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy (e.g. CBT), family therapy, support groups
- pharmacological
  - to relieve symptoms e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials, antiallergy therapy, antihypotensive therapy

Fever
- see Pediatrics, P46

Definition
- oral temperature >37.2°C (AM), 37.7°C (PM)
- fever in children under 2 must be a rectal temperature for accuracy
- TM not accurate for measurement until child is >5 yr

Table 19. Differential Diagnosis of Fever

<table>
<thead>
<tr>
<th>Infection</th>
<th>Cancer</th>
<th>Medications</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Leukemia</td>
<td>Allopurinol</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Viral</td>
<td>Lymphoma</td>
<td>Captopril</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>TB</td>
<td>Other Malignancies</td>
<td>Cimetidine</td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heparin</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INH</td>
<td>Antihistamines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meperidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Irritable Bowel Syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Collagen Vascular Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DVT</td>
</tr>
</tbody>
</table>
Common Presenting Problems

History
- fever
  - peak temperature, thermometer, route, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
  - symptoms of possible source
    - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
    - pneumonia: cough, pleuritic chest pain
    - URTI: cough, coryza, ear pain
    - meningitis: headache, confusion, stiff neck, rash
    - osteomyelitis: bone pain
    - skin: purulent discharge
    - PID: discharge, dyspareunia, lower abdominal pain
    - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
    - medications
      - PE/DVT: swollen legs, pain in calf, SOB, pleuritic chest pain
      - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, day care, contact with TB, foodborne, animals

Possible Investigations
- CBC and differential, blood culture, urine culture, urinalysis
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- LP

Management
- increase fluid intake
- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause

Headache
- see Neurology, N44

Primary Headaches

Table 20. Primary Headaches

<table>
<thead>
<tr>
<th>Migraine</th>
<th>Tension-Type</th>
<th>Cluster</th>
<th>Caffeine Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>12% of adults</td>
<td>38% of adults, can be episodic or chronic</td>
<td>&lt; 0.1% of adults, M &gt; F</td>
</tr>
<tr>
<td>Duration</td>
<td>5-72 h</td>
<td>May occur as isolated incident or daily, duration is variable</td>
<td>&lt; 3 h at same time of day</td>
</tr>
<tr>
<td>Pain</td>
<td>Classically unilateral and pulsatile, but 40% are bilateral, moderate-severe intensity, N/V, photo-/phonophobia</td>
<td>Mild to moderate pain, bilateral, fronto-occipital or generalized pain, band-like pain, ± contracted neck, scalp muscles, associated with little disability</td>
<td>Sudden, unilateral, severe, usually centred around eye, frequently awakens patient, Associated conjunctival injection and tearing, “Suicide” headache</td>
</tr>
<tr>
<td>Triggers</td>
<td>Numerous (e.g. food, sleep disturbance, stress, hormonal, fatigue, weather, high altitude) Aggravated by physical activity</td>
<td>Stressful events NOT aggravated by physical activity</td>
<td>Often alcohol</td>
</tr>
<tr>
<td>Treatment of Acute Headache</td>
<td>1st line: acetaminophen, NSAIDs, ASA ± caffeine</td>
<td>Rest and relaxation</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td></td>
<td>2nd line: NSAIDs</td>
<td>Dihydroergotamine</td>
<td>High-flow O2</td>
</tr>
<tr>
<td></td>
<td>3rd line: 5-HT agonists</td>
<td>Intranasal lidocaine</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Treatment of Prophylactic Therapy</td>
<td>1st line: β blockers</td>
<td>Rest and relaxation, physical activity, biofeedback</td>
<td>Lithium carbonate</td>
</tr>
<tr>
<td></td>
<td>2nd line: TCAs</td>
<td>Prednisone</td>
<td>Methysergide</td>
</tr>
<tr>
<td></td>
<td>3rd line: antimetics</td>
<td></td>
<td>Cut down on caffeine</td>
</tr>
</tbody>
</table>

Secondary Headaches
- caused by underlying organic disease
- account for <10% of all headaches, may be life-threatening
Etiology
- aneurysm
- medication overuse headache
- space-occupying lesion
- systemic infection (meningitis, encephalitis)
- stroke
- subarachnoid hemorrhage
- systemic disorders (thyroid disease, HTN, pheochromocytoma, etc.)
- temporal arteritis
- traumatic head injuries
- TMJ or C-spine pathology
- serious ophthalmological and otolaryngological causes of headache

Investigations
- indicated only when red flags are present and may include:
  - CBC for suspected systemic or intracranial infection
  - ESR for suspected temporal arteritis
  - neuroimaging (CT or MRI) to rule out intracranial pathology
  - CSF analysis for suspected intracranial hemorrhage, infection

Management
- based on underlying disorder
- analgesics may provide symptomatic relief

Hearing Impairment

Definition
- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

Epidemiology
- prevalence increases with age (6% of 35–44 yr old, 43% of 65-84 yr old)
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people >65 yr

Classification
- conductive (external sound does not reach the middle ear)
- sensorineural involving the inner ear, cochlea or auditory nerve
- mixed

Assessment
- universal newborn hearing screening program in infants
- elderly
  - presbycusis is characterized by the progressive, symmetric loss of high-frequency hearing
  - tinnitus, vertigo, and disequilibrium may be present
  - can cause low self-esteem, isolation, and depression
  - whispered-voice test
  - whisper 6 test words 6 in-2 ft away from the patient’s ear out of the visual field, ask patient to repeat the words (with non-test ear distraction)
  - tuning fork test (to distinguish conductive from sensorineural hearing loss)
  - Rinne and Weber (not for general screening)
  - formal audiologic assessment
  - pure tone, air, and bone conduction testing
  - speech audiometry
  - impedance audiometry

Management
- counsel about noise control and hearing protection programs (Grade A evidence)
- investigations in patients with unexplained sensorineural hearing loss
  - blood sugar, CBC and differential, TSH, syphilis testing
- referral
  - refer patients with hearing loss for a complete audiological examination, and to ENT if etiology unknown
  - sudden sensorineural hearing loss: high dose oral steroids and urgent ENT referral
  - patients with progressive asymmetric sensorineural hearing loss should have an MRI/CT scan to exclude vestibular schwannoma (acoustic neuroma)
  - hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life
Hypertension

Hypertension Guidelines are reviewed and updated annually, for up-to-date recommendations, please see www.hypertension.ca/chep

Epidemiology

- 22% of Canadian adults suffer from HTN (prevalence is 52% in the 60-70 age group)
- lifetime risk of developing hypertension is approximately 90%
- 64% of Canadians who have HTN are treated and controlled, while 17% are unaware that they have HTN
- 3rd leading risk factor associated with death
  - risk factor for CAD, CHF, cerebrovascular disease, renal failure, peripheral vascular disease

Definitions

- HTN
  - BP ≥140/90 mmHg, unless DM (≥130/80 mmHg), or age ≥80 yr (≥150/90 mmHg)
- isolated systolic HTN
  - sBP ≥140 and dBP <90
  - associated with progressive reduction in vascular compliance
  - usually begins in 5th decade
- hypertensive urgency
  - sBP >210 or dBP >120 with minimal or no target organ damage
- hypertensive emergency
  - severe HTN (dBP > 120) + acute target-organ damage
- accelerated HTN
  - significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy, but without papilledema
- malignant HTN
  - sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
- white coat hypertension
  - high clinic BP with normal home BP and 24 ambulatory BP, caused by anxiety in clinic
- masked hypertension
  - normal clinic BP with high BP in home and/or ambulatory setting, often provoked by anxiety, job stress, exercise

Etiology

- essential (primary) HTN (>90%)
- undetermined cause
- secondary HTN (10%)

Predisposing Factors

- family history
- obesity (especially abdominal)
- alcohol consumption
- stress
- sedentary lifestyle
- smoking
- male
- age >30
- excessive salt intake/fatty diet
- African American ancestry
- dyslipidemia

Table 21. Causes of Secondary HTN

<table>
<thead>
<tr>
<th>Common Cause</th>
<th>Renovascular HTN</th>
<th>Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>1° hyperaldosteronism</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Pheochromocytoma</td>
<td>Renal artery stenosis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Cushing’s syndrome</td>
<td>Acute aortic dissection</td>
</tr>
<tr>
<td>Drug-Induced</td>
<td>Hypertensive encephalopathy</td>
<td>Acute refractory LV failure</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>Myocardial infarction/ischemia</td>
</tr>
<tr>
<td></td>
<td>Intracerebral hemorrhage</td>
<td>Acute pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>SAH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute aortic dissection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute refractory LV failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction/ischemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td></td>
</tr>
</tbody>
</table>

Investigations

- for all patients with HTN
  - electrolytes, Cr, fasting glucose and/or HbA1c, lipid profile, 12-lead ECG, urinalysis
  - self-measurement of BP at home is encouraged (recommended devices listed at www.hypertension.ca)
- for specific patient subgroups
  - DM or chronic kidney disease: urinary protein excretion
  - if suspected renovascular HTN: renal ultrasound, captopril renal scan (if GFR >60 mL/min), MRA/CTA (if normal renal function)
- if suspected endocrine cause: plasma aldosterone, plasma renin (aldosterone-to-renin ratio)
  - measured from morning samples taken from patients in sitting position after resting 15 min
  - discontinue aldosterone antagonists, ARBs, β-blockers and clonidine prior to testing
- if suspected pheochromocytoma: 24 h urine for metanephrines and creatinine
  - echocardiography for left ventricular dysfunction assessment if indicated

**Diagnosis**
- all Canadian adults should have BP assessed at all appropriate clinical visits, oscillometric preferred to manual

---

**Impact of Health Behaviour on Blood Pressure**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and weight control</td>
<td>-6.0</td>
<td>-4.8</td>
</tr>
<tr>
<td>Reduced salt intake</td>
<td>-5.4</td>
<td>-2.8</td>
</tr>
<tr>
<td>Reduced alcohol intake (heavy drinkers)</td>
<td>-3.4</td>
<td>-3.4</td>
</tr>
<tr>
<td>DASH diet</td>
<td>-11.4</td>
<td>-5.5</td>
</tr>
<tr>
<td>Physical activity</td>
<td>-3.1</td>
<td>-1.8</td>
</tr>
<tr>
<td>Relaxation therapies</td>
<td>-3.7</td>
<td>-3.5</td>
</tr>
</tbody>
</table>


**β-blocker**
- Not recommended as first line for patients of age ≥60

**ACEI**
- Not recommended as monotherapy in people of African descent
<table>
<thead>
<tr>
<th>Condition or Risk Factor</th>
<th>Recommended Drugs</th>
<th>Alternative Drugs</th>
<th>Not Recommended/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated Dystonic HTN</td>
<td>Thiazide diuretic, β-blocker, ACEI, ARB, or long-acting CCB (consider ASA and statin in select patients)</td>
<td>Nifedipine, amlodipine, felodipine</td>
<td>β-blocker monotherapy (age &gt;60) or combination of ACEI with an ARB</td>
</tr>
<tr>
<td>Isolated Systolic HTN</td>
<td>Thiazide diuretic, ARB, or long-acting dihydropyridine CCB</td>
<td>Combinations of first-line drugs</td>
<td>Same as above</td>
</tr>
<tr>
<td>CAD</td>
<td>ACEI or ARB; β-blocker for patients with stable angina</td>
<td>Long acting CCB, when combination therapy for high risk patients, ACEI/DHP CCB is preferred</td>
<td>Short-acting CCB (nifedipine) or ACEI and ARB is not recommended dBP 60 mmHg may exacerbate MI</td>
</tr>
<tr>
<td>Prior MI</td>
<td>β blocker and ACEI (ARB if cannot tolerate ACEI)</td>
<td>Long-acting CCB</td>
<td>ACEI and ARB combination is not recommended</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy</td>
<td>ACEI, ARB, thiazide, or long-acting CCB</td>
<td>Hydralazine and minoxidil</td>
<td>Combination of additional agents</td>
</tr>
<tr>
<td>Cerebrovascular Disease (stroke/TIA)</td>
<td>ACEI and diuretic</td>
<td>Comb nation of additional agents</td>
<td>ACEI and ARB combination after a stroke is not recommended</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>ACEI (ARB if ACEI intolerant) and β-blocker</td>
<td>ARB in addition to ACEI</td>
<td>Non-DHP CCB not recommended</td>
</tr>
<tr>
<td>Dyslipidemias</td>
<td>Does not affect initial treatment recommendations</td>
<td>Combination of additional agents</td>
<td>Carefully monitor for side effects if using ACEI and ARB</td>
</tr>
<tr>
<td>DM with Albuminuria</td>
<td>ACEI or ARB (DHP CCB &gt; hydrochlorothiazide (HCTZ) for combination therapy with ACEI)</td>
<td>Add thiazide diuretic cardioselective β-blocker, long acting CCB</td>
<td>If serum Cr &gt; 150 µmol/L, a loop diuretic should be considered instead of low-dose thiazide diuretic</td>
</tr>
<tr>
<td>DM without Albuminuria</td>
<td>ACEI, ARB, DHP CCB, or thiazide diuretic</td>
<td>Combination of first-line drugs or first-line agents not tolerated, cardioselective β-blocker or non-DHP CCB</td>
<td>ACEI and ARB combination not recommended</td>
</tr>
<tr>
<td>Non-Diabetic Chronic Kidney Disease with Proteinuria (urinary protein &gt;500 mg/24 h or ACR &gt;30 mg/mmol)</td>
<td>ACEI (ARB if ACEI intolerant), diuretic as additive therapy</td>
<td>Thiazide for additive antihypertensive therapy, loop diuretic for volume overload</td>
<td>ACEI and ARB combination is not recommended</td>
</tr>
<tr>
<td>Renovascular Disease</td>
<td>Same as HTN without other indications</td>
<td>Caution in using ACEI or ARB – monitor for AKI</td>
<td>Caution in using ACEI or ARB – monitor for AKI Renal angioplasty and stenting offer no benefits over optimal medical therapy alone</td>
</tr>
<tr>
<td>Asthma</td>
<td>K+-sparing and thiazide diuretic for patients on salbutamol</td>
<td>β-blocker, unless specific indications like angina or post-MI</td>
<td>Thiazide, but asymptomatic hyperuricemia is not a contraindication</td>
</tr>
<tr>
<td>Gout</td>
<td>Thiazide, but asymptomatic hyperuricemia is not a contraindication</td>
<td>Similar</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Low dose thiazide ACEI</td>
<td>β-blocker</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Methyldopa Hydralazine</td>
<td>Labetolol Nifedipine</td>
<td>ACEI</td>
</tr>
<tr>
<td>Elderly (&gt;60 yr)</td>
<td>As for uncomplicated isolated diastolic HTN, except for use of β-blocker</td>
<td>β-blocker not recommended as first line treatment</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>BP &gt; 169/90 = labetolol, nifedipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If &gt;3 Cardiovascular Risk Factors or Established Atherosclerotic Disease</td>
<td>Statin (age &gt;40), low-dose ASA (age &gt;50)</td>
<td>Caution with use of ASA in patients with uncontrolled BP</td>
<td></td>
</tr>
</tbody>
</table>

Follow-Up
- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification q3-6m
- pharmacological
  - q1-2mo until BP under target for 2 consecutive visits
  - more often for symptomatic HTN, severe HTN, antihypertensive drug intolerance, target organ damage
  - q3-6mo once at target BP
- referral is indicated for cases of refractory HTN, suspected secondary cause or worsening renal failure
- hospitalization is indicated for malignant HTN

Joint Pain
- see Rheumatology, RH3

Table 23. Differential Diagnosis of Joint Pain

<table>
<thead>
<tr>
<th>Non-Articular</th>
<th>Generalized</th>
<th>Inflammatory</th>
<th>Articular</th>
<th>Degenerative</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bursts</td>
<td>Fibromyalgia</td>
<td>Seropositive</td>
<td>Primary</td>
<td></td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Tendonitis</td>
<td>Polymyalgia rheumatica</td>
<td>RA</td>
<td>Familial Heberden's node</td>
<td>Drug-induced</td>
<td></td>
</tr>
<tr>
<td>Capsulitis</td>
<td>Myofascial pain syndrome</td>
<td>Systemic lupus erythematosus</td>
<td>Osteoarthritis</td>
<td>Endocrine (hyperthyroid, hypothyroid, hyperparathyroid)</td>
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<td></td>
<td></td>
<td>Scleroderma</td>
<td>Regional hip or knee</td>
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<td></td>
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<td>Polymyositis/Dermatomyositis</td>
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<td></td>
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<td>Sjögren's syndrome</td>
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<td>Seronegative</td>
<td>Secondary</td>
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<td></td>
<td></td>
<td>Ankylosing spondylitis</td>
<td>Metabolic</td>
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<td>Inflammatory bowel disease</td>
<td>Hemophilia</td>
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<td>Psoriatic arthritis</td>
<td>Neuropathic</td>
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<td>Reactive arthritis</td>
<td>Traumatic</td>
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<td></td>
<td></td>
<td>Crystal</td>
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<td></td>
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<td>Gout</td>
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<td></td>
<td></td>
<td>Pseudogout</td>
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<td>Hydroxyapatite</td>
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<td>Infectious/septic</td>
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<td>Gonococcal</td>
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<td>Non-gonococcal</td>
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<td></td>
<td></td>
<td>Systemic vasculitis disease</td>
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</table>

History
- number of joints involved: monoarticular, oligoarticular, polyarticular
- pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
- onset: acute vs. chronic (>6 wk)
- trauma, infection, medications (steroids, diuretics)
- morning stiffness (duration) vs. worse at end of day
- FHx of arthritis
- comorbidities: DM (carpal tunnel syndrome), renal insufficiency (gout) psoriasis (psoriatic arthritis), myeloma (low back pain), osteoporosis (fracture), obesity (OA)
- constitutional symptoms (neoplasms)

Physical Exam
- vitals
- specific joint exams
- systemic features (skin, nails, eyes, hands)

Investigations (Guided by the History and Physical Exam)
- general: CBC and differential, electrolytes, Cr
- acute phase reactants: ESR, CRP, ferritin, albumin, fibrinogen
- complement (C3, C4)
- urinalysis to detect disease complications (proteinuria, active sediment)
- serology (ANA, anti-dsDNA, HLA-B27, anti-Jo-1, anti-Sm, anti-La, anti-Ro, RhF and anti-CCP, etc.)
- synovial fluid analysis (cell count + differential, culture, Gram stain, microscopy)
- tissue cultures
- radiology (plain film, CT, MRI, U/S, bone densitometry, angiography, bone scan)

Treatment
- patient education including lifestyle modifications
- physiotherapy, occupational therapy
- manage pain (acetaminophen, NSAIDs)
- treat specific causes (e.g. antibiotics, DMARDs etc., see Rheumatology, RH26)
Low Back Pain

- see Orthopedics, OR25

Definition
- acute: <6 wk
- subacute: 6-12 wk
- chronic: >12 wk

Epidemiology
- 5th most common reason for visiting a physician
- lifetime prevalence: 90%, and peak prevalence: age 45-60
- largest WSIB category, and most common cause of chronic disability for individuals <45 yr old
- 90% resolve in 6 wk, <5% become chronic

Etiology
- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes
  - pain is worse with movement, better with rest
  - sprain (ligament), strain (muscle), facet joint degeneration, disc degeneration/herniation, spinal stenosis (e.g. spondylosis), spondylolisthesis compression fracture, pregnancy
- 2% are non-mechanical causes
  - surgical emergencies
    - cauda equina syndrome (areflexia, lower extremity weakness, decreased anal tone, saddle anesthesia, fecal incontinence, urinary retention), AAA (pulsatile abdominal mass)
  - medical conditions
    - neoplastic (primary, metastatic, multiple myeloma)
    - infectious (osteomyelitis, TB)
    - metabolic (osteoporosis, osteomalacia, Paget’s disease)
    - rheumatologic (ankylosing spondylitis, polymyalgia rheumatica)
    - referred pain (perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster)

Physical Exam
- inspection: curvature, posture, gait
- palpation: bony deformities/tenderness, paraspinal muscle bulk/tenderness, trigger points
  - percussion of spine to elicit pain due to fracture or infection
- ROM and peripheral pulses
- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes, sensation)
- special tests
  - straight leg raise (positive if pain at <70 degrees and aggravated by ankle dorsiflexion), positive test is indicative of sciatica
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy

Investigations
- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI

Red Flags
- Bowel or bladder dysfunction
- Anesthesia (saddle)
- Constitutional symptoms/malignancy
- Chronic disease
- Paraparetic
- Age >50 and mild trauma
- IV drug use/Infection
- Neuromotor deficits

Indications for Lumbar Spine X-Ray
- No improvement after 6 wk
- Fever >38°C
- Unexplained weight loss
- Prolonged corticosteroid use
- Significant trauma
- Progressive neurological deficit
- Suspicion of ankylosing spondylitis
- History of cancer (rule out metastases)
- Alcohol/drug abuse (increased risk of osteomyelitis, trauma fracture)
A Summary of the Guideline for the Evidence-Informed Primary Care Management of Low Back Pain

This evidence-informed guideline is for non-specific, non-fragile low back pain in adults only.

Red Flags help identify rare, but potentially serious conditions. They include:
- Features of Cauda Equina Syndrome including sudden onset of loss of bladder/bowel control, saddle anesthesia (EMERGENCY)
- Severe worsening pain, especially at night or when lying down (URGENT)
- Significant trauma (URGENT)
- Weight loss, history of cancer, fever (URGENT)
- Use of steroids or intravenous drugs (URGENT)
- Patient with first episode over 50 years old, especially over 65 (SOON)
- Widespread neurological signs (SOON)

Yellow Flags* indicate psychosocial barriers to recovery. They include:
- Belief that pain and activity are harmful
- “Stirnness behaviors” (like extended rest)
- Low or negative mood, social withdrawal
- Treatment expectations do not fit best practice
- Problems with claim and compensation
- History of back pain, time-off, other claims
- Problems at work, poor job satisfaction
- Heavy work, unachievable hours (shift work)
- Depressive or family lack of support

Conduct a full assessment including:
- History taking
- Physical and neurological exam
- Evaluate on 9 Red Flags
- Psychosocial risk factors/ Yellow Flags

Any Red Flags?

Consider referring for evaluation and treatment (e.g., emergency room, surgical evaluation, relevant specialists)

Consider referring for evaluation and treatment (e.g., emergency room, surgical evaluation, relevant specialists)

Reasons (including Red Flags) if patient is not returning to normal function or symptoms are worsening

No irritative findings ± conduction loss

Not better with position changes

No change or worsens with extension

Improves with position changes

Dysphoric or family lack of support

Spinal Manipulative Therapy (SMT) for Acute Low-Back Pain

Cochrane Database Syst Rev 2012;19:CD008840

Purpose: To evaluate spinal manipulative therapy (SMT) for acute low back pain.

Methods: Meta-analysis of RCTs examining effectiveness of SMT (hands-on therapy directed towards spine, including both manipulation and mobilization) in adults with acute low back pain (pain lasting < 6 weeks). Studies involving patients with predominantly low back pain but radiating into the buttocks and legs were also included. Primary outcomes were back pain, back pain-specific functional status and recovery.

Results: 20 RCTs involving 1,674 participants were included. Low to very low quality evidence suggested no difference in effect for SMT compared to inert interventions, sham SMT or as an adjunct to another intervention, for the primary outcomes. Side-lying and supine thrust SMT techniques demonstrated a short-term significance difference when compared to non-thrust SMT techniques for outcomes of pain, functional status and recovery. Conclusions: SMT is not more effective than inert interventions, sham SMT or as an adjunct to another intervention for patients with acute low back pain, and does not appear any better than other recommended therapies either. Decision to refer patients for SMT should be based on costs, patient and provider preferences, and the relative safety of SMT relative to other treatment options.

Table 24. Approach to Non-Traumatic Low Back Pain

<table>
<thead>
<tr>
<th>Back Dominant (Pain greatest above gluteal fold)</th>
<th>Leg Dominant (Pain greatest below gluteal fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td><strong>Physical Exam</strong></td>
</tr>
<tr>
<td>Pattern 1 Worse with flexion Constant/intermittent</td>
<td>Normal neuro exam Fast responder</td>
</tr>
<tr>
<td>Pattern 2 Worse with extension Never worse with flexion Always intermittent</td>
<td>Normal neuro exam ± improves with flexion Worse with extension</td>
</tr>
<tr>
<td><strong>Likely Pathology</strong></td>
<td><strong>Initial Management</strong></td>
</tr>
<tr>
<td>Arising from intervertebral discs or adjacent ligaments</td>
<td>Scheduled extension Lumbar roll Night lumbar roll Medication as required</td>
</tr>
<tr>
<td>Posterior joint complex (associated ligaments and capsular structures)</td>
<td>Scheduled flexion Limited extension Night lumbar roll Medication as required</td>
</tr>
<tr>
<td><strong>Pattern 3</strong> Pain changes with back movement/position Currentlly/previously constant</td>
<td>Protrusion extension</td>
</tr>
<tr>
<td>Leg pain can improve but not disappear Positive straight leg raise ± conduction loss</td>
<td>Supine “Z” lie</td>
</tr>
<tr>
<td>Fast responder</td>
<td>Lumbar roll</td>
</tr>
<tr>
<td>Improves with specific back position</td>
<td>Night lumbar roll</td>
</tr>
<tr>
<td>Slower responder</td>
<td>Medication as required</td>
</tr>
</tbody>
</table>


Figure 13. Low back pain treatment
Menopause/Hormone Replacement Therapy

- see Gynecology, GY34

Epidemiology
- mean age of menopause = 51.4 yr

Clinical Features
- associated with estrogen deprivation
- urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
- blood vessels and heart: vasomotor instability (e.g. hot flashes), increased risk of heart disease
- bones: bone loss, joint/muscle/back pain, fractures, loss of height
- brain: depression, irritability, mood swings, memory loss

Management
- encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1,200-1,500 mg/d) and vitamin D (800-2,000 IU/d)
- hormone replacement therapy (HRT)
  - prescribe for moderate to severe symptoms for no longer than 5 yr; routine use is not recommended
  - regimens: cyclic estrogen-progesterin, continuous estrogen-progesterin, estrogen only (if no uterus), estrogen patch/gel/cream/ring/vaginal tablet
- increases risk of osteoporotic fractures, colorectal cancer
- increases risk of breast cancer, coronary heart disease, stroke, DVT, and PE
- initiation of HRT requires a thorough discussion of short- and long-term benefits and risks
- consider venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

Osteoarthritis

- see Rheumatology, RH5

Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, peri-articular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (OT/PT), assistive devices (e.g. canes, orthotics, raised toilet seats)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs in the lowest effective dose for the shortest duration of time, along with gastroprotection; COX-2 selective inhibitors (celecoxib/Celebrex®, Meloxicam/Mobicox®) are recommended if long-term treatment or if high risk for serious GI problems
  - combination analgesics (e.g. acetaminophen and codeine)
  - intra-articular hyaluronic acid injections
  - intra-articular corticosteroid injections (no more than 3-4x/yr) may be helpful in acute flares (benefits last 4-6 wk, can be up to 6 mo)
  - topical NSAID (diclofenac/Pennsaid®)
  - capsaicin cream (Zostrix®)
  - oral glucosamine
- surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)

Glanosamine Therapy for Treating Osteoarthritis


**Purpose:** To evaluate the effectiveness and toxicity of glucosamine in osteoarthritis (OA) treatment.

**Methods:** Meta-analysis of RCTs evaluating effectiveness and safety of glucosamine relative to other interventions or placebo in OA treatment.

**Results:** 20 analyzed RCTs found glucosamine was superior to placebo with a 28% improvement in pain (standardized mean difference (SMD) -0.61, 95% CI -0.95 to -0.28) and a 21% improvement in function using the Lequesne index (SMD -0.51, 0.96 to 0.06). No statistically significant difference was found in terms of WOMAC pain, function and stiffness. In trials comparing a Rotta preparation of glucosamine to placebo, a statistically significant improvement in pain (SMD -1.31, -1.89 to -0.64) and function using the Lequesne index (SMD -0.51, -0.96 to 0.05) was seen, whereas those using a non-Rotta preparation did not show a significant difference for pain (SMD -0.15, -0.39 to 0.05) or function (SMD 0.02, -0.18 to 0.26). Compared to NSAIDs, Rotta preparation of glucosamine was found to be superior in 2 studies, showing slowing of radiological progression of knee OA over 3 years (SMD -0.24, 0.04 to 0.40), and equivalent in 1 study. Glucosamine was found to be comparable to placebo in number of participants reporting adverse reactions (risk ratio (RR) 0.91, 0.88 to 1.00).

**Conclusion:** While non-Rotta preparation of glucosamine did not show benefit in pain and WOMAC function, Rotta preparation was superior in placebo in treating pain and functional impairment associated with symptomatic OA. WOMAC pain, stiffness and function did not show significant differences between glucosamine and placebo for either glucosamine preparation. Glucosamine was found to be equally safe compared to placebo.

Common Presenting Problems

- see Family Medicine, FM40

Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, peri-articular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (OT/PT), assistive devices (e.g. canes, orthotics, raised toilet seats)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs in the lowest effective dose for the shortest duration of time, along with gastroprotection; COX-2 selective inhibitors (celecoxib/Celebrex®, Meloxicam/Mobicox®) are recommended if long-term treatment or if high risk for serious GI problems
  - combination analgesics (e.g. acetaminophen and codeine)
  - intra-articular hyaluronic acid injections
  - intra-articular corticosteroid injections (no more than 3-4x/yr) may be helpful in acute flares (benefits last 4-6 wk, can be up to 6 mo)
  - topical NSAID (diclofenac/Pennsaid®)
  - capsaicin cream (Zostrix®)
  - oral glucosamine
- surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)
Osteoporosis

- see Endocrinology, E40

Encourage basic bone health for all individuals over age 50, including regular active weight-bearing exercise, calcium (diet and supplements) 1,200 mg daily, vitamin D 800-2,000 IU (20-50 µg) daily and fall-prevention strategies.

<table>
<thead>
<tr>
<th>Age &lt; 50 yr</th>
<th>Age 50-64 yr</th>
<th>Age ≥65 yr</th>
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</thead>
<tbody>
<tr>
<td>Fragility fractures</td>
<td>Fragility fracture after age 40</td>
<td>All men and women</td>
</tr>
<tr>
<td>Use of high-risk medications</td>
<td>Prolonged use of glucocorticoids or other high-risk medications</td>
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<tr>
<td>Hypogonadism</td>
<td>Parental hip fracture</td>
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<tr>
<td>Malabsorption syndromes</td>
<td>Vertebral fracture or osteopenia identified on radiography</td>
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<tr>
<td>Chronic inflammatory conditions</td>
<td>High alcohol intake or current smoking</td>
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<tr>
<td>Primary hyperparathyroidism</td>
<td>Low body weight (&lt; 60 kg) or major weight loss (&gt;10% of body weight at age 25)</td>
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<tr>
<td>Other disorders strongly associated with rapid bone loss or fractures</td>
<td>Other disorders strongly associated with osteoporosis</td>
<td></td>
</tr>
</tbody>
</table>

Initial BMD testing

Assessment of fracture risk

Low risk (10-yr fracture risk <10%)

Moderate risk (10 yr fracture risk 10-20%)

High risk (10 yr fracture risk >20% or prior fragility fracture of hip or spine or >1 fragility fracture)

Lateral thoracolumbar radiography (T4-L4) or vertebral fracture assessment may aid in decision-making by identifying vertebral fractures.

Factors warranting consideration of pharmacologic therapy:
- Additional vertebral fracture(s) (by vertebral fracture assessment or lateral spine radiograph)
- Previous vertebral fracture in individuals aged >65 and those with T-score ≤2.5
- Lumbar spine T-score < <- femoral neck T-score
- Rapid bone loss
- Men undergoing androgen-deprivation therapy for prostate cancer
- Women undergoing aromatase inhibitor therapy for breast cancer
- Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use
- Recurrent falls (≤2 in the past 12 mo)
- Other disorders strongly associated with osteoporosis, rapid bone loss, or fractures

Reassess risk in 5 yr

Repeat BMD in 1-3 yr and reassess risk

Always consider patient preference

How much Calcium do we Need?

<table>
<thead>
<tr>
<th>Age</th>
<th>Amount</th>
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<tbody>
<tr>
<td>4-8</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>9-18</td>
<td>1,300 mg</td>
</tr>
<tr>
<td>19-50</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1,200 mg</td>
</tr>
</tbody>
</table>

Pregnant and lactating women 1,800 mg

Calcium Content of Common Foods
- 1 cup milk = 300 mg
- ¼ cup yogurt = 332 mg
- ½ can salmon with bones = 240 mg
- 1 medium orange = 50 mg

Vitamin D Content in Food
- Milk fortified with vitamin D contains 100 IU/s per 250 mL glass
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish, and fish oils (halibut and cod liver oils) all contain small amounts; supplementation is necessary to obtain adequate levels as dietary intake has minimal impact
- Most multivitamins provide 400 IU/s of vitamin D

Disorders Strongly Associated with Osteoporosis Include:
- Primary hyperparathyroidism, type 1 DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing’s disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. IBD)

10 Yr Fracture Risk Assessment
FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population. FRAX and CAROC are available online from: https://www.osteoporosis.ca/health-care-professionals/clinical-tools-and-resources/

Epidemiology
- for current guidelines and tools see www.osteoporosis.ca
- age-related disease characterized by decreased bone mass and increased susceptibility to fractures
- affects 1 in 4 Canadian women and 1 in 8 Canadian men

Approach to Clinical Assessment
- identify risk factors on history and physical examination
  - history
    - prior falls, fragility fractures, or parental hip fractures, and gait or balance issues
    - glucocorticoid use
    - smoking and alcohol intake (≥3 units per day)
    - rheumatoid arthritis
  - physical examination
    - height annually (prospective loss >2 cm or historical loss >6cm) and weight (weight loss >10% since age 25)
    - rib-to-pelvis distance ≤2 fingers’ breadth
    - occiput-to-wall distance ≥5 cm
    - assess fall risk by ability to get up from chair without support with arms, and walking several steps and return

Assessment of fracture risk

Factors warranting consideration of pharmacologic therapy:
- Additional vertebral fracture(s) (by vertebral fracture assessment or lateral spine radiograph)
- Previous vertebral fracture in individuals aged >65 and those with T-score ≤2.5
- Lumbar spine T-score < <- femoral neck T-score
- Rapid bone loss
- Men undergoing androgen-deprivation therapy for prostate cancer
- Women undergoing aromatase inhibitor therapy for breast cancer
- Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use
- Recurrent falls (≤2 in the past 12 mo)
- Other disorders strongly associated with osteoporosis, rapid bone loss, or fractures

Reassess risk in 5 yr

Repeat BMD in 1-3 yr and reassess risk

Always consider patient preference

Good evidence of benefit from pharmacotherapy

Figure 15. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (integrated management model). Adapted from: CMAJ 2010;182:1864-1873
Investigations
- CBC, Cr, corrected Ca\(^{2+}\), ALP, TSH, 25-OH-D (after 3-4 mo of adequate supplementation), and serum protein electrophoresis if there are vertebral fractures

Indications for Bone Mineral Density Testing and Management
- see Endocrinology, E41

Palliative and End-of-Life Care
- see Geriatric Medicine, GM13

Rash
- see Dermatology, D13

Sexually Transmitted Infections
- see Gynecology, GY27

Definition
- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

Epidemiology
- high incidence rates worldwide
- Canadian prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes (increasing incidence of chlamydia and gonorrhea)
  - less common: hepatitis B, HIV, and syphilis (increasing in incidence), trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venereum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

History
- sexual history
  - age of first intercourse, sexual orientation, sexual activity (oral, anal, and/or vaginal intercourse), sexual activity during travel
  - total number of partners in the past year/month/week and duration of involvement with each
- STI history
  - STI awareness, contraception, previous STIs and testing (including Pap tests), partner communication regarding STIs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

Investigations/Screening
- individuals at increased risk, even those who are asymptomatic, should be screened for chlamydia, gonorrhea, hepatitis B, HIV, and syphilis
- Pap test if none performed in the preceding 12 mo

Management
- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune
- offer Gardasil\(^\text{®}\) to women over 9 years of age (can be offered to men as well but not covered by OHIP)
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use condoms or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- an STI patient is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients diagnosed with bacterial STI or trichomonal infection should abstain from sexual activity until treatment completion and for 7 d after treatment for both partners, or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis

Conclusion
- Systematic review of RCTs involving women between the ages of 9 and 25 years, randomly assigned to receive vaccination with HPV L1 virus-like particle in either quadrivalent (HPV 6, 11, 16, 18), bivalent (HPV 16, 18), or univalent (HPV 16) form or placebo. Main outcomes were prevention of cytologically and/or histologically proven lesions (including LSIL, HSIL, VIN, VAIN, AIN, adenocarcinoma in situ of the cervix, or cancer of the cervix associated with HPV infection).
- Results: Six studies involving 47,236 women were included. Bivalent and quadrivalent vaccines reduced the rate of lesions in the cervix, vulva, vagina, and anogenital region with efficacy of 93% (95% CI 87-96%) and 63% (95% CI 57-70), respectively. More symptoms were found in the bivalent vaccine group (55%, 5-7%) compared to control groups.
- Conclusion: Prophylactic vaccination can prevent HPV infection in women aged 9 to 26 years not previously infected with HPV subtypes covered by the vaccines.
### Table 25. Diagnosis and Treatment of Common STIs

<table>
<thead>
<tr>
<th>STI</th>
<th>Signs and Symptoms</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
</table>
| **Gonococcal Urethritis/Cervicitis** *(Neisseria gonorrhoeae)* | M: urethral discharge, unexplained pyuria, dysuria, irritation, testicular swelling, Sx of epididymitis  
F: mucopurulent endocervical discharge, vaginal bleeding dysuria, pelvic pain, dyspareunia  
M and F: often asymptomatic, can involve rectal symptoms in cases of unprotected anal sex | M: u etral swab for Gram stain and culture  
F: urine PCR, endocervical swab for Gram stain and culture, vaginal swab for wet mount (to rule out trichomons)  
M and F: urine PCR, rectal/ pharyngeal swabs if indicated | Ceftriaxone 250 mg IM single dose*  
If risk factors for treatment failure (e.g. pregnancy, pharyngeal/rectal infection, potentially reduced susceptibility) Test of cure: culture 4 d post-treatment (preferred) or urine PCR 2 wk post treatment (alternative)  
If no risk factors, rescreeen 6-12 months post treatment | M: urethral strictures, epididymitis, infertility  
F: PID, infertility, ectopic pregnancy, perinatal infection, chronic pelvic pain  
M and F: Arthritis, increased risk of acquiring and transmitting HIV |
| **Human Papillomavirus** *(genital warts, cervical dysplasia)* | ~70% asymptomatic  
If symptoms appear (usually 2-5 wk after infection) then similar to gonococcal symptoms (see above)  
M: cauliflower lesions (condylomata acuminata) on skin/mucosa of perineum or anal area  
F: cauliflower lesions and/or pre-neoplastic/neoplastic lesions on cervix/vagina/vulva | Same as above  
None needed if simple condylomata  
F: screening for cervical dysplasia through regular Pap smears | Same as above  
Azithromycin 1 g PO single dose + ceftriaxone 250 mg IM single dose*  
Same follow-up as above | Same as above |
| **Genital Herpes** *(HSV-1 and -2)* | 1° episode: painful vesiculocervate genital lesions = fever, tender lymphadenopathy, protracted course  
Recurrent episodes: less extensive lesions shorter course may have “trigger factors” | Swab of vesicular content for culture, type-specific serologic testing for HSV-1 vs. HSV-2 antibodies and to determine 1° vs. recurrent episode | Same follow-up as above  
Acyclovir 200 mg PO 5x/d x 5-10 d or Famiciclovir 250 mg PO tid x 5 d or Valacyclovir 1,000 mg PO bid x 10 d  
Famciclovir 125 mg PO bid x 5 d or Acyclovir 200 mg PO 5x/d x 5d or 800 mg PO tid x 2 d or Famiciclovir 125 mg PO bid x 5 d or Valacyclovir 500 mg PO bid x 3 d or 1,000 mg PO OD x 3 d | Same follow-up as above  
Valacyclovir 1,000 mg PO bid x 10 d  
Famciclovir 250 mg PO tid x 5 d  
Acyclovir 200 mg PO 5x/d x 5d or 800 mg PO tid x 2 d or Famiciclovir 125 mg PO bid x 5 d or Valacyclovir 500 mg PO bid x 3 d or 1,000 mg PO OD x 3 d | Same follow-up as above  
Acyclovir 200 mg PO 5x/d x 5d or 800 mg PO tid x 2 d or Famiciclovir 125 mg PO bid x 5 d or Valacyclovir 500 mg PO bid x 3 d or 1,000 mg PO OD x 3 d |
| **Infectious Syphilis** *(Treponema pallidum)* | 1°: chancre (painless sore), regional lymphadenopathy  
2°: rash and flu-like symptoms, meningoencephalitis, headache, uveitis, retinitis, condyloma lata, mucus lesions, alopecia  
Latent Phase: asymptomatic  
3°: neurologic, cardiovascular, and tissue complications | Specimen collection from 1° and 2° lesions, screen high risk individuals with serologic syphilis testing (VORL), universal screening of pregnant women | Benzathine penicillin G IM (dose depends on stage and patient population. Check Public Health Canada guideline | Chronic neurologic and cardiovascular sequelae, increased risk of acquiring and transmitting HIV |

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**Sinusitis**

- **see Otolaryngology, OT24**

**Etiology**

- viral etiology is more common  
- viral: rhinovirus, influenza, parainfluenza  
- bacterial: *S. pneumoniae, H. influenzae, M. catarrhalis*

**Management of Acute Sinusitis**

- may provide symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical or oral decongestants  
- do not prescribe antihistamines  
- intra-nasal corticosteroids if diagnosed with mild to moderate acute bacterial sinusitis  
- antibiotics and intra-nasal corticosteroids if diagnosed with severe acute bacterial sinusitis  
- first-line antibiotic is amoxicillin, and second line is amoxicillin-clavulanic acid or a fluoroquinolone  
- ENT referral if: anatomic defect, polyph, adenoid hypertrophy, failure of second-line therapy, or ≥4 episodes/yr, refer urgently when there is development of complications (e.g. orbital extension, meningitis, intra-cranial abscess, venous sinus thrombosis), altered mental status, headache, systemic toxicity, or neurological findings
Sleep Disorders

- see Respiratory, R32 and Neurology, N46

Definition
- most often characterized by one of three complaints
  - insomnia
    - difficulty falling asleep, difficulty maintaining sleep, early-morning wakening, non-refreshing sleep
  - parasomnias
    - night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
  - excessive daytime sleepiness

Epidemiology
- 1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems
Etiology
- primary sleep disorders
  - primary insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, periodic limb movements of sleep
- secondary causes
  - medical: COPD, asthma, GHE, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD, pregnancy, neurological disorders
  - drugs: alcohol, caffeine, nicotine, nicotine replacement therapy, β-agonists, antidepressants, steroids
  - psychiatric: mood and anxiety disorders
  - lifestyle factors: shift work, jet-lag

Investigations
- complete sleep diary every morning for 1-2 wk
  - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (e.g. CBC and differential, TSH)
- refer for sleep study nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

Treatment of Specific Problems

Primary insomnia
- majority of cases
  - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
  - treat any suspected medical or psychiatric cause
  - exercise regularly, avoid heavy exercise within 3 h of bedtime
  - first-line treatment (CBT)
    - sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
    - relaxation therapy: deep breathing, meditation, biofeedback
    - stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
    - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient (improves sleep efficacy)
    - address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
  - pharmacologic treatment (used to supplement CBT; short-term prescription of <14 d with appropriate follow-up in 7-14 d):
    - short-acting benzodiazepines (e.g. lorazepam, oxazepam, temazepam) at the lowest effective dose should be used <7 consecutive nights to break cycle of chronic insomnia or to manage an exacerbation of previously controlled primary insomnia
    - non-benzodiazepines: zopiclone (Imovane®), zolpidem (Sublinox®), melatonin, low dose antidepressants with sedating properties (amitriptyline, trazadone, mirtazapine)
    - if no progress or limited improvement, consider referral to sleep medicine program

Snoring
- results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  - physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)
  - treatment
    - sleep on side (position therapy), weight loss
    - nasal dilators (noninvasive external dilator made with elastic adhesive backing applied over nasal bridge), tongue-retaining devices, mandibular advancement devices
    - at risk of developing obstructive sleep apnea

Obstructive Sleep Apnea (OSA)
- apnea (no breathing for ≥10 s) resulting from upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present
- leads to a distinctive snoring, choking, awakening type pattern as the body rouses itself to open the airway (resusciative breath)
- apneic episodes can last from 20 s-3 min and occur 100-600 episodes/night
- diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes per hour of sleep with arousal recorded
- consequences
  - daytime somnolence; non-restorative sleep
  - poor social and work performance
  - mood changes: anxiety, irritability, depression
  - sexual dysfunction: poor libido, impotence
  - morning headache (due to hypercapnia)
  - HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
  - OSA is an independent risk factor for CAD
  - pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
  - memory loss, decreased concentration, confusion

Risk Factors for Obstructive Sleep Apnea
- 2% of women, 4% of men between ages 30-60
- obesity (due to upper airway narrowing), BMI >28 kg/m² present in 60-90% of cases
- children (commonly due to large tonsils and adenoids)
- aging (due to decreased muscle tone)
- persistent URTIs, allergies, nasal tumours, hypothyroidism (due to macroGLOSSIA), neuroMuscular disease
- family history
Common Presenting Problems

■ investigations
  ◆ measure BP; inspect nose and oropharynx (enlarged adenoids or tonsils)
  ◆ blood gas not helpful, TSH if clinically indicated
  ◆ nocturnal polysomnography

■ treatment
  ◆ modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
  ◆ primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
  ◆ surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy, and adenoidectomy (in children)
  ◆ report patient to Ministry of Transportation if OSA is not controlled by CPAP

Sore Throat (Pharyngitis)

Definition

- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

Etiology

- viral: adenovirus, rhinovirus, influenza virus, RSV, EBV, coxsackie virus, herpes simplex virus, CMV, HIV
- bacterial: Group A β-Hemolytic Streptococcus (GABHS), Group C and Group B-Hemolytic Streptococcus, Neisseria gonorrhoeae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Corynebacterium diphtheriae

Epidemiology

- viral
  - most common cause (90% in adults is viral), occurs year round
- bacterial
  - GABHS (Group A β Hemolytic Streptococcal Infections)
    - most common bacterial cause
    - occurs most often in winter months
    - 5-15% of adult cases and up to 50% of all pediatric cases of acute pharyngitis
    - most prevalent between 5-17 yr old

Clinical Features

- viral
  - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  - nonspecific flu-like symptoms such as fever, malaise, and myalgia
  - often mimics bacterial infection
  - common viral infections
    - EBV (infectious mononucleosis)
      - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
    - coxsackie virus (hand, foot, and mouth disease)
      - primarily late summer, early fall
      - sudden onset of fever, pharyngitis, headache, abdominal pain, and vomiting
      - appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
      - ulcers are pale grey and several mm in diameter, have surrounding erythema, and may appear on hands and feet
    - herpes simplex virus
      - like coxsackie virus but ulcers are fewer and larger
    - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
- bacterial
  - symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
  - signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
  - complications: rheumatic fever, glomerulonephritis, suppurative complications (abscess, sinusitis, otitis media, cervical adenitis, pneumonia), meningitis, impetigo

Investigations

- suspected GABHS
  - see Table 26 for approach to diagnosis and management of GABHS
  - gold standard for diagnosis is throat culture
  - rapid test for streptococcal antigen: high specificity (95%) but low sensitivity (50-90%)
  - suspected EBV (infectious mononucleosis)
    - peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or "monospot")
Table 26. Modified Centor Score: Approach to Diagnosis and Management of GABHS

<table>
<thead>
<tr>
<th>POINTS</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough absent?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of fever &gt;38°C?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tonsillar exudate?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Swollen, tender anterior nodes?</td>
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<td></td>
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<td></td>
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<tr>
<td>Age 3-14</td>
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<td></td>
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<tr>
<td>Age 15-44</td>
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<td></td>
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<tr>
<td>Age &gt;45</td>
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<td></td>
</tr>
</tbody>
</table>

In communities with moderate levels of strep infection (10-20% of sore throats):

<table>
<thead>
<tr>
<th>Score</th>
<th>1-2.5%</th>
<th>5-10%</th>
<th>11-17%</th>
<th>28-35%</th>
<th>51-53%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested action</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO culture or antibiotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture all, treat with antibiotics only if culture is positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture all, treat with antibiotics on clinical grounds1, discontinue antibiotics if culture comes back negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Management

- viral pharyngitis
  - antibiotics not indicated
  - symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants
- GABHS
  - antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and supplicative complications
  - incidence of glomerulonephritis is not decreased with antibiotic treatment
  - no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
  - routine F/U and/or post-treatment throat cultures are not required for most patients
  - F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier
- infectious mononucleosis (EBV)
  - self-limiting course; antibiotics are not indicated
  - symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
  - avoid heavy physical activity and contact sports for at least one month or until splenomegaly resolves because of risk of splenic rupture
  - if acute airway obstruction, give corticosteroids and consult ENT

Epidemiology

- 50-75% of Canadians report some use of CAM over their lifetime and only half will disclose this use to their physician
- use is highest in Western provinces and lowest in Atlantic provinces
- more likely to be used by younger patients and those with higher education and income
  - examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy

Herbal Products

- over 50% of Canadians use natural health products (NHPs)
- most commonly used include echinacea, ginseng, ginkgo, garlic, St. John’s wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  - Are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  - Are you allergic to any plant products?
  - Are you pregnant or breastfeeding?
- information resources: National Centre for CAM (www.nccam.nih.gov), Health Canada website
### Table 27. Common Herbal Products

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Reported Uses</th>
<th>Possible Adverse Effects</th>
<th>Possible Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Cohosh</td>
<td>Menopausal symptoms, PMS, labour induction, arthritis</td>
<td>Hepatitis, liver failure, headaches, GI discomfort, heaviness in legs, weight problems</td>
<td>None reported</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Mild sedative, anxiolytic, GI complaints, common cold</td>
<td>Allergic/contact dermatitis, anaphylaxis</td>
<td>Anxiolytics, sedatives</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Common cold, flu, wound treatment, UTI, cancer</td>
<td>Hypersensitivity, hepatotoxicity with prolonged use, avoid use if immunosuppressed</td>
<td>Potentiates warfarin</td>
</tr>
<tr>
<td>Evening Primrose</td>
<td>Dysmenorrhea, menopausal Sx, inflammation, allergies, eczema, arthritis, MS</td>
<td>Headache, restlessness, nausea, diarhea, may decrease seizure threshold</td>
<td>Anticoagulants, antiplatelets</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Migraine prevention, RA, anti-inflammatory</td>
<td>Anxiety, upset stomach, skin rash, miscarriage</td>
<td>Anticoagulants, antiplatelets</td>
</tr>
<tr>
<td>Flaxseed Oil</td>
<td>Laxative, menopausal symptoms, source of omega-3 fatty acids</td>
<td>Diarhea</td>
<td>Do not take with other medications as fibre content can bind drugs</td>
</tr>
<tr>
<td>Garlic</td>
<td>Elevated lipids, HTN, hyperglycemia, antimicrobial</td>
<td>GI irritation, contact dermatitis, may increase post-operative bleeding</td>
<td>Anticoagulants, potentiates antihypertensives</td>
</tr>
<tr>
<td>Ginger</td>
<td>Nausea, motion sickness, dyspepsia, anti-inflammatory</td>
<td>Heartburn, not to be used for morning sickness</td>
<td>None known</td>
</tr>
<tr>
<td>Ginkgo Biloba</td>
<td>Increases peripheral circulation (AD dementia, intermittent claudication), premenstrual syndrome, vertigo</td>
<td>Headache, cramping, bleeding, mild digestive problems; reports of intracranial hemorrhage</td>
<td>Anticoagulants, thiazide diuretics, MAO inhibitors</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Energy enhancer, decreases stress, adjunct support for chemotherapy/radiation</td>
<td>HTN, nervousness, insomnia, breakthrough bleeding, palpitations</td>
<td>Stimulant medications, antihypertensives, hormonal therapies</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Osteoarthritis</td>
<td>GI distress, headache, drowsiness, palpitations</td>
<td>Caution if shellfish allergy</td>
</tr>
<tr>
<td>(Chondroitin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saw Palmetto</td>
<td>BPH, adjunct to finasteride</td>
<td>Mild GI distress</td>
<td>α-adrenergics, finasteride</td>
</tr>
<tr>
<td>St. John's Wort</td>
<td>Mild to moderate depression</td>
<td>Photosensitivity, increased liver enzymes, drowsiness, dizziness, nausea, headache</td>
<td>CNS depressants, contraindicated with indinavir</td>
</tr>
<tr>
<td>Valerian Root</td>
<td>Sedative, anxiolytic, muscle relaxant, PMS</td>
<td>Drowsiness, headache, digestive problems, paradoxical insomnia</td>
<td>CNS depressants, antihistamines</td>
</tr>
</tbody>
</table>


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### Primary Care Models

#### Table 28. Primary Care Models (Adapted from www.healthforceontario.ca)

<table>
<thead>
<tr>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comprehensive Care Model</strong></td>
</tr>
<tr>
<td><strong>Payment model:</strong> fee-for-service</td>
</tr>
<tr>
<td><strong>Family Health Team</strong></td>
</tr>
<tr>
<td><strong>Wider range of services</strong> (e.g. rehabilitation, palliative care), with increased after-hours availability</td>
</tr>
<tr>
<td><strong>Receives provincial funding for allied health</strong></td>
</tr>
<tr>
<td><strong>Patient enrolment is strongly encouraged</strong></td>
</tr>
<tr>
<td><strong>Payment model:</strong> paid annually per patient rostered depending on demographic category (blended capitation model)</td>
</tr>
<tr>
<td><strong>Family Health Group</strong></td>
</tr>
<tr>
<td><strong>Physicians commit to enroll patients</strong></td>
</tr>
<tr>
<td><strong>Payment model:</strong> blended capitation model i.e. age- and sex-adjusted base rate remuneration plus bonuses and incentives</td>
</tr>
<tr>
<td><strong>Family Health Network</strong></td>
</tr>
<tr>
<td><strong>Payment model:</strong> salary-based</td>
</tr>
<tr>
<td><strong>Family Health Organization</strong></td>
</tr>
<tr>
<td><strong>Physicians commit to enroll patients</strong></td>
</tr>
<tr>
<td><strong>Must sign governance and Family Health Organization agreements to join</strong></td>
</tr>
<tr>
<td><strong>Payment model:</strong> blended capitation model i.e. age- and sex-adjusted base rate remuneration plus bonuses and incentives</td>
</tr>
</tbody>
</table>

**FP** = family physician; **GP** = general practitioner; **RN** = registered nurse; **NP** = nurse practitioner; **FHT** = family health team
### Antimicrobial Quick Reference

<table>
<thead>
<tr>
<th>Condition</th>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATORY/ENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Rhinitis</td>
<td>Rhinovirus, coronavirus, influenza, RSV, parainfluenza, adenovirus</td>
<td>None</td>
</tr>
<tr>
<td>Pharyngitis (sore throat)</td>
<td>Rhinovirus, adenovirus, influenza, parainfluenza, coxsackievirus, coronavirus</td>
<td>None</td>
</tr>
<tr>
<td>Strep Pharyngitis</td>
<td>Group A β-Hemolytic Streptococcus</td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: penicillin V 40 mg/kg/d PO div bid-tid (max 750 mg/d) x 10 d (use adult dose if &gt; 27 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin 40 mg/kg/d PO div bid-tid x 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cephalexin 25 mg/kg/d PO div qid x 10 d</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus</td>
<td>Adults:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 80 mg/kg/d PO div bid-tid x 5-10 d (max 3 g/d) x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d div bid (max 3 g/d) x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 15 mg/kg/d PO div bid x 10-14 d</td>
</tr>
<tr>
<td>Acute Otitis Media</td>
<td>S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus</td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td>Otitis Externa</td>
<td>P. aeruginosa, Coliforms, S. aureus</td>
<td>Cortisporin® otic solution 4 drops tid or qid (3 drops tid or qid for children)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TM defect: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO OD x 4-8 wk</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>H. influenzae, parainfluenza, coronavirus, rhinovirus, RSV</td>
<td>None</td>
</tr>
<tr>
<td>Community Acquired Pneumonia: Outpatient without Comorbidity</td>
<td>S. pneumoniae, M. pneumoniae, C. pneumoniae</td>
<td>1st line: amoxicillin 1,000 mg PO tid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(for patients over age 50 where mycoplasma infection is less likely)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>erythromycin 500 mg PO qid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 500 mg PO bid or 1,000 mg (ER) PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin 500 mg PO on 1st d then 250 mg PO OD x 4 or 500 mg PO OD x 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: doxycycline 100 mg PO on 1st d then 100 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PLUS ONE of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 500 mg PO bid or 1,000 mg (ER) PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin 500 mg PO OD on 1st d then 250 mg PO OD x 4 or 500 mg PO OD x 4 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>doxycycline 100 mg PO bid on 1st d then 100 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR ANY ONE of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>levofoxacin 750 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>moxifloxacin 400 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td>Dental Infections/Periapical and Periodontal Abscesses</td>
<td>Oral Flora</td>
<td>penicillin V potassium 500 mg PO qid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin 300 mg PO qid or 600 mg bid x 7-10 d</td>
</tr>
<tr>
<td>Condition</td>
<td>Microorganisms</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>GASTROENTEROLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea – Enteritis</strong></td>
<td><em>Enterotoxigenic E. coli (ETEC)</em></td>
<td>Mild to moderate (i.e., &lt;3 bowel movements per day, no blood, no fever): OTC loperamide 4 mg PO STAT then 2 mg PO after each loose stool (max 8 doses/d). OTC bismuth subsalicylate (Pepto Bismol&lt;sup&gt;®&lt;/sup&gt;) 2 tabs or 30 mL, repeat q30min pm (max 8 doses/d) (prevention: 2 tabs or 30 mL qid with meals and in the evening)</td>
</tr>
<tr>
<td>    <strong>Campylobacter</strong>     <strong>Salmonella</strong>     <strong>Shigella</strong>  </td>
<td>  <em>Viruses</em>  </td>
<td>Moderate to severe (i.e., &gt;3 BM/d, blood, fever): ofloxacin 400 mg PO single dose or 300 mg PO bid x 3 d (prevention: 300 mg PO OD) norfloxacin 800 mg PO single dose or 400 mg PO bid x 1-3 d (prevention: 400 mg PO OD) ciprofloxacin 750 mg PO single dose or 500 mg PO bid x 1-3 d (prevention: 500 mg PO OD) levofloxacin 500 mg PO OD x 1-3 d (prevention: 500 mg PO OD) azithromycin 1,000 mg PO single dose or 500 mg PO OD x 1-3 d (children: 10 mg/kg/d x 3 d)</td>
</tr>
<tr>
<td> </td>
<td>  <em>Protozoa</em></td>
<td>Azithromycin:</td>
</tr>
<tr>
<td><strong>Diarrhea – Post Antibiotics</strong> (common with clindamycin)</td>
<td>C. difficile</td>
<td>Mild to moderate (WBC &lt;5 x 10^9/L and Cr &lt;1.5 x baseline): metronidazole 500 mg PO tid or 250 mg PO qid x 10 d (children: 15-30 mg/kg/d PO div tid-qid max 4 g/d)</td>
</tr>
<tr>
<td>  <strong>Peptic Ulcer Disease</strong> (non-NSAID related)</td>
<td>H. pylori</td>
<td>1st line: (PPI PO bid + amoxicillin 1,000 mg PO bid + clarithromycin 500 mg PO bid x 7 d (e.g. HP-PAC: lansoprazole 30 mg PO bid + amoxicillin 1,000 mg PO bid + clarithromycin 500 mg PO bid x 7 d)) (PPI PO bid + metronidazole 500 mg PO bid + clarithromycin 500 mg or 250 mg PO bid x 7 d) 2nd line: (PPI PO bid + metronidazole 500 mg PO bid + amoxicillin 1,000 mg PO bid x 7 d) (PPI PO bid + bismuth subsalicylate 2 tabs or 30 mL qid + metronidazole 250 mg PO qid + tetracycline 500 mg PO qid x 7-14 d)</td>
</tr>
<tr>
<td></td>
<td> </td>
<td>  Azithromycin:</td>
</tr>
<tr>
<td>DERMATOLOGIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Head and Pubic Lice</strong> (crabs)</td>
<td>Pediculosis humanus capitis</td>
<td>Permethrin cream 1%: apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk</td>
</tr>
<tr>
<td>  <strong>Pthirius pubis</strong></td>
<td>Vulvovaginal Candidiasis</td>
<td>Candida: Treat only if patient is symptomatic fluconazole 150 mg PO single dose micocinazole 2% cream (Monistat 7&lt;sup&gt;®&lt;/sup&gt;): one applicator (5 g) intravaginally qhs x 7 d multiple other OTCazole treatments</td>
</tr>
<tr>
<td></td>
<td>Bacterial Vaginosis</td>
<td>Overgrowth of: G. vaginalis M. hominis Anaerobes</td>
</tr>
<tr>
<td></td>
<td><strong>Herpes</strong></td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td></td>
<td>Gonorrhea/Chlamydia</td>
<td>N. gonorrhoeae C. trachomatis</td>
</tr>
<tr>
<td></td>
<td>Mastitis</td>
<td>S. aureus S. pyogenes</td>
</tr>
<tr>
<td></td>
<td>Tinea Cruris/Pedis (jock itch/athlete’s foot)</td>
<td>Trichophyton</td>
</tr>
<tr>
<td>Uncomplicated Cellulitis</td>
<td>S. aureus Group A Streptococcus</td>
<td>Children: 1&lt;sup&gt;st&lt;/sup&gt; line: cephalexin 50-100 mg/kg/d div qid x 10-14 d 2&lt;sup&gt;nd&lt;/sup&gt; line: clindamycin 25 mg/kg/d x 10-14 d Adults: 1&lt;sup&gt;st&lt;/sup&gt; line: cephalexin 500 mg PO qid x 10-14 d 2&lt;sup&gt;nd&lt;/sup&gt; line: clindamycin 300 mg PO x 10-14 d</td>
</tr>
</tbody>
</table>
Acronyms ................................................. 2

Anatomy Review ........................................... 2
Overview of Gastrointestinal Tract
Visualizing the GI Tract

Differential Diagnosis of Common Complaints . . 4

Esophagus .................................................. 6
Gastroesophageal Reflux Disease
Barrett’s Esophagus
Dysphagia
Esophageal Motor Disorders
Esophageal Diverticula
Peptic Stricture (from Esophagitis)
Esophageal Carcinoma
Webs and Rings
Infectious Esophagitis

Stomach and Duodenum ............................... 10
Dyspepsia
Stomach
Gastritis
Peptic Ulcer Disease
H. pylori-Induced Peptic Ulceration
NSAID-Induced Ulceration
Stress-Induced Ulceration
Gastric Carcinoma

Small and Large Bowel ................................. 14
Classification of Diarrhea
Acute Diarrhea
Traveller’s Diarrhea
Chronic Diarrhea
Maldigestion and Malabsorption
Celiac Disease (Gluten Enteropathy/Sprue)
Inflammatory Bowel Disease
Crohn’s Disease
Ulcerative Colitis
Irritable Bowel Syndrome
Constipation
Upper Gastrointestinal Bleeding
Esophageal Varices
Mallory-Weiss Tear
Lower Gastrointestinal Bleeding
Colorectal Carcinoma
Colorectal Polyps
Familial Colon Cancer Syndromes
Benign Anorectal Disease

Liver .......................................................... 28
Investigations of Hepatobiliary Disease
Acute Viral Hepatitis (General)
Hepatitis A Virus
Hepatitis B Virus
Hepatitis D
Hepatitis C Virus
Autoimmune Chronic Active Hepatitis
Drug-Induced Liver Disease
Wilson’s Disease
Hemochromatosis
Alcoholic Liver Disease
Non-Alcoholic Fatty Liver Disease
Acute Liver Failure (formerly Fulminant
Hepatic Failure)
Cirrhosis
Hepatocellular Carcinoma
Liver Transplantation
Portal Hypertension
Hepatic Encephalopathy
Ascites

Biliary Tract .................................................. 40
Jaundice
Gilbert’s Syndrome
Primary Sclerosing Cholangitis
Primary Biliary Cholangitis (formerly cirrhosis)
Secondary Biliary Cirrhosis
Biliary Colic, Cholecystitis
Ascending Cholangitis

Pancreas ..................................................... 43
Pancreatic Enzyme Abnormalities
Acute Pancreatitis
Chronic Pancreatitis
Autoimmune Pancreatitis

Clinical Nutrition ......................................... 47
Determination of Nutritional Status
Enteral Nutrition
Parenteral Nutrition

Common Medications ................................. 49

Landmark Gastroenterology Trials ............... 51

References ................................................ 52
**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALF</td>
<td>acute liver failure</td>
</tr>
<tr>
<td>BE</td>
<td>Barrett’s esophagus</td>
</tr>
<tr>
<td>BT</td>
<td>biologic therapy</td>
</tr>
<tr>
<td>CCX</td>
<td>cholecystokinin</td>
</tr>
<tr>
<td>CO</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>DPG</td>
<td>deamidated gliadin peptides</td>
</tr>
<tr>
<td>DES</td>
<td>diffuse esophageal spasm</td>
</tr>
<tr>
<td>EM</td>
<td>extraintestinal manifestation</td>
</tr>
<tr>
<td>EN</td>
<td>enteral nutrition</td>
</tr>
<tr>
<td>ERCP</td>
<td>endoscopic retrograde cholangiopancreatography</td>
</tr>
<tr>
<td>EUS</td>
<td>endoscopic ultrasound</td>
</tr>
<tr>
<td>EVL</td>
<td>endoscopic variceal ligation</td>
</tr>
<tr>
<td>FAP</td>
<td>familial adenomatous polyposis</td>
</tr>
<tr>
<td>GE</td>
<td>gastroesophageal</td>
</tr>
<tr>
<td>GERD</td>
<td>gastroesophageal reflux disease</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>HAV</td>
<td>hepatitis A virus</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HNPCC</td>
<td>hereditary non-polyposis colorectal cancer</td>
</tr>
<tr>
<td>HRS</td>
<td>hepatorenal syndrome</td>
</tr>
<tr>
<td>HVPG</td>
<td>hepatic venous pressure gradient</td>
</tr>
<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>IBS</td>
<td>irritable bowel syndrome</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>INH</td>
<td>isoniazid</td>
</tr>
<tr>
<td>LE3</td>
<td>lower esophageal sphincter</td>
</tr>
<tr>
<td>MIRCP</td>
<td>magnetic resonance cholangiopancreatography</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>NAC</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>NAFLD</td>
<td>non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>NEND</td>
<td>non-erosive reflux disease</td>
</tr>
<tr>
<td>NMS</td>
<td>neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>NOD</td>
<td>non-organ transplant nutrition</td>
</tr>
<tr>
<td>OGD</td>
<td>oesophagogastroduodenoscopy</td>
</tr>
<tr>
<td>PBC</td>
<td>primary biliary cirrhosis</td>
</tr>
<tr>
<td>PN</td>
<td>parenteral nutrition</td>
</tr>
<tr>
<td>PPI</td>
<td>proton pump inhibitor</td>
</tr>
<tr>
<td>PSC</td>
<td>primary sclerosing cholangitis</td>
</tr>
<tr>
<td>PTC</td>
<td>percutaneous transhepatic cholangiography</td>
</tr>
<tr>
<td>PTX</td>
<td>percutaneous transhepatic cholangiography</td>
</tr>
<tr>
<td>PUD</td>
<td>peptic ulcer disease</td>
</tr>
<tr>
<td>SSB</td>
<td>spontaneous bacterial peritonitis</td>
</tr>
<tr>
<td>TIPS</td>
<td>transjugular intrahepatic cholangiography</td>
</tr>
<tr>
<td>TPN</td>
<td>total parenteral nutrition</td>
</tr>
<tr>
<td>TTG</td>
<td>tissue transglutaminase</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
</tbody>
</table>

**Anatomy Review**

**Overview of Gastrointestinal Tract**

- The gastrointestinal tract runs from mouth to anus ("gum to bum")

---

*Figure 1. Overview of gastrointestinal tract*
### Table 1. Summary of Gastrointestinal Tract Structure and Function

<table>
<thead>
<tr>
<th>Organ</th>
<th>Function</th>
<th>Blood Supply</th>
<th>Innervation</th>
<th>Histology and Structural Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophagus</strong></td>
<td>Muscular tube approximately 40 cm long with a diameter of 2 cm Extends from pharynx to the stomach</td>
<td>Arterial: left gastric artery and left inferior phrenic artery Venous Left gastric vein → portal venous system Esophageal veins → azygos vein → IVC (systemic)</td>
<td>Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks) Sympathetic innervation via thoracic trunks of the greater splanchnic nerves</td>
<td>Mucosa: stratified squamous epithelium Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells Muscularis propria (muscularis externa); inner circular, outer longitudinal muscle Upper 1/3: stratified muscle Middle 1/3: transition zone Lower 1/3: smooth muscle</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>Delivers food to intestine for digestion and absorption Secretes acid, probably to reduce enteric infections/pneumonia; facilitate digestion of protein/iron/B12 Secretes intrinsic factor to facilitate B12 absorption Minor contribution to initial protein digestion via pepsin</td>
<td>Lesser curvature Right and left gastric arteries (from celiac trunk) Greater curvature Right and left gastro-omental (gastroepiploic) arteries (from gastroduodenal and splenic arteries respectively) Fundus: short and posterior gastric arteries (from the splenic artery)</td>
<td>Parasympathetic innervation via vagus nerve Sympathetic innervation via vagus nerve Sympathetic innervation via vagus nerve Parasympathetic innervation via vagus nerve (from T6-T9)</td>
<td>5 parts Cardia Fundus Body Antrums Pylorus 4 parts Superior (5 cm) Descending (7-10 cm) Horizontal (6-6 cm) Ascending (5 cm) 1st part is intrapertoneal; rest is retroperitoneal</td>
</tr>
<tr>
<td><strong>Duodenum</strong></td>
<td>Modulates enteral pH via secretin → decreased gastric acid secretion, increased bicarbonate secretion Secretes CCK to stimulate bile secretion Site of iron absorption</td>
<td>Branches of celiac artery and superior mesenteric artery</td>
<td>Parasympathetic innervation via vagus nerve Sympathetic innervation via greater and lesser splanchnic nerves</td>
<td>4 parts Cardia Fundus Body Antrums Pylorus 1st part is intrapertoneal; rest is retroperitoneal</td>
</tr>
<tr>
<td><strong>Jejunum</strong></td>
<td>Absorption of sodium, water, and nutrients (protein, carbohydrates, fat, folic acid, and vitamin A, B, C, D, E, K) Absorption of water (5-10% of total water)</td>
<td>Superior mesenteric artery</td>
<td>Parasympathetic innervation via fibres of the posterior vagal trunk Sympathetic innervation via fibres of T8 T10</td>
<td>Deep red colour 2-4 cm in thickness Thick and heavy wall Plicae circulares are large, tall, and closely packed Has long vasa recta Scant fat in mesentery Scant Peyer’s patches</td>
</tr>
<tr>
<td><strong>Ileum</strong></td>
<td>Absorption of sodium, water, nutrients, soluble vitamins (only site of vitamin B12 absorption), and bile salts (entero-hepatic circulation)</td>
<td>Superior mesenteric artery</td>
<td>Same as jejunum</td>
<td>When compared to jejunum Paler pink colour 2-3 cm in thickness Thin and light walls Plicae circulares are small and sparse Contains more mesenteric fat Many Peyer’s patches</td>
</tr>
<tr>
<td><strong>Large Bowel</strong></td>
<td>Absorption of water (5-10% of total water) Bacteria: further digestion of chyme and metabolism of undigested CHO to short chain fatty acids Formation and storage of feces</td>
<td>Branches of superior and inferior mesenteric arteries Rectal blood supply; sigmoid, right pudendal, and rectal arteries</td>
<td>Parasympathetic innervation via vagus nerve Sympathetic innervation via greater and lesser splanchnic nerves</td>
<td>Consists of cecum, colon (ascending, descending, and sigmoid), rectum and anal canal Features include teniae coli, haustra, and omental appendices</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Glucose homeostasis Plasma protein synthesis Lipid and lipoprotein synthesis Bile acid synthesis and secretion Vitamin A, D, E, K, B12 storage Biotransformation, detoxification Excretion of compounds</td>
<td>2 sources Portal vein (75-80%) Hepatic artery (20-25%)</td>
<td>Parasympathetic innervation via fibres of the anterior and posterior vagal trunks Sympathetic innervation via fibres of the celiac plexus</td>
<td>Largest internal organ Composed of 4 lobes (left, right, caudate, quadrate), and divided into 8 segments</td>
</tr>
<tr>
<td><strong>Biliary Tract</strong></td>
<td>Gallbladder functions to store and release bile that is produced in the liver Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids, and bilirubin CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release</td>
<td>Cystic artery</td>
<td>Parasympathetic innervation via vagus nerve Sympathetic and visceral innervation via celiac nerve plexus Somatic afferent fibres via I sigh phrenic nerve</td>
<td>Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct, and ampulla of Vater</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td>Endocrine function: islets of Langerhans produce glucagon, insulin, and somatostatin (from the a, j, and B cells, respectively) Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase</td>
<td>Anterior superior pancreaticoduodenal artery (from the celiac trunk) Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery) Dorsal pancreatic artery (from the splenic artery) Pancreatic veins drain into the portal, splenic, and superior mesenteric veins</td>
<td>Parasympathetic innervation via vagus nerve Sympathetic innervation via abdominopelvic splanchnic nerves</td>
<td>4 parts of pancreas: head (includes uncinate process), neck, body, and tail (Major) pancreatic duct connecting to common bile duct prior to ampulla of Vater Accessory pancreatic duct connected directly to duodenum</td>
</tr>
</tbody>
</table>
Visualizing the GI Tract

- see Medical Imaging, MI15

Esophagus, Stomach, Duodenum
OGD: best visualization of mucosa; also allows for therapeutic intervention (e.g. banding varices, thermal therapy/clipping/injecting bleeding ulcers, and dilatation e.g. treatment of esophageal strictures)
- consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation), possibility of fistulas
- endotracheal intubation first if massive upper GI bleed, acidemia, or inability to protect airway

Small Bowel
- most difficult to visualize, especially if mucosal detail is needed
- CT enterography more accurate than small bowel follow through, but both have low sensitivity
- MRI small bowel imaging increasingly available, especially useful if radiation exposure is an issue (e.g. young patient, multiple radiological images already done)
- note: MRI enteroclysis: luminal contrast administered by nasojejunal tube to dilate the small bowel – disliked by both radiologist and patient, but may improve sensitivity
- “double balloon” enteroscopy (enteroscope with proximal and distal balloons to propel endoscope into jejunum from mouth or into jejunum/ileum or into ileus from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction) is also accurate in diagnosis but unable to provide any therapeutic intervention

Colon and Terminal Ileum
- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis, and severe colitis (increased risk of perforation)
- CT colonography (“virtual colonoscopy”) more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), and fistulae; increasing evidence for use in colorectal cancer screening, especially for assessment of right side of colon in cases where colonoscopy is less sensitive. Most often used when optical endoscopic colonoscopy is a risk (e.g. frail elderly) or unsuccessful (e.g. stricture)
- most often used when optical endoscopic colonoscopy is a risk (e.g. frail elderly) or unsuccessful (e.g. stricture)

Pancratic/Biliary Duct
- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if therapeutic intervention likely to be required: strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required

Differential Diagnosis of Common Complaints

- see General Surgery GS4

Table 2. Differential Diagnosis of Common Presenting Complaints

<table>
<thead>
<tr>
<th>CHRONIC/RECURRENT ABDOMINAL PAIN</th>
<th>INFLAMMATORY</th>
<th>Neoplastic/Vascular</th>
<th>TOXIN</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUD</td>
<td>Recurrent bowel obstruction</td>
<td>Mesenteric ischemia</td>
<td>Lead poisoning</td>
<td>Miettelschmidt</td>
</tr>
<tr>
<td>Biliary colic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>ACUTE DIARRHEA</th>
<th>INFLAMMATORY</th>
<th>NON-INFLAMMATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yers.*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli (HEC 0157:H7)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protozoal</td>
<td>E. histolytica* (amebiasis)</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Stranglesides</td>
<td></td>
<td>C. perfringens</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>B. cereus</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td>E. coli (ETEC, EPEC)</td>
</tr>
<tr>
<td>IBD*</td>
<td></td>
<td>Salmonella enteritis</td>
</tr>
<tr>
<td>Ischemic*</td>
<td></td>
<td>Vibrio cholera</td>
</tr>
<tr>
<td>Protozoal</td>
<td></td>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td>Rotavirus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norwalk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CMV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colchicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laxatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antacids (magnesium)</td>
</tr>
</tbody>
</table>

Acute Upper Abdominal Pain
Remember to rule out thoracic sources, e.g. myocardial infarction, pneumonia, dissecting aneurysm

Obscure But Treatable Causes of Abdominal Pain
- Acute Intermittent Porphyria
- Hereditary Angioedema
- Familial Mediterranean Fever
- Vasculitis (e.g. polyarteritis nodosa)

Inflammatory Diarrhea: Occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids. Diarrhea may be profuse or very small in volume. Often associated with abdominal pain = fever and chills

Non-Inflammatory Diarrhea: No damage to the mucosal lining, N/V may be present. Fever, chills, blood in the stool, severe abdominal pain or tenderness are not present.
<table>
<thead>
<tr>
<th>CHRONIC DIARRHEA</th>
<th>Inflammatory</th>
<th>Secretory</th>
<th>Steatorrhea</th>
<th>Osmotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDD*</td>
<td>Infections</td>
<td>Stimulant laxatives</td>
<td>Celiac sprue</td>
<td>Constipation (overflow diarrhea)</td>
</tr>
<tr>
<td>(TB, CMV, HSV)</td>
<td>(TB, CMV, HSV)</td>
<td>Post-ileal resection</td>
<td>Chronic pancreatitis</td>
<td>Anal sphincter dysfunction</td>
</tr>
<tr>
<td>Ischemic bowel</td>
<td>Drugs</td>
<td>Cholecystectomy (bile salts)</td>
<td>Lactose intolerance</td>
<td></td>
</tr>
<tr>
<td>Radiation colitis</td>
<td>Other</td>
<td>Bacterial toxins</td>
<td>Chronic cholelithiasis</td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td></td>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. difficile</td>
<td></td>
<td>Neoplasia* (colon, carcinoi, V/Poma)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIFFERENTIAL DIAGNOSIS OF COMMON PRESENTING COMPLAINTS (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISTENTION</td>
</tr>
<tr>
<td>Abdominal</td>
</tr>
<tr>
<td>Odynophagia</td>
</tr>
<tr>
<td>Odynophagia</td>
</tr>
<tr>
<td>Odynophagia</td>
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<tr>
<td>Odynophagia</td>
</tr>
<tr>
<td>Odynophagia</td>
</tr>
<tr>
<td>Odynophagia</td>
</tr>
</tbody>
</table>

| DISTENTION | ABDOMINAL | ODYNOPHAGIA | INFLAMMATION/UCLERATION | FLATULENCE | FECES | OTHER |
| Abdominal | Odynophagia | ULCER | CAUSES OF BLOODY DIARRHEA | Constipation | Colon | Other |
| Odynophagia | Peptic ulcer | ULCER | | Colon | Other |
| Odynophagia | Esophageal varices | ULCER | | Other | |
| Odynophagia | Mallory-Weiss tears | ULCER | | Other | |
| Odynophagia | Erosive esophagitis | ULCER | | Other | |
| Odynophagia | Erosive gastritis | ULCER | | Other | |
| Odynophagia | *Causes of bloody diarrhea | ULCER | | Other | |

| DISTENTION | ABDOMINAL | ODYNOPHAGIA | INFLAMMATION/UCLERATION | FLATULENCE | FECES | OTHER |
| Abdominal | Odynophagia | ULCER | CAUSES OF BLOODY DIARRHEA | Constipation | Colon | Other |
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| Odynophagia | Mallory-Weiss tears | ULCER | | Other | |
| Odynophagia | Erosive esophagitis | ULCER | | Other | |
| Odynophagia | Erosive gastritis | ULCER | | Other | |
| Odynophagia | *Causes of bloody diarrhea | ULCER | | Other | |

| DISTENTION | ABDOMINAL | ODYNOPHAGIA | INFLAMMATION/UCLERATION | FLATULENCE | FECES | OTHER |
| Abdominal | Odynophagia | ULCER | CAUSES OF BLOODY DIARRHEA | Constipation | Colon | Other |
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| Odynophagia | Mallory-Weiss tears | ULCER | | Other | |
| Odynophagia | Erosive esophagitis | ULCER | | Other | |
| Odynophagia | Erosive gastritis | ULCER | | Other | |
| Odynophagia | *Causes of bloody diarrhea | ULCER | | Other | |
Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

<table>
<thead>
<tr>
<th>JAUNDICE (UNCONJUGATED BILIRUBIN)</th>
<th>Overproduction</th>
<th>Decreased Hepatic Intake</th>
<th>Decreased Conjugation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
<td>Gilbert’s syndrome</td>
<td>Drug inhibition (e.g. chloramphenicol)</td>
<td>Neutrothal jaundice</td>
</tr>
<tr>
<td>Ineffective erythropoiesis (e.g. megaloblastic anemias)</td>
<td>Drugs (e.g. rifampin)</td>
<td>Crigler-Najjar syndromes type I and II</td>
<td></td>
</tr>
<tr>
<td>JAUNDICE (CONJUGATED BILIRUBIN)</td>
<td>Common</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular disease</td>
<td>Intraductal obstruction</td>
<td>Gallstones</td>
<td>Bilirubin strictures</td>
</tr>
<tr>
<td>Drugs</td>
<td>Biliary strictures</td>
<td>Parasites</td>
<td>Malignancy (cholangiocarcinoma)</td>
</tr>
<tr>
<td>Cirrhosis (any cause)</td>
<td>Inflammation (hepatitis, any cause)</td>
<td>Malignancy (cholelithiasis)</td>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Infiltrative (e.g. hemochromatosis)</td>
<td>Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy)</td>
<td>Extraductal obstruction</td>
<td>Malignancy (e.g. pancreatic cancer, lymphoma)</td>
</tr>
<tr>
<td>PBC</td>
<td>PSC</td>
<td>Metastases in peri-portal nodes</td>
<td></td>
</tr>
<tr>
<td>Sepris</td>
<td>Post-operative/TPN</td>
<td>Inflammation (e.g. pancreatitis)</td>
<td></td>
</tr>
</tbody>
</table>

Esophagus

Gastroesophageal Reflux Disease

**Definition**
- a condition which develops when the reflux of gastric content causes troublesome symptoms or complications

**Etiology**
- inappropriate transient relaxations of LES – most common cause
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, obesity, pregnancy, acid hypersecretion (rare) from Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see General Surgery, GS13)

**Clinical Features**
- “heartburn” (pyrosis) and acid regurgitation (together are 80% sensitive and specific for reflux) ± sour regurgitation; less sensitive and less specific: water brash, sensation of a lump in the throat (globus sensation), and frequent belching
- non-esophageal symptoms are increasingly recognized of being poor predictors of reflux

**Investigations**
- usually, a clinical diagnosis is sufficient based on symptom history and relief following a trial of pharmacotherapy (PPI: symptom relief 80% sensitive for reflux)
- gastroscopy indications (*Ann Intern Med* 2012;157:808-816)
  - absolute indications
    - heartburn accompanied by red-flags (bleeding, weight loss, etc.)
    - persistent reflux symptoms or prior severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI 2x daily
    - history suggests esophageal stricture especially dysphagia
    - high risk for Barrett’s (male, age >50, obese, white, tobacco use, long history of symptoms)
    - repeat esophagoscopy after 6-8 wks of PPI therapy indicated if: severe esophagitis because it can mask Barrett’s esophagus or symptoms

**Figure 2. Signs and symptoms of GERD**

**Figure 3. Classification and gastroscopic findings of GERD**

**Bowel Ischemia**
- The splenic flexure and rectosigmoid junction are watershed areas and are susceptible to ischemia. History and symptoms include acute onset crampy left abdominal pain, absence of abdominal tenderness on exam, rectal bleeding, and risk factors for embolization, atherosclerosis and atrial fibrillation

**Dyspepsia**
- postprandial fullness, early satiety, epigastric pain, or burning

**Foods/Substances that may aggravate GERD**
- Alcohol
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices
• esophageal manometry (study of esophageal motility)
  • done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure intact esophageal function; exclude alternative diagnoses like scleroderma and achalasia
  • surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to alleviate symptoms if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
  • 24 h pH monitoring: most accurate test for reflux, but not required or performed in most cases
  • most useful if PPIs do not improve symptoms

Treatment

• PPIs are the most effective therapy and usually need to be continued as maintenance therapy
  • on-demand: antacids (Mg(OH)2, Al(OH)3, alginate), H2-blockers, or PPIs can be used for NERD
  • diet helps symptoms, not the disease; avoid alcohol, coffee, spices, tomatoes, and citrus juices
  • only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)
  • symptoms may recur if therapy is discontinued

Complications

• esophageal stricture disease – scarring can lead to dysphagia (solids)
• esophagitis
• ulcer
• bleeding
• Barrett’s esophagus and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

Barrett’s Esophagus

Definition

• metaplasia of normal squamous esophageal epithelium to abnormal columnar epithelium containing-type intestinal mucosa (intestinal metaplasia)

Etiology

• thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Epidemiology

• in North America and Western Europe, 0.5-2.0% of adults are thought to have Barrett’s esophagus
• up to 10% of GERD patients will have already developed BE by the time they seek medical attention
• more common in males, age >50, Caucasians, smokers, overweight, hiatus hernia, and long history of reflux symptoms

Pathophysiology

• endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
• BE predisposes first to premalignant changes characterized as low or high-grade dysplasia, which then progresses to adenocarcinoma

Significance

• rate of malignant transformation is approximately 0.12% per yr for all BE patients prior to dysplasia
• risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 3-8 yr of surveillance
• increased gastric acid secretion is more frequently associated with Barrett’s esophagus as opposed to reflux alone

Treatment

• acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication)
• surveillance gastroscopy every 3 years if no dysplasia
• high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/ resection, or esophagectomy produce similar outcomes; however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation
• if low grade dysplasia, both surveillance and endoscopic ablation/resection are satisfactory options

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Dysphagia

**Definition**
- difficulty swallowing

**Clinical Features**
- dysphagia with solids and liquids
- chest pain (in some disorders)

**Diagnosis**
- motility study (esophageal manometry)
- barium swallow sometimes helpful

**Causes**
- idiopathic
- achalasia (painless)
- scleroderma (painless)
- DM
- DES: rare and can be difficult to diagnose due to intermittent presentation

**Table 3. Esophageal Motor Disorder**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Achalasia</th>
<th>Scleroderma</th>
<th>Diffuse Esophageal Spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Failure of smooth muscle relaxation at LES</td>
<td>Systemic disease characterized by vascopathy and tissue fibrosis (especially skin thickening)</td>
<td>Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Usually idiopathic</td>
<td>Includes autoimmune, genetic, hormonal, and environmental factors</td>
<td>Idiopathic</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Inflammatory degeneration of Auerbach’s plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis</td>
<td>Bld d vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia</td>
<td>Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>CXR: no air in stomach, dilated esophagus</td>
<td>Clinical features of scleroderma: Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus</td>
<td>Barium x-ray: “Corkscrew pattern”</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Dilatation of LES with balloon, GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%)</td>
<td>Medical: aggressive GERD therapy (PPIs bd)</td>
<td>Reassurance not cardiac pain, medical: nitrates, calcium channel blockers, anticholinergics have variable benefit</td>
</tr>
</tbody>
</table>
**Esophageal Diverticula**

**Definition**
- outpouchings of one or more layers of the esophageal tract

**Clinical Features**
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

**Classification**
- classified according to location
  - pharyngoesophageal (Zenker’s) diverticulum
    - most frequent form of esophageal diverticulum
    - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
    - symptoms: dysphagia, regurgitation of undigested food, halitosis
    - treatment: small and asymptomatic: no treatment required, large and symptomatic: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac.
  - mid-esophageal diverticulum
    - secondary to mediastinal inflammation (‘traction diverticulae), motor disorders
    - usually asymptomatic; no treatment required
  - just proximal to LES (pulsatile type)
    - usually associated with motor disorders
    - usually asymptomatic, no treatment required

**Peptic Stricture (from Esophagitis)**
- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

**Treatment**
- endoscopic dilatation and indefinite PPI

**Esophageal Carcinoma**
- see General Surgery, GS15

**Webs and Rings**
- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

**Clinical Features**
- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Schatzki ring
  - mucosal ring at squamo-columnar junction above a hiatus hernia
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic bougie

**Infectious Esophagitis**

**Definition**
- severe mucosal inflammation and ulceration as a result of a viral or a fungal infection

**Risk Factors**
- DM
- chemotherapeutic agents
- immunocompromised states

**Clinical Features**
- characteristically odynophagia, less often dysphagia
- diagnosis is via endoscopic visualization and biopsy

**Appearance**
- Candida (most common): whitish-yellow plaques without visible ulceration or inflammation
- Herpes (second most common), CMV: focal ulcers

*Plummer-Vinson Syndrome Triad*
- Iron deficiency anemia
- Dysphagia
- Esophageal webs
* rare (prevalence <1 in 1,000,000) but good prognosis when treated with iron and esophageal dilatation

*Eosinophilic Esophagitis*
- Eosinophils infiltrate the epithelium of the esophagus
- Causes odynophagia, dysphagia, common cause of bolus food impaction
- Usually primary, but can be part of the spectrum of eosinophilic gastroenteritis, secondary to drugs, parasites etc.
- Often associated with allergies
- Most characteristically occurs in young men
- Diagnosis established by endoscopic biopsy, suggested by mucosal rings seen in the esophageal mucosa at endoscopy
- Treatment: (a) diet, (b) swallowed corticosteroid nasal spray (fluticasone), (c) swallowed viscous corticosteroid (budesonide mixed with sucralose)
Stomach and Duodenum

Dyspepsia

Definition
- one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain or burning (Rome IV criteria)
- multiple causes: esophagitis, GERD, peptic ulcer, stomach cancer, drugs, but overall functional disease is most common

History and Physical Exam
- history: most important are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical exam: adenopathy, abdominal mass/organomegaly, Carnett’s sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

Investigations
- laboratory: usual (CBC, liver enzymes, glucose, Cr, etc.), amylase, albumin, calcium, protein electrophoresis, TSH, H. pylori serology
- consider trial of empiric anti-secretory drug therapy, non-invasive testing for H. pylori infection, endoscopy; barium radiography is outdated

Table 4. Cells of the Gastric Mucosa

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Secretory Product</th>
<th>Important Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal Cells</td>
<td>Gastric acid (HCl) and intrinsic factor</td>
<td>Stimulated by histamine, Ach, gastrin</td>
</tr>
<tr>
<td>Chief Cells</td>
<td>Pepsinogen</td>
<td>Stimulated by vagal input and local acid</td>
</tr>
<tr>
<td>D-Cells</td>
<td>Somatostatin</td>
<td>Inhibits release of hormones including gastrin</td>
</tr>
<tr>
<td>G-Cells</td>
<td>Gastrin</td>
<td>Stimulates H+ production from parietal cells</td>
</tr>
<tr>
<td>Superficial Epithelial Cells</td>
<td>Mucus, HCO3-</td>
<td>Protect gastric mucosa</td>
</tr>
</tbody>
</table>

Figure 5. Stimulation of H+ secretion from the parietal cell

The most common cause of dyspepsia is functional (idiopathic) dyspepsia

Red Flags of Dyspepsia (raise suspicion of gastric malignancy):
- Unintended weight loss
- Persistent vomiting
- Progressive dysphagia
- Odynophagia
- Unexplained anemia or iron deficiency
- Hematemesis
- Jaundice
- Palpable abdominal mass or lymphadenopathy
- Family history of upper GI cancer
- Previous gastric surgery

Investigations via endoscopic visualization and biopsy

Treatment
- Candida: nystatin swish and swallow, ketoconazole/fluconazole
- Herpes: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV ganciclovir, famciclovir, or oral valganciclovir
Gastritis

Definition
• defined histologically: inflammation of the stomach mucosa

Etiology
• some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

Table 5. Updated Sydney Classification of Gastritis

<table>
<thead>
<tr>
<th>Type</th>
<th>Common Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Gastritis</td>
<td>Alcohol, Aspirin®/NSAID, shock/physiological stress (seen in ICU patients)</td>
</tr>
<tr>
<td>Hemorrhagic/erosive gastritis</td>
<td></td>
</tr>
<tr>
<td>Helicobacter gastritis</td>
<td></td>
</tr>
<tr>
<td>Chronic Gastritis</td>
<td></td>
</tr>
<tr>
<td>Non-atrophic</td>
<td>H. pylori</td>
</tr>
<tr>
<td>Atrophic</td>
<td>H. pylori, dietary, environmental factors (multi-focal), autoimmunity</td>
</tr>
<tr>
<td>Chemical</td>
<td>NSAID, bile</td>
</tr>
<tr>
<td>Radiation</td>
<td>Radiation injury</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>Celiac disease, drug</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>Food allergies</td>
</tr>
<tr>
<td>Non-infectious granulomatous</td>
<td>Crohn’s disease, sarcoidosis</td>
</tr>
<tr>
<td>Other infectious gastritides</td>
<td>Bacteria, viruses, fungi parasite, TB, syphilis</td>
</tr>
</tbody>
</table>

Clinical Features
• non-erosive gastritis is asymptomatic (except in certain rare causes like Crohn’s disease), does not cause pain; difficult to diagnose clinically or endoscopically – requires biopsy for diagnosis
• erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

Treatment
• determined by etiology (see H. pylori, G13, NSAID, G13 and Stress-Induced Ulceration, G14)
• non-pharmacological: avoidance of mucosal irritants such as alcohol, NSAIDs, and foods that trigger symptoms

Peptic Ulcer Disease

Definition
• focal defects in the mucosa that penetrate the muscularis mucosal layer results in scarring (defects superficial to the muscularis mucosa are erosions and do not cause scarring)
• peptic ulcer disease includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

Etiology

Table 6. Etiology of Peptic Ulcer Disease

<table>
<thead>
<tr>
<th></th>
<th>Duodenal</th>
<th>Gastric</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori Infection</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>Physiologic Stress-Induced</td>
<td>&lt;3%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Zollinger-Ellison Syndrome</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

NSAID negative, H. pylori negative ulcers becoming more commonly recognized
• others: CMV, ischemic, idiopathic
• alcohol: damages gastric mucosa but rarely causes ulcers
• peptic ulcer associated with cigarette smoking, cirrhosis of liver, COPD, and chronic renal failure

Clinical Features
• dyspepsia: most common presenting symptom
  • only 5% of patients with dyspepsia have ulcers, while most have functional disease
  • may present with complications
  • bleeding 10% (severe if from gastroduodenal artery), perforation 2% (usually anterior ulcers), gastric outlet obstruction 2%
  • posterior inflammation (penetration) 2%; may also cause pancreatitis
• duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  • epigastric pain; may localize to tip of xiphoid
  • burning
  • develops 1-3 h after meals
  • relieved by eating and antacids
  • interrupts sleep
  • periodicity (tends to occur in clusters over wk with subsequent periods of remission)
• gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

Investigations
• endoscopy (most accurate)
• upper GI series
• H. pylori tests (see Table 7)
• fasting serum gastrin measurement if Zollinger-Ellison syndrome suspected (but most common cause of elevated serum gastrin level is atrophic gastritis)

Treatment
• specific management depends on etiology; (see H. pylori, G13, NSAID-Induced Ulceration, G13 and Stress-Induced Ulceration, G14)
• eradicate H. pylori if present; chief advantage of triple therapy over PPI is to lower ulcer recurrence rate
• stop NSAIDs if possible
• start PPI: inhibits parietal cell H+/K+-ATPase pump which secretes acid
• heals most ulcers, even if NSAIDs are continued
• other medications (e.g. histamine H2-agonists) less effective
• discontinue cigarette smoking
• no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol, and spices

Management of Bleeding Peptic Ulcers
• OGD to explore upper GI tract
• IV pantoprazole continuous drip
• establish risk of rebleeding/continuous bleed (since most ulcers stop bleeding spontaneously)
  • clinical risk factors: increased age (>60), bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  • endoscopic signs of recurrent bleeding (active bleeding visible vessel, clot, red spot) more predictive than clinical risk factors
  • if ulcer possesses high risk stigmata, then endoscopic therapy should be performed, consider ICU admission

Suspected Bleeding Peptic Ulcer
ABCs: assess vitals (BP and HR, orthostatic changes)
CBC, lytes, BUN, Cr, INR, blood type, cross and type
Resuscitate: crystalloids and blood products if indicated
Consider
NG tube placement + aspiration: confirm upper GI source
IV pantoprazole: 80 mg starting dose + 8 mg/h continuous infusion
Erythromycin 250 mg 30 min before endoscopy
Endoscopy
Active bleeding or visible vessel
High Risk:
Hemostasis: clips, thermal coagulation ± epinephrine injection
Continue (or start) IV PPI
Monitor for re-bleeding in hospital
If adherent clot: consider removal
Low Risk:
No hemostasis necessary
Continue (or start) oral PPI
Decreased need for in-hospital monitoring
Post-Endoscopy
Resume clear fluids 6 hours post-endoscopy
Test for H. pylori
Counsel re: most likely causes (NSAIDs, anti-platelet agents)
If re-bleeding: repeat endoscopy with aim of hemostasis
Consult interventional radiology or surgery if needed

Figure 6. Approach to management of suspected bleeding peptic ulcer
Adapted from: Grahek C, Barkan A, Barbour M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937
### H. pylori-Induced Peptic Ulceration

**Pathophysiology**
- *H. pylori*: Gram-negative flagellated rod that resides within the gastric mucosa, causing persistent infection and inflammation
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- theories of how *H. pylori* causes ulcers: none satisfactory, but pattern of colonization correlates with outcome
- gastritis only in antrum (15% of patients), high gastric acid, associated with duodenal ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
- gastritis throughout stomach (“pangastritis” – 85% of patients), low gastric acid associated with stomach ulcer and cancer

**Epidemiology**
- *H. pylori* is found in about 20% of all Canadians
- highest prevalence in those raised during 1930s
- infection most commonly acquired in childhood, presumably by fecal-oral route
- high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

**Outcome**
- gastritis (non-erosive) in 100% of patients but asymptomatic
- peptic ulcer in 15% of patients
- gastric carcinoma and mucosal associated lymphomatous tissue [MALT] lymphoma in 0.5% of patients
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children <5 yr of age)

**Diagnosis**

| Table 7. Diagnosis of *H. pylori* Infection |
|-------------------------------|------------------|------------------|
| **Test**                      | **Sensitivity**  | **Specificity**  | **Comments**                      |
| Non-invasive Tests            |                  |                  |                                  |
| Urea breath test              | 90-100%          | 89-100%          | Affected by PPI therapy (false negatives) |
| Serology                      | 88-99%           | 89-95%           | Can remain positive after treatment |
| Feca antigen                  |                  |                  | Only rarely used in clinical practice |
| Invasive Tests (require endoscopy) |                  |                  |                                  |
| Histology                     | 93-99%           | 95-99%           | Gold standard; affected by PPI therapy (false negatives) |
| Rapid urease test (on biopsy) | 89-98%           | 93-100%          | Rapid                           |
| Microbiology culture          | 98%              | 95-100%          | Research only                    |

**Treatment: *H. pylori* Eradication**
- Bismuth quadruple therapy recommended for 10-14 d: PPI (e.g. lansoprazole 30mg bid) + bismuth 525 mg qid + metronidazole 250mg qid + tetracycline 500mg qid
- Alternatively, concomitant nonbismuth quadruple therapy for 10-14 d: PPI + amoxicillin + metronidazole + clarithromycin

**NSAID-Induced Ulceration**
- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
- erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically silent: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

**Pathophysiology**
- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (intravenous NSAID causes ulcers, but not erosions). NSAIDs also inhibit mucosal cyclooxygenase, leading to decreased prostaglandin synthesis. This results in ulcers from reduced secretion of protective bicarbonate and mucous, and decreased mucosal blood flow.
Risk Factors for NSAID-induced Peptic Ulcer
- previous peptic ulcers/UGIB
- age (≥65 yr)
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

Treatment
- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol (less effective) in one tablet
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration

Stress-Induced Ulceration

Definition
- ulceration or erosion in the upper GI tract of ill patients, usually in ICU (stress is physiological, not psychiatric)
- lesions most commonly in fundus of stomach

Pathophysiology
- unclear: likely involves ischemia; may be caused by CNS disease, acid hypersecretion, Cushing ulcers
- mechanical ventilation is the most important risk factor

Risk Factors
- mechanical ventilation
- anti-coagulation
- multi-organ failure
- sepsis
- severe surgery/trauma
- CNS injury (“Cu hing’s ulcers”)
- burns involving more than 35% of body surface

Clinical Features
- UGIB (see Upper Gastrointestinal Bleeding, G25)
- painless

Treatment
- prophylaxis with gastric acid suppressants decreases risk of UGIB; PPI most potent but may increase risk of pneumonia; H2 blockers less potent but less likely to cause pneumonia
- treatment same as for bleeding peptic ulcer but often less successful

Gastric Carcinoma
- see General Surgery, GS19

Small and Large Bowel

Classification of Diarrhea

Definition
- clinically: diarrhea defined as stools that are looser and/or more frequent than normal (i.e. ≥3x per day); physiologically: 24 h stool weight >200 g (less useful clinically)

Classification
- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) vs. large volume (>1/2 cup stool; typical of small bowel diseases)
- watery: secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)
- steatorrhea
- inflammatory
- functional

Stool Osmotic Gap

Stool osmolality is normally about 290 mOsm/kg and can be approximated by the calculated stool osmolality

\[ 2 \times [\text{Na}^+]_{\text{stool}} + [\text{K}^+]_{\text{stool}} \]

In osmotic diarrhea, measured stool osmolality > calculated stool osmolality
In secretory diarrhea measured stool osmolality = calculated stool osmolality
Stool osmolality is always the same as serum
### Acute Diarrhea

#### Definition
- passage of frequent unformed stools for <14 d

#### Etiology
- most commonly due to infections
- most infections are self-limiting and resolve within 7 d

#### Risk Factors
- food (raw or undercooked meat and seafood, unpasteurized dairy products)
- medications: antibiotics, laxatives
- others: high risk sexual activity, infectious outbreaks, occupational exposures (daycare workers), family history (IBD)

#### Table 8. Classification of Acute Diarrhea

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Disruption of intestinal mucosa</td>
</tr>
<tr>
<td>Site</td>
<td>Usually colon</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Organisms and cytotoxins invade mucosa, killing mucosal cells, and further perpetuating the diarrhea</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>Usually abnormal mucosa seen</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Bloody (not always)</td>
</tr>
<tr>
<td></td>
<td>Small volume, high frequency</td>
</tr>
<tr>
<td></td>
<td>Often lower abdominal cramping with urgency ± tenesmus</td>
</tr>
<tr>
<td></td>
<td>May have fever ± shock</td>
</tr>
<tr>
<td>Investigations</td>
<td>Fecal WBC and RBC positive</td>
</tr>
<tr>
<td>Etiology</td>
<td>See Differential Diagnosis of Presenting Complaints, G4</td>
</tr>
<tr>
<td>Differential Diagnosis</td>
<td>Acute presentation of idiopathic inflammatory bowel disease</td>
</tr>
<tr>
<td>Significance</td>
<td>Higher yield with stool C&amp;S</td>
</tr>
<tr>
<td></td>
<td>Can progress to life-threatening megacolon, perforation, hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Antibiotics may benefit</td>
</tr>
</tbody>
</table>

#### Investigations
- stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (day care worker, nursing home resident, community outbreaks, e.g. Walkerton, etc.)
  - C&S only tests *Campylobacter*, *Salmonella*, *Shigella*, *E. coli*.
  - other organisms must be ordered separately
- flexible sigmoidoscopy (without bowel preparation): useful if inflammatory diarrhea suspected
- biopsies are the most useful method of distinguishing idiopathic IBD (Crohn’s disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- *C. difficile* toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home, or recent chemotherapy

#### Treatment
- fluid and electrolyte replacement orally in most cases, intravenous if severe extremes of age/coma
- anti-diarrheals
  - antimotility agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
  - side effects: abdominal cramps, toxic megacolon
  - absorbents: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
  - act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
  - much less effective than antimotility agents
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful (but should not be used in the presence of bloody diarrhea or fever)
- antibiotics: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially *Salmonella*)
    - drug side effects (including *C. difficile* infection)
    - development of resistant strains
    - renal failure/hemolysis (enteroheamorrhagic *E. coli* O157:H7)

#### Infectious Causes of Inflammatory Diarrhea
- *Yersinia*
- *Shigella*
- *Salmonella*
- *E. coli* (IEC 0157:H7), *E. histolytica*
- *Campylobacter*, *C. difficile*
indications for antimicrobial agents in acute diarrhea
- septicemia
- prolonged fever with fecal blood or leukocytes
- likely indicated: Shigella, V. cholerae, C. difficile, traveller’s diarrhea (enterotoxigenic E. coli [ETEC]), Giardia, Entamoeba histolytica, Cyclospora
- situational: Salmonella, Campylobacter, Yersinia, non-enterotoxigenic E. coli
- Salmonella: always treat Salmonella typhi (typhoid or enteric fever); treat other Salmonella only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease

Traveller’s Diarrhea

- see Infectious Diseases, ID13

Chronic Diarrhea

Definition
- passage of frequent unformed stool for >4 wk (persistent diarrhea as 14-30 d)
- approach is similar to that of acute diarrhea except that the majority of cases are non-infectious

Etiology/Classification
- see Differential Diagnosis of Common Presenting Complaints, G4

Investigations
- guided by history
- stool analysis for: C. difficile toxin, C&S, O&P ± fecal fat, WBC
- blood for: CBC, electrolytes, CRP, TSH, celiac serology (IgA anti-tTG; ask for serum protein electrophoresis or immunoglobulin quantitation to rule out IgA deficiency which has an increased frequency in celiac disease)
- colonoscopy and ileoscopy with biopsy
- upper Gi endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (low yield)
- trial of lactose free diet
- caveat: may delay diagnosis of IBD and celiac disease

Maldigestion and Malabsorption

Definition
- maldigestion: inability to break down large molecules in the lumen of the intestine into their component small molecules
- malabsorption: inability to transport molecules across the intestinal mucosa into circulation

Etiology
- maldigestion
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis cancer)
  - bile salt deficiency
    - terminal ileal disease (impaired recycling), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic, e.g. primary biliary cirrhosis)
  - specific enzyme deficiencies (e.g. lactase)
- malabsorption
  - inadequate absorptive surface
  - infections/infestations (e.g. Whipple's disease, Giardia)
  - immunologic or allergic injury (e.g. celiac disease)
  - infiltration (e.g. lymphoma, amyloidosis)
  - fibrosis (e.g. systemic sclerosis, radiation enteritis)
  - bowel resection (length, site, location, presence/absence of ileocecal valve are important)
  - extensive ileal Crohn’s disease
  - drug-induced
    - cholestyramine, ethanol, neomycin, tetracycline, and other antibiotics
  - endocrine
    - DM (complex pathogenesis)

Clinical Features
- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency
Table 9. Absorption of Nutrients and Fat Soluble Vitamins

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Absorption</th>
<th>Clinical Disease and/or Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Duodenum, upper jejunum</td>
<td>Hypochromic anemia, microcytic anemia, glossitis, koilonychia (spoon nails), pica</td>
<td>↓ Hb, ↓ serum Fe, ↓ serum ferritin</td>
</tr>
<tr>
<td>Calcium</td>
<td>Duodenum, upper jejunum (binds to Ca&lt;sup&gt;2+&lt;/sup&gt; binding-protein in cells; levels increased by Vit D)</td>
<td>Metabolic bone disease, may get tetany and paresthesias if serum calcium falls (see Endocrinology, E36)</td>
<td>↓ serum Ca&lt;sup&gt;2+&lt;/sup&gt;, ↓ serum Mg&lt;sup&gt;2+&lt;/sup&gt;, and ↑ ALP. Evaluate for ↓ bone mineralization radiographically (DEXA)</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Jejunum</td>
<td>Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)</td>
<td>↓ serum folic acid</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>B&lt;sub&gt;12&lt;/sub&gt; ingested and bound to R proteins mainly from salivary glands; stomach secretes intrinsic factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B&lt;sub&gt;12&lt;/sub&gt;-IF complex forms, protecting B&lt;sub&gt;12&lt;/sub&gt; from further protease attack; B&lt;sub&gt;12&lt;/sub&gt; absorbed in ileum and binds to transcobalamin (TC)</td>
<td>Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis</td>
<td>Differentiate causes by nuclear Schilling test (when available). Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H24)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Complex polysaccharides hydrolyzed to oligosaccharides, and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum</td>
<td>Generalized malnutrition, weight loss, flatus, and diarrhea</td>
<td>Hydrogen breath test Trial of carbohydrate-restricted diet D-xylose test</td>
</tr>
<tr>
<td>Protein</td>
<td>Digestion at stomach, brush border, and inside cell Absorption occurs primarily in the jejunum</td>
<td>General malnutrition and weight loss, amenorrhea, and ↓ libido if severe</td>
<td>↓ serum albumin (low sensitivity)</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipase, colipase, phospholipase A (pancreatic enzymes), and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Fatty acids diffuse into cell cytoplasm</td>
<td>Generalized malnutrition, weight loss, and diarrhea Foul-smelling feces + gas Steatorrhea</td>
<td>Small bowel biopsy MRCP, ERCP, pancreatic function tests (not routinely available) Quantitative stool fat test (72 h) May start with qualitative stool fat test (Sudan stain of stool) C-trolein breath test (not routinely available)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)</td>
<td>Night blindness Dry skin Keratomalacia</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)</td>
<td>Osteomalacia in adults Rickets in children</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)</td>
<td>Retinopathy, neurological problems</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation</td>
<td>Prolonged INR may cause bleeding</td>
<td></td>
</tr>
</tbody>
</table>

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone.

Investigations
- transglutaminase (tTG) antibody serology/immunoglobulin quantitation and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea (gold standard)
- fecal elastase to screen for pancreatic insufficiency and/or consider empiric trial of pancreatic enzymes based on clinical context
- serum carotene (precursor to vitamin A), folate, Ca<sup>2+</sup>, Mg<sup>2+</sup>, vitamin B12, albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear stained with Sudan (rarely used)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)

Treatment
- dependent on underlying etiology
Celiac Disease (Gluten Enteropathy/Sprue)

Definition
- abnormal small intestine mucosa due to intestinal reaction to gluten, a protein found in wheat, barely, rye, and possibly oats (pure oats likely okay)

Etiology
- only autoimmune disease in which antigen (various gliadin peptides) is recognized
- associated with other autoimmune diseases, especially Sjögren's, thyroid disease
- gluten is broken down to gliadin, which is the toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; celiac also associated with HLA DQ8 (note: up to 40% of Caucasians carry the HLA alleles, but will never develop celiac disease)

Epidemiology
- more common in women
- family history: 10-15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy

Clinical Features
- classic presentation: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; more common current presentation: bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
- thus iron, calcium, and folic acid deficiency (proximal absorption) more common than vitamin B12 deficiency (absorbed in ileum)
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

Investigations
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - IgA deficient patients have false-negative anti-tTG
    - therefore, measure serum IgA concomitantly (via serum quantitative protein electrophoresis)
  - incorporate serum testing tTG and/or DGP IgG in IgA deficiencies
- small bowel mucosal biopsy (usually duodenum) is diagnostic with increased intraepithelial lymphocytes (earliest pathologic finding)
  - crypt hyperplasia
  - villous atrophy
  - note: villous atrophy also seen in small bowel overgrowth, Crohn's, lymphoma, Giardia, HIV
  - improvement with a gluten-free diet, but should not be started before serological tests and biopsy
  - consider CT enterography to visualize small bowel to rule out lymphoma
  - evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, Ca++, Fe, albumin, cholesterol, carotene, B12 absorption
  - fecal fat >7%

Treatment
- dietary counselling
  - gluten free diet; avoid barley, rye, wheat (as these grains are related and also have toxic factor, similar to gliadin)
  - oats allowed if not contaminated by other grains (grown in soil without cross-contamination)
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
  - if poor response to diet change, consider
    - alternate diagnosis
    - non-adherence to gluten-free diet
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
  - development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
  - development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)

Prognosis
- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon; slight increase compared with general population), autoimmune diseases
- risk of lymphoma may be lowered by dietary gluten restriction
Inflammatory Bowel Disease

Definition
- Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis or IBD-unclassified (IBDU)

Pathophysiology
- poorly understood
- most likely a sustained response of the immune system, perhaps to enteric flora
- lack of appropriate down-regulation of immune responsiveness after an infection in a genetically predisposed individual

Genetics
- increased risk of both UC and CD in relatives of patients with either disease, especially siblings, early onset disease
  - familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 9 gene loci are associated
  - CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially Ashkenazi Jews, early onset disease, ileal involvement, fistulizing and stenotic disease
    - CARD15 gene product modulates NFκβ, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

Clinical Features

Table 10. Clinical Differentiation of Ulcerative Colitis from Crohn's Disease

<table>
<thead>
<tr>
<th></th>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Any part of GI tract</td>
<td>Isolated to large bowel</td>
</tr>
<tr>
<td></td>
<td>Small bowel + colon: 50%</td>
<td>Always involves rectum, may progress proximally</td>
</tr>
<tr>
<td></td>
<td>Small bowel only: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colon only: 20%</td>
<td></td>
</tr>
<tr>
<td><strong>Rectal Bleeding</strong></td>
<td>Uncommon; possible if colonic disease</td>
<td>Very common (90%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Less prevalent, large volume, watery</td>
<td>Frequent, mucous, bloody, small volume stools</td>
</tr>
<tr>
<td></td>
<td>Usually non-bloody (may be bloody, particularly if</td>
<td></td>
</tr>
<tr>
<td></td>
<td>distal colonic involvement)</td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>Post-prandial/colicily</td>
<td>Uncommon; predefecation</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Urgency/Tenesmus</strong></td>
<td>Uncommon (unless rectum involved)</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Palpable Mass</strong></td>
<td>Frequent (25%), RLQ</td>
<td>Rare (if present, often related to cecum full of stool)</td>
</tr>
<tr>
<td><strong>Recurrence After Surgery</strong></td>
<td>Common</td>
<td>None post-colectomy</td>
</tr>
<tr>
<td><strong>Endoscopic Features</strong></td>
<td>Segmental inflammation, ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning</td>
<td>Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps</td>
</tr>
<tr>
<td><strong>Histologic Features</strong></td>
<td>Transmural distribution with skip lesions</td>
<td>Mucosal distribution, continuous disease (no skip lesions)</td>
</tr>
<tr>
<td></td>
<td>Focal inflammation</td>
<td>Architectural distortion, gland disruption, crypt abscess</td>
</tr>
<tr>
<td></td>
<td>± noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures</td>
<td>Granulomas absent</td>
</tr>
<tr>
<td></td>
<td>Glands intact</td>
<td></td>
</tr>
<tr>
<td><strong>Radiologic Features</strong></td>
<td>Cobblestone mucosa</td>
<td>Lack of haustra</td>
</tr>
<tr>
<td></td>
<td>Frequent strictures and fistulae</td>
<td>Strictures rare; need to rule out complicating cancer</td>
</tr>
<tr>
<td></td>
<td>AXR: bowel wall thickening &quot;string sign&quot;</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Strictures, fistulae, perianal disease</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td><strong>Colon Cancer Risk</strong></td>
<td>Increased if &gt;30% of colon involved</td>
<td>Increased except in proctitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 11. Extraintestinal Manifestations (EIM) of IBD

<table>
<thead>
<tr>
<th>System</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>10%</td>
<td>Less common</td>
</tr>
<tr>
<td>Perianal skin tags</td>
<td>75-80%</td>
<td>Rare</td>
</tr>
<tr>
<td>Oral mucosal lesions</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Statistically associated in 5-10% of those with IBD but not an EIM</td>
<td></td>
</tr>
<tr>
<td><strong>Rheumatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>15-20% of those with IBD (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>10% of those with IBD (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Sacroilitis</td>
<td>Occurs equally in CD and UC</td>
<td></td>
</tr>
<tr>
<td><strong>Ocular (~10% of IBD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis (vision threatening)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episcleritis (benign)</td>
<td>3-4% of IBD patients (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>15-35% of patients with ileal Crohn’s</td>
<td></td>
</tr>
<tr>
<td>PSC</td>
<td>1-5% of IBD cases involving colon</td>
<td></td>
</tr>
<tr>
<td>Fatty liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallstones</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculi</td>
<td>Most common in CD, especially following ileal resection</td>
<td></td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td>Characteristic of Crohn’s</td>
<td></td>
</tr>
<tr>
<td>Fistulæ</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin deficiencies (B12, Vit ADEK)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis (rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Crohn’s Disease**

**Definition**
- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region (“gum to bum”)

**Epidemiology**
- incidence 1-6/100,000; prevalence 10-100/100,000
- bimodal: onset before 30 yr, second smaller peak age 60; M=F
- incidence of Crohn’s increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in Crohn’s patients is higher than general population

**Pathology**
- most common location: ileum + ascending colon
- linear ulcers leading to mucosal islands and “cobblestone” appearance
- granulomas are found in 50% of surgical specimens 15% of mucosal biopsies

**Clinical Features**
- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- most often presents as recurrent episodes of abdominal cramps, non-bloody diarrhea, and weight loss
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- extra-intestinal manifestations are more common with colonic involvement
- fistulæ, fissures, abscesses are common
- deep fissures with risk of perforation into contiguous viscera (leads to fistulæ and abscesses)
- enteric fistulæ may communicate with skin, bladder, vagina, and other parts of bowel

**Investigations**
- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response (especially acutely in UC)
- bacterial cultures, O&P, C. difficile toxin to exclude other causes of inflammatory diarrhea
Management (see Figure 7)

Table 12. Management of Crohn’s Disease

<table>
<thead>
<tr>
<th>Management/Diet</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Lifestyle/Diet | Smoking cessation  
Fluids only during acute exacerbation  
Enteral diets may aid in remission only for Crohn’s ileitis, not colitis  
No evidence for any non-enteral diet changing the natural history of Crohn’s disease, but may affect symptoms  
Those with extensive small bowel involvement or extensive resection require electrolyte, mineral, and vitamin supplements (vit D, Ca++, Mg++, zinc, Fe, B12)  
5-ASA**  
*5-ASA use in Crohn’s is controversial. However, initial trial for mild ileitis only is warranted (induction and maintenance if clinical response) |
| Antidiarrheal Agents* | Loperamide (Imodium®) > diphenoxylate (Lomotil®) > codeine (cheap but addictive)  
All work by decreasing small bowel motility, used only for symptom relief  
CAUTION if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups  
5-ASA**  
Efficacy controversial: Is currently used for mild ileitis  
Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine  
Hydrolysis by intestinal bacteria releases 5-ASA (active component)  
Dose-dependent efficacy |
| Antibiotics | e.g. metronidazole (20 mg/kg/d, bid or tid dosing) or ciprofloxacin  
Immunosuppressives  
Corticosteroids |
| Corticosteroids | Prednisone: starting dose 40 mg OD for acute exacerbations; IV methylprednisolone if severe  
No proven role for steroids in maintaining remissions; masks intra-abdominal sepsis  
Most commonly used as steroid-sparing agents  
i.e. to lower risk of relapse as corticosteroids are withdrawn  
May require >3 mo to have beneficial effect; usually continued for several years  
May help to heal fistulae, decrease disease activity  
Increases efficacy of biologicals plus lowers chances of biological dosing efficacy (tolerance) so often given in combination with biologics  
Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy (i.e. lymphoma)  
Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α  
Proven effective for treatment of fistulose and patients with medically refractory CD  
First line immunosuppressive therapy with infliximab + azathioprine more effective than using either alone  
Ustekinumab, monoclonal antibody against P40 subunit of interleukin 12 and 23  
Vedolizumab, monoclonal antibody directed against integrin α4β7 thereby reducing lymphocyte traffic to gut-now indicated for UC and Crohn’s |
| Biologics | Induction of Remission  
Maintenance |
| 5-ASA* | ?  
Steroids | + |
| Immunosuppressive | + + |
| Antibiotics | + |
| MTX | + |
| Infliximab | + + |

**Prognosis**
- Highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- Increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- Complications include
  - Intestinal obstruction/perforation
  - Fistula formation
  - Malignancy (lower risk compared to UC)
  - Surveillance colonoscopy same as ulcerative colitis (see Ulcerative Colitis) if more than 1/3 of colon involved

**Ulcerative Colitis**

**Definition**
- Inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

**Epidemiology**
- Incidence 2-10/100,000; prevalence 35-100/100,000 (more common than Crohn’s)
- 2/3 onset by age 30 (with second peak after 50); M:F
- Small hereditary contribution (15% of cases have 1st degree relative with disease)
- Risk is less in smokers
- Inflammation limited to rectum or left colon is more common than pancolitis
**Pathology**
- Disease can involve any portion of the lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis).
- Inflammation is diffuse, continuous, and confined to mucosa.

**Clinical Features**
- Rectal bleeding is the hallmark feature; diarrhea present if more than the rectum is involved.
  - Can also have abdominal cramps/pain, especially with defecation.
  - Severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool).
  - Tenesmus, urgency, incontinence.
  - Systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases.
  - Extra-intestinal manifestations (see Table 11).
  - Characteristic exacerbations and remissions; 5% of cases are fulminant.

**Investigations**
- Sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis.
- Colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation.
- CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease.
- Stool culture, microscopy, C. difficile toxin assay necessary to exclude infection.
- No single confirmatory test.

**Treatment**
- Mainstays of treatment: 5-ASA (mesalamine) derivatives (only in mild to moderate disease).
- Diet of little value in decreasing inflammation but may alleviate symptoms.
- Anti-diarrheal medications generally not indicated in UC.
- 5-ASA:
  - Topical (suppository or enema): effective for distal disease (rectum to splenic flexure) if inflammation is mild, preferable to corticosteroids.
  - Oral: effective for mild to moderate, but not severe colitis (e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d).
  - Commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%).
  - May decrease rate of colorectal cancer.
- Corticosteroids:
  - To remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h).
  - Limited role as maintenance therapy for mild to moderate disease.
  - Use suppositories for proctitis.
  - Use enemas and topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure.
- Immunosuppressants (steroid-sparing):
  - In hospitalized patients with severe UC – add IV infliximab if no response to IV methylprednisolone within 3 days; then colectomy if inadequate response.
  - Biologics (infliximab, adalimumab, golimumab, vedolizumab) can also be used for outpatients with moderate-severe disease, particularly those that are steroid-unresponsive or steroid-dependent.
  - Azathioprine and 6-mercaptopurine: too slow to rapidly resolve acute relapse.
  - Most commonly used to maintain remission as corticosteroids withdrawn.
  - Given with biologics: increase efficacy of biologics and decrease likelihood of tolerance to biologics (~ 10% chance/yr).
- Surgical treatment curative:
  - Aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastomosis (IPAA).
  - Indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids, overt malignancy.

**Complications**
- Similar to CD, except:
  - More liver problems (especially PSC in men).
  - Greater risk of colorectal cancer.
  - Risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%).
  - Risk also increases with active mucosal inflammation and sclerosing cholangitis.
  - Thus, regular colonoscopy and biopsy in pancolitis of ≥8 yr is indicated.
  - Toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery, GS37).

**Immunosuppressive ± +**
- Steroids +
- 5-ASA + +
- Azathioprine and 6-mercaptopurine
- Biologics (infliximab, adalimumab, golimumab, vedolizumab) can also be used for outpatients with severe UC – add IV infliximab if no response to IV methylprednisolone.

**Medical Management of Ulcerative Colitis**

<table>
<thead>
<tr>
<th>Induction of Remission</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>+</td>
</tr>
<tr>
<td>Steroids</td>
<td>+</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>± +</td>
</tr>
</tbody>
</table>

When considering complications of IBD, think:

**Ulcerative Colitis**
- Urinary calculi
- Liver problems
- Epithelial problems
- Retardation of growth/sexual maturation
- Arthritis
- Thrombophlebitis
- Isotopic complications
- Vitamin deficiencies
- Eyes
- Colorectal cancer
- Obstruction
- Leakage (perforation)
- Iron deficiency
- Toxic megacolon
- Infection (wasting)
- Strictures
Prognosis
- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st yr correlates with increased severity of attacks and increased colectomy rate
  - colectomy rate = 1% for all patients after the 1st yr; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course
- stool calprotectin increasingly recognized as a marker of bowel mucosal inflammation, reported especially to be useful in monitoring the activity of inflammatory bowel disease, but accuracy is still controversial

Irritable Bowel Syndrome

Definition
- a form of functional bowel disease; more than just a label for GI symptoms unexplained after normal investigations

Epidemiology
- 20% of North Americans
- onset of symptoms usually in young adulthood
- F>M

Pathophysiology
- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associations or if causative
- psychological: stress may increase IBS symptoms but probably does not cause IBS
- types of IBS: IBS with diarrhea, IBS with constipation, IBS-mixed type (both diarrhea and constipation), and IBS untyped (insufficient abnormality in stool consistency to meet other types)

Diagnosis

Table 13. Rome IV Criteria for Diagnosing Irritable Bowel Syndrome

<table>
<thead>
<tr>
<th>IBS Rome IV Criteria</th>
<th>Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Related to defecation</td>
</tr>
<tr>
<td></td>
<td>2. Associated with a change in frequency of stool</td>
</tr>
<tr>
<td></td>
<td>3. Associated with a change in form (appearance) of stool</td>
</tr>
<tr>
<td>Symptom onset at least 6 months before diagnosis and criteria present during the last 3 months</td>
<td></td>
</tr>
<tr>
<td>The following are supportive, but not essential to the diagnosis:</td>
<td></td>
</tr>
<tr>
<td>Abnormal stool frequency (&gt;3/d or &lt;3/wk)</td>
<td></td>
</tr>
<tr>
<td>Abnormal stool form (lumpy/hard/loose/watery) &gt;1/4 of defecations</td>
<td></td>
</tr>
<tr>
<td>Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) &gt;1/4 of defecations</td>
<td></td>
</tr>
<tr>
<td>Passage of mucus &gt;1/4 of defecations</td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis of IBS Less Likely in Presence of “Red Flag” Features

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Blood or pus in stool</td>
</tr>
<tr>
<td>Nocturnal defecation</td>
<td>Abnormal gross findings on flexible sigmoidoscopy</td>
</tr>
</tbody>
</table>

Investigations
- if history consistent with Rome IV criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS, particularly celiac disease and IBD
- investigations can be limited to CBC, inflammatory markers (ESR, CRP) and celiac serology
- if available, fecal calprotectin is likely more reliable test to rule out IBD
- consider TSH, stool cultures depending on clinical circumstances
- consider colonoscopy (e.g. if alarming features present, family history of IBD or age >50)

Treatment
- reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction, probably exercise
- low FODMAP diet for pain, bloating gas, irregular bowel movements
- no therapeutic agent consistently effective, pain most difficult to control, no drug changes natural history so the drug should be “wanted, since it is not needed”
Symptoms of IBS can be symptom-guided treatment. Pain predominant can be treated with antispasmodic medication before meals (e.g., hyoscine, pinaverium, trimebutine - low level evidence). Tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI - moderate level of evidence).

- **IBS with diarrhea (IBS-D)**: To increase stool consistency, dietary fibre (bran or psyllium) is recommended, but it may worsen abdominal gas. Loperamide (Imodium®), diphenoxylate (Lomotil®), and cholestyramine can be used.

- **IBS with constipation (IBS-C)**: To increase fibre in diet, linaclotide, osmotic or other laxatives (help more with constipation than pain), and mixed (alternating constipation and diarrhea) (IBS-M)

**Prognosis**
- 80% improve over time
- Most have intermittent episodes
- Normal life expectancy

**Constipation**

**Definition**
- Passage of infrequent or hard stools with straining (stool water <50 mL/d); bowel frequency <3x/wk

**Epidemiology**
- Increasing prevalence with age; F>M
- Rare in Africa and India where stool weight is 3-4x greater than in Western countries

**Etiology**
- Most common: idiopathic attributed to colon dysmotility but this is difficult to measure
- Organic causes
  - Medication side effects (narcotics, antidepressants) are the most common
  - Intestinal obstruction, left-sided colon cancer (consider in older patients), and fecal impaction
- Metabolic
  - DM
  - Hypothyroidism
  - Hypercalcemia, hypokalemia, uremia
- Neurological
  - Intestinal pseudo-obstruction
  - Parkinson’s disease
  - MS
  - Collagen vascular disease (e.g., scleroderma)
  - Painful anal conditions (e.g., fissures)

**Clinical Presentation**
- Overlaps with IBS
- Stool firm, difficult to expel, passed with straining, abdominal pain relieved by defecation, flatulence, overflow diarrhea, tenesmus, abdominal distension, infrequent BMs (<3/wk)

**Investigations**
- Underlying disease rarely found if constipation is the only presenting symptom
  - Only test indicated in this situation is a CBC (2013 recommendation of American Gastroenterology Association), but also consider TSH, calcium, and glucose, X-ray of abdomen
  - Colon visualization if concomitant symptoms such as rectal bleeding, weight loss, or anemia (colonoscopy, CT colonography)
  - If refractory to treatment, consider classification based on colon transit time; can measure colonic transit time with radio-opaque markers that are ingested and followed with a series of plain film abdominal x-rays (normal: 70 h)
  1. Normal = misperception of normal defecation (IBS)
  2. Prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
  3. Outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- Combination of 1 and 3 common
Treatment (in order of Increasing Potency)
• dietary fibre
  ▪ useful if mild or moderate constipation, but not if severe
  ▪ aim for 30 g daily, increase dose slowly
• surface-acting (soften and lubricate)
  ▪ docusate salts, mineral oils
• osmotic agents (effective in 2-3 d)
  ▪ lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, i.e. milk of magnesia), lactitol (β-galactosido-sorbitol), polyethylene glycol 3350
• cathartics/stimulants (effective in 24 h)
  ▪ castor oil, senna (avoid prolonged use to prevent melanosi... infusion of 50 µg/h
• prokinetic agents (prucalopride)
• linaclotide (increases water secretion into the intestinal lumen)

Upper Gastrointestinal Bleeding

Definition
• bleeding proximal to the ligament of Treitz, see Gastrointestinal Tract, G2 (75% of GI bleeds)
  ▪ ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

Etiology
• above the GE junction
  ▪ epistaxis
  ▪ esophageal varices (10-30%)
  ▪ esophagitis
  ▪ esophageal cancer
  ▪ Mallory-Weiss tear (10%)
• stomach
  ▪ gastric ulcer (20%) (see Peptic Ulcer Disease, G11)
  ▪ erosive gastritis (e.g. from EtOH or post-surgery) (20%)
  ▪ gastric cancer
  ▪ gastric antral vascular ectasia (rare, associated with cirrhosis and CTD)
  ▪ Dieulafoy’s lesion (very rare)
• duodenum
  ▪ ulcer in bulb (25%)
  ▪ aortoenteric fistula: usually only if previous aortic graft (see sidebar)
• coagulopathy (drugs, renal disease, liver disease)
• vascular malformation (Dieulafoy’s lesion, AVM)

Clinical Features
• in order of decreasing severity of the bleed: hematochezia (brisk upper GI bleed) > hematemesis > coffee ground emesis > melena > occult blood in stool

Treatment
• stabilize patient (1-2 large bore IVs, IV fluids, monitor)
• send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
• keep NPO
• consider NG tube to determine upper vs. lower GI bleeding in some cases
• IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  ▪ given to stabilize clot, not to accelerate ulcer healing
  ▪ if given before endoscopy, decreases need for endoscopic therapeutic intervention
• for variceal bleeds, octreotide 50 µg loading dose followed by constant infusion of 50 µg/h
• consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach
• endoscopy (OGD): establish bleeding site + treat lesion
  ▪ if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  ▪ endoclips
  ▪ hemoacrylate
  ▪ hemospray

Prognosis
• 80% stop spontaneously
• peptic ulcer bleeding: lower mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
• endoscopic predictors of rebleeding (Forrest classification): spurt or ooze, visible vessel, fibrin clot
• can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no high risk predictors of rebleeding
• H2-antagonists should not be used since they impact minimally on rebleeding rates and need for surgery
• esophageal varices have a high rebleeding rate (55%) and mortality (29%)

Forrest Prognostic Classification of Bleeding Peptic Ulcers

<table>
<thead>
<tr>
<th>Forrest Class</th>
<th>Type of Lesion</th>
<th>Risk of Rebleed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Arterial bleed (oozing/spurting)</td>
<td>55-100</td>
</tr>
<tr>
<td>IIa</td>
<td>Visible vessel</td>
<td>43</td>
</tr>
<tr>
<td>IIb</td>
<td>Sentinel clot</td>
<td>22</td>
</tr>
<tr>
<td>IIc</td>
<td>Hematomax covered flat spot</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>No stigma of hemorrhage</td>
<td>5</td>
</tr>
</tbody>
</table>

Lancet 1974;2:394-397
**Esophageal Varices**

**Etiology**
almost always due to portal hypertension

**Clinical Features**
- characteristically massive upper GI bleeding

**Prognosis**
- risk of bleeding: 30% in 1st yr
- risk of rebleeding: 50-70% (20% mortality at 6 wk)

**Investigations**
- endoscopy

**Management**

1. Assess hemodynamic stability and resuscitate*

2. IV octreotide
   - Causes splanchnic vasoconstriction
   - Decreases portal collateral circulation and pressure

3. Endoscopic therapy: variceal ligation (EVL) or sclerotherapy

**Long-term treatment to decrease risk of recurrent bleed**
- β-blocker (e.g. nadolol)
- Repeat EVL/sclerotherapy
- Nitrates
- Follow-up

**PERSISTENT or RECURRENT bleed – treatment options**
- Transjugular intrahepatic portosystemic shunt (TIPS)
- Balloon tamponade
- Live transplant

*MIV c ftri xone lowers risk of sepsis, especially spontaneous bacterial peritonitis

---

**Mallory-Weiss Tear**

**Definition**
- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

**Etiology**
- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia usually present

**Clinical Features**
- hematemesis ± melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

**Management**
- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection ± clips or surgical repair

---

* Wireless endoscopy capsule results help double balloon endoscopy localize source of bleeding
* Angiography if overt bleeding hemodynamically significant, estimated >0.5 cc/min
* CT enterography if wireless endoscopy capsule/double balloon endoscopy not available
Lower Gastrointestinal Bleeding

Definition
• bleed distal to ligament of Treitz

Etiology
• if blood per rectum with hemodynamic instability, rule out upper GI source
• diverticular (60% from right colon)
• vascular
  ■ angiodysplasia (small vascular malformations of the gut)
  ■ anorectal (hemorrhoids, fissures)
• neoplasm
  ■ cancer
  ■ polyps
• inflammation
  ■ colitis (ulcerative, infectious, radiation, ischemic)
  ■ post-polypectomy

Clinical Features
• hematochezia
• anemia
• occult blood in stool
• rarely melena

Treatment
• treat underlying cause

Figure 10. Approach to hematochezia

Colorectal Carcinoma
• see General Surgery, GS34

Colorectal Polyps
• see General Surgery, GS33

Familial Colon Cancer Syndromes
• see General Surgery, GS33

Benign Anorectal Disease
• see General Surgery, GS38
Liver

Investigations of Hepatobiliary Disease

A. Tests of Liver Function

Table 14. Liver Function Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>What Do Levels Correlate With?</th>
<th>Increased by</th>
<th>How to Interpret</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin</td>
<td>Hepatic protein synthesis All coagulation factors except VIII</td>
<td>Hepatocellular dysfunction Vitamin K deficiency (due to malnutrition, malabsorption, etc.)</td>
<td>PT/INR will promptly correct if vitamin K is administered, so increased PT/INR in absence of vitamin K deficiency is a reliable marker of hepatocellular dysfunction</td>
</tr>
<tr>
<td>(PT or INR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>Hepatic protein synthesis and other causes listed in next column</td>
<td>Hepatocellular dysfunction Malnutrition Renal or GI losses Significant inflammation Malignancy</td>
<td>Rule out potential causes other than hepatocellular dysfunction</td>
</tr>
<tr>
<td>Serum Direct</td>
<td>Hepatic excretion from hepatocyte to biliary system</td>
<td>Liver dysfunction</td>
<td>Conjugation is preserved even in end stage liver failure, thus increased direct bilirubin indicates liver dysfunction</td>
</tr>
<tr>
<td>Bilirubin*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Serum Bilirubin
  * canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
  * direct bilirubin = conjugated; indirect = unconjugated bilirubin

B. Tests of Liver Injury

- disproportionately increased AST or ALT = hepatocellular damage
  - ALT more specific to liver; AST from multiple sources (especially muscle)
  - elevation of both highly suggestive of liver injury
  - most common cause of elevated ALT is fatty liver
- disproportionately increased ALP (and GGT) = cholestasis (stasis of bile flow)
  - if ALP is elevated alone, rule out bone disease by fractionating ALP and/or checking GGT
  - if ALP elevation out of proportion to ALT/AST elevation, consider
    1. obstruction of common bile duct (e.g. extraluminal = pancreatic Ca, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths)
    2. destruction of microscopic ducts (e.g. PBC)
    3. bile acid transporter defects (e.g. drugs, intrahepatic cholestasis of pregnancy)
    4. infiltration of the liver (e.g. liver metastases, lymphoma, granulomas, amyloid)

Acute Viral Hepatitis (General)

Definition
- viral hepatitis lasting <6 mo

Clinical Features
- most are subclinical
  - flu-like prodrome may precede jaundice by 1-2 wk
    - nausea/vomiting, anorexia, headaches, fatigue, myalgia, low-grade fever, arthralgia and urticaria (especially HBV)
  - only some progress to icteric (clinical jaundice) phase, lasting days to weeks
    - pale stools and dark urine 1-5 d prior to icteric phase
    - hepatomegaly and RUQ pain
    - splenomegaly and cervical lymphadenopathy (10-20% of cases)

Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP minimally elevated
- viral serology, particularly the IgM antibody directed to the virus

Treatment
- supportive (hydration  diet)
- usually resolves spontaneously, but if severe HBV infection, treatment with entecavir should be considered; in anicteric hepatitis C, anti-viral treatment should be considered (see hepatitis C)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin (>340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia
Complications
• cholestasis (most commonly associated with HAV infection)
• hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

Hepatitis A Virus

• RNA virus
• fecal-oral transmission; incubation period 4-6 wk
• diagnosed by elevated transaminases, positive anti-HAV IgM
• in children: characteristically asymptomatic
• can cause acute liver failure and subsequent death (<1-5%)
• can relapse (rarely), but never becomes chronic

Hepatitis B Virus

Table 15. Hepatitis B Serology

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>Anti-HBc</th>
<th>Liver Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>IgM</td>
</tr>
<tr>
<td>Chronic (e-Ag positive)HBV (generally high HBV DNA)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>IgG</td>
</tr>
<tr>
<td>ALT, AST may or may not be elevated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic (e-Ag negative)HBV (generally low HBV DNA)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>IgG</td>
<td>ALT, AST may or may not be normal</td>
</tr>
<tr>
<td>Resolved infection</td>
<td>–</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>±</td>
<td>IgG</td>
</tr>
<tr>
<td>Immunization</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Figure 11. Time course of acute hepatitis B infection

Epidemiology
• 4 phases of chronic hepatitis B: not all carriers will go through all 4 phases, but all carriers will have positive HBsAg
  1. immune tolerance: extremely high HBV-DNA (>20,000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or ‘incubation period’ in adult with newly-acquired HBV)
  2. immune clearance (or immunoactive): HBV-DNA levels (>20,000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment
  3. immune control: lower HBV-DNA (<20,000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
  4. immune escape (“core or precore mutant”): elevated HBV-DNA (>2,000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

DDx for Hepatitis
• Viral infection
• Alcohol
• Drugs
• Immune-mediated
• Toxins

Causes of Elevated Serum Transaminases in Chronic Hepatitis B
• Ongoing immune-mediated liver injury without immune control of HBV (HBeAg positive)
• Immune escape (anti-HBe positive)
• Reactivation, seroconversion (conversion from anti-HBe to HBeAg)
• Hepatitis D
• Hepatocellular carcinoma
• Other liver insult (fatty liver, alcohol, drugs, hepatitis A)

Risk Factors for Progression
• EtOH
• HIV coinfection
• Old age at diagnosis

In acute hepatitis B, HDV coinfection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis

Risk of hepatocellular carcinoma in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis, and serum HBV-DNA
Risk of hepatocellular carcinoma in HCV increases only after cirrhosis develops

Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury

HCV (and HBV) treatment lowers the risk of hepatocellular carcinoma
Hepatitis D

- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with HBV; causes more aggressive disease than hepatitis B virus alone
- coinfection: acquire HDV and HBV at the same time
- HDV can present as ALF and/or accelerate progression to cirrhosis
- treatment: low-dose interferon (20% response) and liver transplant for end-stage disease

Hepatitis C Virus

- RNA virus (7 genotypes; genotype 1 is most common in North America)
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factors: injection drug use
- other risk factors: blood transfusion received before 1990 (or received in developing world), tattoos, intranasal cocaine use
- clinical manifestation develops 6-8 wk after exposure
  - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage

Diagnosis

- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- virus genotype correlates with response to treatment but not prognosis
- serum HCV-RNA inversely correlates with response to treatment
- normal transaminases may have underlying cirrhosis on biopsy, but otherwise excellent prognosis

Treatment

- blood-borne precautions; vaccine for hepatitis A and B if serology negative; avoid alcohol
- clearest indication for treatment is in subgroup likely to develop clinically significant liver disease, i.e., persistently elevated transaminases, liver biopsy showing fibrosis/cirrhosis, and at least moderately severe necrosis/inflammation
- treatment depends partly on genotype; length of treatment depends on degree of fibrosis, level of serum HCV-RNA, comorbidities, and previous treatment
- oral interferon-free regimens (for all genotypes) (e.g., sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir+dasabuvir, or elbasvir/grazoprevir and sofosbuvir/velpatasvir) are now the standard of care with >90% success rate without significant side-effects including those who failed previous interferon-based treatment

Prognosis

- 80% of acute hepatitis C become chronic (of these 20% evolve to cirrhosis)
- risk of hepatocellular carcinoma increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma
Table 16. Characteristics of the Viral Hepatitides

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
<th>CMV</th>
<th>EBV</th>
<th>Yellow Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus Family</td>
<td>Picornaviridae</td>
<td>Hepadnaviridae</td>
<td>Flaviviridae</td>
<td>Deltaviridae</td>
<td>Caliciviridae</td>
<td>Herpesviridae</td>
<td>Herpesviridae</td>
<td>Flavivirus</td>
</tr>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Envelope</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral</td>
<td>Parenteral/sexual or equivalent</td>
<td>Vertical</td>
<td>Parenteral/sexual (transfusion, NDU, sexual (&lt;HBV))</td>
<td>Non-parenteral (close contact in endemic areas)</td>
<td>Parenteral (blood products, NDU)-sexual transmission is inefficient</td>
<td>Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan)</td>
<td>Close contacts, most body fluids</td>
</tr>
<tr>
<td>Incubation</td>
<td>4-6 wk</td>
<td>6 wk 6 mo</td>
<td>2-26 wk</td>
<td>3-13 wk</td>
<td>2-8 wk</td>
<td>20-60 d</td>
<td>30-50 d</td>
<td>3-6 d</td>
</tr>
<tr>
<td>Onset</td>
<td>Usually abrupt</td>
<td>Usually insidious</td>
<td>Insidious</td>
<td>Usually abrupt</td>
<td>Usually abrupt</td>
<td>Variable</td>
<td>Variable</td>
<td>Usually abrupt</td>
</tr>
<tr>
<td>Communicability</td>
<td>2-3 wk in late incubation to early clinical phase</td>
<td>Acute hepatitis in most adults, 10% of children</td>
<td>Acute hepatitis in most adults, 10% of children</td>
<td>Most have no known risk factors</td>
<td>Most have no known risk factors</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Chronicity</td>
<td>None, although can relapse</td>
<td>5% adults, 90% infants</td>
<td>80%, 20% of which develop cirrhosis</td>
<td>5%</td>
<td>None</td>
<td>Common; latent</td>
<td>Common; latent</td>
<td>Infection confers lifelong immunity</td>
</tr>
<tr>
<td>Serology</td>
<td>Anti-HAV (IgM)</td>
<td>See Table 15</td>
<td>HCV-RNA</td>
<td>Anti-HCV (IgG/IgM)</td>
<td>HBsAg</td>
<td>Anti-HDV (IgG/IgM)</td>
<td>Anti-CMV (IgM/IgG)</td>
<td>Anti-YF (IgM/IgG)</td>
</tr>
<tr>
<td>Immunity</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Havrix, 2 doses q6mo, combined with Twinrix at 0, 7, and 21 d</td>
<td>Recombivax HBTM, age 11-15, 2 doses q6mo</td>
<td>HBIG</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prevention</td>
<td>Prevention: HBV vaccine and/or hepatitis B (HBIG) for needlestick, sexual contact, infants of infected mothers unless already immune</td>
<td>Prevention: no vaccine Rx: IFN + ribavirin (= protease inhibitor; although all oral anti-viral (IFN-free) therapy now available is highly efficacious</td>
<td>Prevention: general hygiene, no vaccine</td>
<td>Prevention: general hygiene, no vaccine</td>
<td>Insulin in high risk transplant patients: CMV Ig and anti-virals (penciclovir, valganciclovir)</td>
<td>Supportive treatment post infection</td>
<td>Prevention</td>
<td>Supportive treatment post infection</td>
</tr>
<tr>
<td>Acute Mortality</td>
<td>0.1-0.3%</td>
<td>0.5-2%</td>
<td>1%</td>
<td>2-20% coincident with HBV, 30% superinfection</td>
<td>1-2% overall, 10-20% in pregnancy</td>
<td>Rare in immunocompetent adults</td>
<td>Rare</td>
<td>20-80% in developing countries</td>
</tr>
<tr>
<td>Oncogenicity</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Complications</td>
<td>Hepatocellular carcinoma secondary to cirrhosis, serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda</td>
<td>Hepatocellular carcinoma in 2-5% of cirrhosis per yr, cryptoglycocalcemia, B-cell lymphoma, non-Hodgekin lymphoma</td>
<td>Leukocytoclastic vasculitis membranous glomerulonephropathy</td>
<td>Leukocytoclastic vasculitis membranous glomerulonephropathy</td>
<td>Malignant, except in third trimester (10-20% fulminant liver failure)</td>
<td>5% of newborns with multiple handicaps</td>
<td>Associated with Bariot’s lymphoma and nasopharyngeal carcinoma (rare in Western world)</td>
<td>Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates</td>
</tr>
</tbody>
</table>

Autoimmune Liver Disease

- diagnosis of exclusion: rule out viruses, drugs/alcohol, metabolic, or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrhepatic manifestations
  - sicca, Raynauds, thyroiditis, Sjögrens, arthralgias
  - hypergammaglobulinemia (particularly elevated IgG)
  - anti-smooth muscle antibody elevation is most characteristic
  - anti-LKM elevation (liver kidney microsome), especially in children
  - less specific: elevated ANA, RF
  - can have false positive viral serology (especially anti-HCV)
  - biopsy – periporal (zone 1) and interface inflammation and necrosis
- treatment: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)
### Drug-Induced Liver Disease

#### Table 17. Classification of Hepatotoxins

<table>
<thead>
<tr>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example</strong></td>
<td>Acetaminophen, CCl4</td>
</tr>
<tr>
<td><strong>Dose-Dependence</strong></td>
<td>Usual</td>
</tr>
<tr>
<td><strong>Latent Period</strong></td>
<td>Hours-days</td>
</tr>
<tr>
<td><strong>Host Factors</strong></td>
<td>Not important</td>
</tr>
<tr>
<td><strong>Predictable</strong></td>
<td>Yes</td>
</tr>
</tbody>
</table>

- many different patterns of liver injury (i.e. hepatocellular, cholestatic, mixed, granulomatous, acute liver failure) can be seen in drug-induced liver injury and thus this requires a high index of suspicion.
- see: LiverTox for Information regarding drug-specific risks and patterns of hepatotoxicity (http://livertox.nih.gov)

#### Specific Drugs

- acetaminophen
  - metabolized by hepatic cytochrome P450 system
  - can cause ALF (transaminases >1,000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite is formed → covalently binds to hepatocyte membrane
  - presentation
    - first 24 h: N/V (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with ALF or resolution
  - note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy
    - gastric lavage/emesis (if <2 h after ingestion)
    - oral activated charcoal
    - N-acetylcysteine (NAC, Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given no matter when time of ingestion)
    - promotes hepatic glutathione regeneration
    - no recorded fatal outcomes if NAC given before increase in transaminases
- chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus, and eosinophilia
- INH (isoniazid)
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age
- methotrexate
  - causes fibrosis/cirrhosis; increased risk in the presence of obesity, DM, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
- others: azoles, statins, methyldopa, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines
- herbs: chaparral, Chinese herbs (e.g. germander, comfrey, bush tea)

#### Wilson’s Disease

**Definition**
- autosomal recessive defect in copper metabolism (gene ATP7B)

**Etiology**
- decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin

**Clinical Features**
- liver: acute hepatitis, acute liver failure, chronic active hepatitis, cirrhosis, low risk of hepatocellular carcinoma
- eyes: Kayser-Fleischer rings (copper deposits in Descemet’s membrane); more common in patients with CNS involvement, present in 50% if only liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi’s syndrome (proximal tubule transport defects) and stones
- blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
- joints: arthritis, bone demineralization, calcifications

**Clinical Manifestations of Wilson’s Disease**

<table>
<thead>
<tr>
<th>ABCD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Asterixis</td>
</tr>
<tr>
<td>B</td>
<td>Basal ganglia degeneration: suspect if parkinsonian features in the young</td>
</tr>
<tr>
<td>C</td>
<td>Ceruloplasmin decreases</td>
</tr>
<tr>
<td>D</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>C</td>
<td>Cornea deposits (Kayser-Fleischer ring)</td>
</tr>
<tr>
<td>E</td>
<td>Copper</td>
</tr>
<tr>
<td>F</td>
<td>Dementia</td>
</tr>
</tbody>
</table>
**Investigations**
- suspect if increased liver enzymes with clinical manifestations at young age (<30); especially combination of liver disease with dystonia, psychiatric symptoms
- screening tests
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion
- gold standard
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible

**Treatment**
- 4 drugs available
  1. penicillamine chelates copper, poorly tolerated
  2. trientine chelates copper
  3. zinc impairs copper excretion in stool and decreases copper absorption from gut
  4. tetrathiomolybdate preferred if neurological involvement
- screen relatives
- liver transplant in severe cases

---

**Hemochromatosis**

**Definition**
- excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body stores of iron increased to 20–40 g (normal 1 g)

**Etiology**
- primary (hereditary) hemochromatosis
  - hepcidin deficiency results in ongoing gut absorption of iron despite adequate iron stores
- secondary hemochromatosis
  - parental iron overload (e.g. transfusions)
  - chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
  - excessive iron intake

**Epidemiology**
- hereditary hemochromatosis most common in Northern European descent
- primarily due to common recessive gene (HFE, 5%); 1/400 patients are homozygotes

**Clinical Features**
- usually presents with trivial elevation in serum transaminases
- liver: cirrhosis (30%), HCC (200x increased risk) - most common cause of death (1/3 of patients)
- pancreas: DM, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: dilated cardiomyopathy
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint, but especially MCP joints), chondrocalcinosis

**Investigations**
- screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
  - transferrin saturation (free Fe²⁺/TIBC) >45%
  - serum ferritin >400 ng/mL
  - HFE gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
  - liver biopsy (generally used to detect cirrhosis or if potential for other causes of liver disease)
    - markers of advanced fibrosis if any of the following are present at the time of diagnosis → age >40, elevated liver enzymes, or ferritin >1000
    - considered if compound heterozygote and potential other cause of liver injury (e.g. fatty liver, etc.)
    - if C282Y/C282Y and no markers of advanced fibrosis, then biopsy generally not needed
  - HCC screening if cirrhosis

**Treatment**
- phlebotomy: weekly or q2wk then lifelong maintenance phlebotomies q2-6mo
- deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

**Prognosis**
- normal life expectancy if treated before the development of cirrhosis or DM
Alcoholic Liver Disease

Definition
- spectrum of diseases, ranging from:
  - fatty liver (all alc.): always reversible if alcohol stopped
  - alcoholic hepatitis (35% of alc.): usually reversible if alcohol stopped
  - cirrhosis (10-15% of alc.): potentially irreversible

Pathophysiology
- several mechanisms, poorly understood
  - ethanol oxidation to acetaldehyde
    - reduces NAD+ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
    - binds to hepatocytes evoking an immune reaction
  - ethanol increases gut permeability leading to increased bacterial translocation
  - alcohol metabolism causes
    - relative hypoxia in liver zone III (near central veins; poorly oxygenated) > zone I (around portal tracts, where oxygenated blood enters)
    - necrosis and hepatic vein sclerosis
  - histology of alcoholic hepatitis
    - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
    - large fat globules
    - fibrosis: space of Disse and perivenular

Clinical Features
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10-20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not accurately predict type of liver involvement
  - fatty liver
    - mildly tender hepatomegaly; jaundice rare
    - mildly increased transaminases <5x normal
  - alcoholic hepatitis
    - variable severity: mild to fatal liver failure
    - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice, and mildly elevated INR)
    - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased white blood cell count – mimics RLL pneumonia and cholecystitis

Investigations
- blood tests are non-specific, but in general
  - AST:ALT >2:1 (both usually <300)
  - CBC: increased MCV, increased WBC often seen with alcoholic hepatitis but not necessarily in other alcohol-related liver injury.
  - Increased GGT

Treatment
- alcohol cessation (see Psychiatry, PS23)
  - Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
  - multivitamin supplements (especially thiamine)
  - caution with drugs metabolized by the liver
  - prednisone and pentoxifylline less used since most definitive trial did not show efficacy

Prognosis
- Maddrey’s discriminant function (based on PT and bilirubin) and MELD predict mortality and guide treatment (consideration for corticosteroids for severe disease based on Maddrey ≥ 32 or MELD ≥21)
  - fatty liver: complete resolution with cessation of alcohol intake
  - alcoholic hepatitis mortality
    - immediate: 30%-60% in the first 6 mo if severe
    - with continued alcohol: 70% in 5 yr
    - with cessation: 30% in 5 yr

Standard Drink Equivalent
- 1 standard drink = 14 g EtOH
  - 12 oz beer (5% alcohol)
  - 5 oz wine (12-17%)
  - 3 oz fortified wine (17-22%)
  - 1.5 oz liquor (40%)
**Non-Alcoholic Fatty Liver Disease**

**Definition**
- spectrum of disorders characterized by macrovesicular hepatic steatosis, sometimes with inflammation and/or fibrosis
- most common cause of liver disease in North America

**Etiology**
- pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- histological changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

**Risk Factors**
- likely a component of the metabolic syndrome along with type 2 DM, HTN, hypertriglyceridemia
- rapid weight loss or weight gain

**Clinical Features**
- often asymptomatic
- may present with fatigue, malaise, and vague RUQ discomfort
- elevated serum triglyceride/cholesterol levels and insulin resistance

**Investigations**
- elevated serum AST, ALT ± ALP; AST/ALT <1
- presents as echogenic liver texture on ultrasound
- liver biopsy diagnostic, but often necessary only for prognosis

**Treatment**
- mainstay is gradual weight loss (0.5-1 kg/wk) as rapid weight loss can worsen liver disease
  - ideally, aim to lose at least 7-10% of body weight
  - some evidence for vitamin E (800 U daily) if there is hepatic inflammation
  - some evidence for benefits of coffee drinking (3 cups per day) and vitamin D

**Prognosis**
- most die from cardiovascular or cerebrovascular disease
- better prognosis than alcoholic hepatitis
  - <25% progress to cirrhosis over a 7-10yr period
- risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
- other clinical indicators of unfavourable prognosis: DM, age, metabolic syndrome

**Acute Liver Failure (formerly Fulminant Hepatic Failure)**

**Definition**
- severe decline in liver function characterized by coagulation abnormality (INR>1.5) and encephalopathy
- in setting of previously normal liver
- rapid (<26 wk duration)

**Etiology**
- drugs (especially acetaminophen), hepatitis B (measure anti-HBc, IgM fraction because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic

**Treatment**
- correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, monitor for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value of biopsy is to exclude chronic disease, less helpful for prognosis
- liver transplant (King's College criteria can be used as prognostic indicator): consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), age <10 or >40, cause is drug or unknown, bilirubin >300 µmol/L, INR >3.5, creatinine >200 µmol/L
Cirrhosis

Definition
- liver damage characterized by diffuse distortion of the basic architecture and replacement with scar tissue and formation of regenerative nodules
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 yr with almost normal life expectancy
- Stage 2 cirrhosis is decompensation, typically development of ascites (most common), variceal bleeding, encephalopathy, characteristically presents abruptly even though histologically the liver fibrosis is gradually progressive

Etiology
- fatty liver (alcoholic or non-alcoholic fatty liver disease)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- hemochromatosis
- primary biliary cirrhosis
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- cryptogenic (i.e. no identifiable cause, although many of these patients may represent "burnt-out NASH")
- rare Wilson’s disease, Gaucher’s disease, α1-antitrypsin deficiency

Investigations
- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive
  - blood work: fall in platelet count <150 is the earliest finding, followed many years later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event)
  - FibroTest: combination of various clinical and biochemical markers that can predict degree of fibrosis
  - imaging
    - U/S is the primary imaging modality but only finds advanced cirrhosis
    - CT to look for varices, nodular liver texture, splenomegaly
  - Transient Ultrasound Elastography (Fibroscan®): non-invasive tool using elastography (variable availability) for measuring liver compliance
  - rapidly replacing liver biopsy to determine extent of liver fibrosis and make the diagnosis of cirrhosis
- gastroscopy: varices or portal hypertensive gastropathy

Treatment
- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs, immunize for Hep A and B if non-immune)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score and MELD score
- liver transplantation for end-stage disease if no alcohol for >6 mo; use MELD score

Table 18. Child-Pugh Score and Interpretation

<table>
<thead>
<tr>
<th>Classification</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (µmol/L)</td>
<td>&lt;34</td>
<td>34-51</td>
<td>&gt;51</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>Absent</td>
<td>Controllable</td>
<td>Refractory</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Absent</td>
<td>Minimal</td>
<td>Severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Points</th>
<th>Class</th>
<th>Life Expectancy</th>
<th>Perioperative Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>15-50 yr</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>Candidate for transplant</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>1-3 mo</td>
<td>82%</td>
<td></td>
</tr>
</tbody>
</table>

Score: 5-6 (Child’s A), 7-9 (Child’s B), 10-15 (Child’s C)
*Note: Child’s classification is rarely used for shunting (TIPS or other surgical shunts), but is still useful to quantitate the severity of cirrhosis

Complications
- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR
  - relationship of INR to bleeding tendency is controversial; some patients may be hypocoagulable, others may be hypercoagulable
- variceal bleeds

MELD-Na (Model for End Stage Liver Disease)
- Predicts 3 mo survival and used to stratify patients on transplant list
- Based on creatinine, INR, total bilirubin, and serum sodium concentration

Figure 12. Progression of liver dysfunction based on liver function tests – the “W”
Half of patients with cirrhosis have gastroesophageal varices and one-third of these develop hemorrhage with an overall mortality of >30%. Hepatic venous pressure gradient (HVPG) ≥10 mmHg is the strongest predictor of variceal development. Treatment: resuscitation, antibiotic prophylaxis, vasoactive drugs (e.g. octreotide IV) combined with endoscopic band ligation or sclerotherapy, Transjugular Intrahepatic Portosystemic Shunt (TIPS).

Renal failure in cirrhosis
- Classifications
  - Pre-renal (usually due to over-diuresis)
  - Acute tubular necrosis
  - Hepatorenal Syndrome (HRS)
    - Type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
    - Type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
  - HRS can occur at any time in severe liver disease, especially after
    - Overdiuresis or dehydration, such as diarrhea, vomiting, etc.
    - GI bleed
    - Sepsis
  - Treatment for hepatorenal syndrome (generally unsuccessful at improving long-term survival)
    - For type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
    - Definitive treatment is liver transplant

Hepatopulmonary syndrome
- Majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal HTN
- Thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators vs. production of a vasodilating substance by the liver
- Clinical features
  - Hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary systemic resistance (int apulmonary shunting)
  - Dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency), and orthodeoxia (desaturation in the upright position, improved by recumbency)
  - Diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
  - Only proven treatment is liver transplantation

Hepatocellular Carcinoma
- See General Surgery, GS44

Liver Transplantation
- See General Surgery, GS45

Portal Hypertension

Definition
- Pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

Pathophysiology
- 3 sites of increased resistance (remember pressure = flow x resistance)
  - Pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - Sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - Post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)
Complications
- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

Treatment
- non-selective β-blockers (propanolol, nadolol, carvedilol) decrease risk of bleeding from varices
- TIPS: to decrease portal venous pressure
  - radiologically inserted stent between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute bleeding or prevent rebleeding or treat ascites
  - complications: hepatic encephalopathy, deterioration of hepatic function
  - contraindicated with severe liver dysfunction, uncontrolled hepatic encephalopathy, and congestive heart failure
  - most commonly used as a “bridge” to liver transplant
- other surgically created shunts: portacaval, distal spleno-renal (Warren shunt) - all used only rarely in the modern era

Hepatic Encephalopathy

Definition
- spectrum of potentially reversible neuropsychiatric syndromes secondary to liver disease diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

Pathophysiology
- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain

Precipitating Factors
- nitrogen load (GI bleed, protein load from food intake renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

Stages
- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar response (upgoing Babinski)
- IV: coma (response to painful stimuli only)

Investigations
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia hypoglycemia)
  - characteristic EEG findings: diffuse (non-focal) slow, high amplitude waves serum ammonia levels increased, but not often necessary to measure in routine clinical use

Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - routine protein restriction is no longer recommended given patients generally have concurrent malnutrition and muscle wasting; however, vegetable protein is better tolerated than animal protein
  - lactulose: titrated to achieve 2-3 soft stools/d
    - prevents diffusion of NH₃ (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH₄ (ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
  - oral rifaximin for both acute treatment and maintenance therapy has high level evidence for efficacy
  - best acute treatment in comatose patient is lactulose enemas
**Ascites**

**Definition**
- accumulation of excess fluid in the peritoneal cavity

**Etiology**

<table>
<thead>
<tr>
<th>Serum (Alb) – Ascitic (Alb) &gt; 11 g/L (1.1 g/dL)</th>
<th>Serum (Alb) – Ascitic (Alb) &lt; 11 g/L (1.1 g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Portal Hypertension Related</td>
<td>Non-Portal Hypertension Related</td>
</tr>
<tr>
<td>Cirrhosis/severe hepatitis</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>Chronic hepatic congestion (right heart failure, Budd-Chiari)</td>
<td>TB</td>
</tr>
<tr>
<td>Massive liver metastases</td>
<td>Pancreatic disease</td>
</tr>
<tr>
<td>Myxedema</td>
<td>Serositis</td>
</tr>
<tr>
<td>Nephrotic syndrome*</td>
<td></td>
</tr>
</tbody>
</table>

* In nephrotic syndrome: decreased serum (Alb) to begin with therefore gradient not helpful

**Pathophysiology**
- Key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - Underfill hypothesis: first step in ascites formation is increased portal pressure and low oncotic pressure (e.g., low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney
  - Overfill hypothesis: cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily
  - Peripheral arterial vasodilation theory (most popular): as portal HTN develops in cirrhosis, production of local mediators such as nitric oxide lead to splanchnic arterial vasodilation which ultimately results in reduction of effective arterial volume and compensatory sodium and fluid retention by the kidneys (i.e., circulation volume is increased, as per overflow hypothesis, but relatively underfilled, as per underfill hypothesis)

**Diagnosis**
- Abdominal ultrasound
- Physical exam (clinically detectable when > 500 mL)
  - Bulging flanks, shifting dullness, fluid-wave test positive
  - Most sensitive symptom: ankle swelling

**Investigations**
- Diagnostic paracentesis
  - 1st aliquot: cell count and differential
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis; TG and chylomicrons if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

**Treatment**
- Non-refractory ascites
  - Na+ restriction (daily sodium intake < 2 g)
  - Diuretics: spironolactone, furosemide
  - Aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - If target weight loss is not achieved and there are no complications, increase dose to achieve target while monitoring for complications
- Refractory ascites (diuretics are inadequate or not tolerated)
  - Therapeutic paracentesis with intravenous albumin
  - TIPS in an appropriate patient (no contraindications) with potential transplant-free survival advantage
  - Liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis is associated with 50% 2 yr mortality
Complication: Primary/Spontaneous Bacterial Peritonitis
- primary/spontaneous bacterial peritonitis (SBP)
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: E. coli (most common), Streptococcus, Klebsiella
  - diagnosis
    - absolute neutrophil count in peritoneal fluid >0.25x10^9 cells/L (250 cells/mm^3)
    - Gram stain positive in only 10-50% of patients
    - culture positive in <80% of patients (not needed for diagnosis)
  - prophylaxis: consider in patients with
    - cirrhosis or GI bleed: ceftriaxone IV daily or norfloxacin bid x 7 d
    - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
  - treatment
    - IV antibiotics (cefotaxime 2 g IV q8h or ceftriaxone 2 g IV daily is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
    - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

Biliary Tract

Jaundice
- see Table 2 and Figures 14 and 15

Signs and Symptoms
- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic tumour (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer, although most patients with pancreatic cancer have pain
- kernicterus: rarely seen in adults due to maturation of blood brain barrier

Investigations
- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
- U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
- direct bile duct visualization
- magnetic resonance cholangiopancreatography (MRCP): non-invasive
- endoscopic ultrasound (EUS): sensitive for stones and pancreatic tumours
- endoscopic retrograde cholangiopancreatography (ERCP): invasive, most accurate, allows for therapeutic intervention
- percutaneous transhepatic cholangiography (PTC): if ERCP fails (endoscopic access not possible)

Jaundice (↑ serum bilirubin)
- Fractionate bilirubin
  - Primarily unconjugated
    - Hemolysis
    - Gilbert’s syndrome
  - Primarily conjugated
    - Hepatocellular disease
      - Drugs
      - Alcohol
      - Virus
      - Autoimmune
      - Hemochromatosis
      - Wilson’s disease, etc.
    - Hematobiliary disease
      - Abdominal ultrasound
        - Bile duct normal
        - Bile duct dilated
        - Bile duct obstruction
          - Visualize bile duct
            - Endoscopic bile duct decompression not likely to be necessary
              - MRCP
            - Endoscopic bile duct decompression likely to be necessary
              - ERCP
      - Biliary excretion into duodenum
        - Intestinal flora
        - Urobilinogen: 70-85%
        - Stercobilinogen: 10% excreted via urine
      - Liver
        - Glucuronyl transferase conjugates bilirubin
        - Biliubin (unconjugated)
          - Alb
          - Bilirubin – Alb
        - Biliubin (conjugated)
          - Hb → Globin
          - Heme → Conversion

Figure 14. Approach to jaundice
Figure 15. Production and excretion of bilirubin
Gilbert’s Syndrome

Definition
- mild decrease in glucuronyltransferase activity leading to defective conjugation of bilirubin
- an abnormality of bilirubin metabolism with no clinical relevance

Etiology/Epidemiology
- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

Clinical Features
- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting, or at times of acute illness; no other clinical implications

Treatment
- none indicated (entirely benign)

Primary Sclerosing Cholangitis

Definition
- narrowing of biliary tree (intra and/or extrahepatic bile ducts) from scarring

Etiology
- primary/idiopathic (most common)
  - associated with IBD, more commonly UC, in up to 70% of patients (usually male)
  - one of the most common indications for liver transplant
- secondary (less common)
  - long-term choledocholithiasis
  - cholangiocarcinoma
  - surgical/traumatic injury (iatrogenic)
  - contiguous inflammatory process
  - post-ERCP
  - associated with HIV/AIDS (“HIV cholangiopathy”)
  - IgG4-related disease

Signs and Symptoms
- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction

Investigations
- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- MRCP and ERCP shows narrowing and dilatations of bile ducts that may result in “beading”, both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC

Complications
- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%) difficult to diagnose and treat

Treatment
- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma (controversial)
- endoscopic sphincterotomy, biliary stent in selected cases of dominant CBD stricture
- antibiotics for cholangitis
- suppurative cholangitis requires emergency drainage of pus in CBD
- liver transplantation appears to be the best treatment for advanced sclerosing cholangitis (nearly 90% 1 yr survival; mean follow-up time from diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that at least in high doses it increases mortality

Prognosis
- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 yr
Primary Biliary Cholangitis (formerly cirrhosis)

**Definition**
- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

**Etiology/Epidemiology**
- likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome, RA, thyroiditis)
- affects mainly middle-aged women (M:F = 1:9)

**Signs and Symptoms**
- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal HTN, ascites
- high incidence of osteoporosis

**Investigations**
- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- elevated IgM
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
- may have: xanthelasmata, xanthomas
- liver biopsy confirms diagnosis and stages severity
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- recently described “overlap” syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis

**Treatment**
- drugs that treat the underlying disease:
  - ursodiol (usual first line treatment)
  - obeticholic acid (particularly if inadequate response to urosioli)
  - cholestyramine (for pruritus and hypercholesterolemia)
  - calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
  - monitor for thyroid disease
  - liver transplant if disease severe, progressive

**Prognosis**
- can be fatal, although not all asymptomatic patients show progression

Table 20. Primary Sclerosing Cholangitis vs Primary Biliary Cholangitis

<table>
<thead>
<tr>
<th>Predominant Gender</th>
<th>Primary Sclerosing Cholangitis</th>
<th>Primary Biliary Cholangitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant Gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Associated Comorbidities</td>
<td>IBD, especially UC</td>
<td>Other autoimmune disorders (Sjögren’s, CREST, RA)</td>
</tr>
<tr>
<td>Affects Ducts</td>
<td>Both intra- and extra-hepatic</td>
<td>Intrahepatic only</td>
</tr>
<tr>
<td>Investigations</td>
<td>ERCP/MRCP (narrowing and dilatations of ducts visualized)</td>
<td>Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)</td>
</tr>
</tbody>
</table>

Secondary Biliary Cirrhosis

**Definition**
- cirrhosis from prolonged partial or total obstruction of major bile ducts

**Etiology**
- acquired: post-operative strictures, chronic pancreatitis, sclerosing cholangitis, stone in bile duct
- congenital: CF, congenital biliary atresia, choledochal cysts

**Investigations**
- cholangiography and liver biopsy

**Treatment**
- treat obstruction, give antibiotics for cholangitis prophylaxis

Biliary Colic, Cholecystitis

- see General Surgery, GS47
Ascending Cholangitis

- see Gene al Surgery, GS49

**Definition**
- infection of the biliary tree

**Etiology**
- stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
- infection originates in the duodenum or spreads hematogenously from the portal vein
- bacteria
  - *E. coli, Klebsiella, Enterobacter, Enterococcus*
  - co-infection with *Bacteroides* and *Clostridia* can occur

**Signs and Symptoms**
- Charcot's triad: fever, RUQ pain, jaundice (50-70%)
- Reynolds' Pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

**Investigations**
- increased WBC
- usually increased ALP and bilirubin, ALT variably elevated
- blood culture
- abdominal U/S: CBD dilation, stones

**Treatment**
- most important is drainage, ideally via ERCP, but if not possible technically by percutaneous biliary or least often by surgical routes
- antibiotic therapy: broad spectrum to cover Gram-negatives, Enterococcus, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

**Prognosis**
- good with effective drainage and antibiotics in mild to moderate cases
- high mortality (~50%) in patients with Reynolds Pentad

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Pancreas

**Pancreatic Enzyme Abnormalities**

**Causes of Increased Serum Amylase**
- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

**Causes of Increased Serum Lipase**
- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure
**Acute Pancreatitis**

**Etiology** (most common are alcohol and gallstones)

- Idiopathic: thought to be hypertensive sphincter or microlithiasis
- Gallstones (45%)
- Ethanol (35%)
- Tumours: pancreas, ampulla, choledochocele
- Scorpion stings

**Microbiological**
- Bacterial: *Mycoplasma, Campylobacter, TB, M. avium intracellulare, Legionella, leptospirosis*
- Viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
- Parasites: ascariasis, clonorchiasis, echinococcosis

**Autoimmune:** SLE, polyarteritis nodosa (PAN), Crohn’s disease

**Surgery/trauma**
- Manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer

**Hyperlipidemia** (TG >11.3 mmol/L; >1000 mg/dL), Hypercalcemia, Hypothermia

**Emboli or ischemia**

**Drugs/toxins**
- Azathioprine, mercaptopurine, furosemide, estrogens, methyldopa, H2-blockers, valproic acid
- Antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

**Pathophysiology**
- Activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- In gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
- In ethanol-related pancreatitis, pathogenesis is unknown
- In rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in SPINK 1 gene which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

**Pathology**
- Mild (interstitial)
  - Per-pancreatic fat necrosis
  - Interstitial edema
- Severe (necrotic)
  - Extensive peri-pancreatic and intra-pancreatic fat necrosis
  - Parenchymal necrosis and hemorrhage → infection in 60%
  - Release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- Severity of clinical features may not always correlate with pathology
- 3 phases
  - Local inflammation + necrosis → hypovolemia
  - Systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  - Local complications two weeks after presentation → pancreatic sepsis/abscess

**Signs and Symptoms**
- Pain: epigastric, non-colicky, constant
- Jaundice: compression or obstruction of bile duct
- Can radiate to back
- May improve when leaning forward (Inglefinger’s sign)
- Tetany: transient hypocalcemia
- Tender rigid abdomen; guarding
- N/V
- Abdominal distention from paralytic ileus
- Fever: chemical, not due to infection
- Cullen’s/Grey-Turner’s signs
- Hypovolemic shock: can lead to renal failure
- Acute respiratory distress syndrome
- Coma

**Investigations**
- Increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >150 specific for biliary cause
- Increased WBC, glucose, low calcium
- Imaging: CT most useful for diagnosis and prognosis
  - X-ray: “sentinel loop” (dilated proximal jejunum), calcification, and “colon cut-off sign” (colonic spasm)
  - U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  - CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
- ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

When thinking about the causes of acute pancreatitis remember: I GET SMASHED, but vast majority due to gallstones or ethanol.
Classification
- interstitial edematous vs. necrotizing
- mild, moderate, severe

Prognosis
- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to
  ■ shock
  ■ pulmonary edema
  ■ multi-organ dysfunction syndrome
  ■ GI ulceration due to stress
  ■ death
- numerous scales to describe severity; probably most useful is proportion of pancreas not taking up contrast on CT done 48 h after presentation (necrotic pancreas does not take up the contrast dye)
- presence of organ failure, particularly organ failure that persists > 48 h, is associated with worse outcomes

Table 21. Collections in pancreatitis (Revised 2012 Atlanta Classification)

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Acute peripancreatic fluid collection (APFC)</td>
</tr>
<tr>
<td>Chronic</td>
<td>Pancreatic pseudocyst</td>
</tr>
</tbody>
</table>

All of these collections are classified as infected or not infected

Treatment
- goals (only supportive therapy available)
  1. hemodynamic stability
  2. analgesia
  3. oxygen
  4. stop progression of damage (difficult)
  5. treat local and systemic complications
- antibiotics controversial except in documented infection (use cephalosporins, imipenem)
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
- beware third spacing of fluid, monitor urine output carefully
- NG suction (lets pancreas rest) if vomiting, stomach very dilated
- endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
- nutritional support: nasojejunal feeding tube or TPN if cannot tolerate enteric feeds
- recent evidence supports nasogastric enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, aprotinin, H₂-blockers, peritoneal lavage
- follow clinically and CT/ultrasound to exclude complications
- chief role of invasive intervention is to excise necrotic tissue (necrosectomy) in the case of infected pancreatic necrosis (try to delay for > two weeks to allow demarcation between viable and necrotic tissue), better done endoscopically or radiologically than surgically if technically possible

Late Complications
- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
- drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
- infected necrosis/abscesses: antibiotics + percutaneous drainage, endoscopic vs. surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: DM, pancreatic duct damage

Chronic Pancreatitis

Definition
- irreversible damage to pancreas characterized by
  1. pancreatic cell loss (from necrosis)
  2. inflammation
  3. fibrosis

Etiology/Pathophysiology
- alcohol (most common)
  ■ causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
  ■ changes composition of pancreatic juice (e.g. increases viscosity)
• decreases pancreatic secretion of pancreatic stone protein (lithostathine) which normally solubilizes calcium salts
  ◆ precipitation of calcium within pancreatic duct results in duct and gland destruction
  • toxic effect on acinar and duct cells – directly or via increasing free radicals
  • acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
  • varying degrees of ductular dilatation, strictures, protein plugs, calcification
  • no satisfactory theory to explain why only a minority of alcoholics develop pancreatitis
  • unusual causes
    ◆ cystic fibrosis
    ◆ severe protein-calorie malnutrition
    ◆ hereditary
    ◆ idiopathic

**Signs and Symptoms**

• early stages
  • recurrent attacks of severe abdominal pain (upper abdomen and back)
  • chronic painless pancreatitis: 10%
• late stages: occurs in 15% of patients
  • malabsorption syndrome when >90% of function is lost, steatorrhea
  • diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed

**Investigations**

• laboratory
  • increase in serum glucose
  • increase in serum ALP, less commonly bilirubin (jaundice)
  • serum amylase and lipase usually normal
  • stool elastase is low in steatorrhea
  • AXR: pancreatic calcifications
  • U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
  • MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
  • EUS: abnormalities of pancreatic parenchyma and pancreatic ducts, most sensitive test
  • 72 h fecal fat test: measures exocrine function
  • secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
  • fecal pancreatic enzyme measurement (elastase-1, chymotrypsin): available only in selected centres

**Treatment**

• most common problem is pain, difficult to control
  • general management
    ◆ total abstinence from alcohol
    ◆ enzyme replacement may help pain by resting pancreas via negative feedback
    ◆ analgesics
    ◆ celiac ganglion blocks
    ◆ time: pain decreases with time as pancreas "burns out"
  • endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct
  • surgery: drain pancreatic duct (pancreatecojejunostomy) if duct dilated (more effective than endoscopy); resect pancreas if duct contracted
  • steatorrhea
  • pancreatic enzyme replacement
  • restrict fat, increase carbohydrate and protein (may also decrease pain)
  • neither endoscopy nor surgery can improve pancreatic function

**Autoimmune Pancreatitis**

• most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice ± abdominal pain)

**Investigations**

• histology: lymphocyte and plasma cell infiltration of pancreas
• imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage shaped, low density rim around pancreas
• serology: increased serum IgG4
• other organ involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

**Treatment**

• responds to prednisone
Clinical Nutrition

Determination of Nutritional Status

- corrected weight loss (expressed as body mass index [kg/m²]) is most important parameter in assessing need for nutritional support
- Subjective Global Assessment: simple bedside tool to assess nutritional status, to help identify those who will benefit from nutritional support

Investigations
- plasma proteins: albumin, pre-albumin (shorter half life than albumin), transferrin
- decrease may indicate decreased nutritional status or disease state
- thyroid-binding globulin, retinol-binding protein (may be too sensitive)
- anthropometry (e.g. triceps skinfold thickness), grip strength less often used

<table>
<thead>
<tr>
<th>Table 22. Areas of Absorption of Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>Duodenum</td>
</tr>
<tr>
<td>Jejunum</td>
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<tr>
<td>Ileum</td>
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</tbody>
</table>

Enteral Nutrition

Definition
- enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
- choice of tubes: nasogastric (NG), nasojejunal (NJ), percutaneous endoscopic gastrostomy (“G-tube” or “PEG tube”), percutaneous endoscopic jejunostomy (J-tube)
- tubes can also be placed endoscopically, radiologically or surgically

Indications
- oral feeding inadequate or contraindicated

Feeds
- polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fibre
- elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolarity)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

Relative Contraindications
- non-functioning gut (e.g. intestinal obstruction, enteroenteral or enterocutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding

Complications
- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)
Parenteral Nutrition

Definition
- parenteral nutrition (PN) is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications
- short-term (<1 mo)
  - whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively, and in difficult to control sepsis
  - pre-operative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)
  - some evidence for efficacy, but convincing data not available for
    - radiation/chemotherapy-induced enteritis
    - AIDS with wasting diarrhea
    - severe acute pancreatitis
- long-term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of small bowel (e.g. small bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

Relative Contraindications
- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem
- unreliable patient or clinical setting

Complications of PN
- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: CHF, hyperglycemia, gallstones, cholestasis

Enteral Nutrition vs. Parenteral Nutrition
- fewer serious complications (especially sepsis)
- nutritional requirements for enterally administered nutrition better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection

Enteral vs. Parenteral Nutrition for Acute Pancreatitis
Cochrane DB of Syst Rev 2010;1:CD002837
Purpose: Compare EN vs TPN on mortality, morbidity, and hospital stay in patients with pancreatitis.
Study Selection: RCTs of TPN vs. EN in pancreatitis.
Results: Eight trials (n=348) were included. Enteral nutrition decreases RR of death (0.50), multiple organ failure (0.55), infection (0.39), and other local complications (0.70). It also decreased hospital stay by 2.37 d.
Conclusion: EN reduces mortality, organ failure, infections, and length of hospital stay in patients with pancreatitis.
### Table 23 Common Drugs Prescribed in Gastroenterology

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proton Pump Inhibitors</strong></td>
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<tr>
<td></td>
<td>Omeprazole</td>
<td>Losec®, Prilosec®</td>
<td>20 mg PO OD</td>
<td>Inhibits gastric enzymes H+/K+-ATPase (proton pump)</td>
<td>Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis,</td>
<td>Hypersensitivity to drug</td>
<td>Dizziness, headache, flatulence, abdominal pain, nausea, rash increased risk of osteoporotic fracture (secondary to impaired calcium absorption)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of H. pylori (combined with antibiotics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>Prevacid®</td>
<td>Oral therapy: lansoprazole 15-30 mg OD (before breakfast), lansoprazole 30-60mg OD (does not need to be taken before breakfast)</td>
<td>Same as above</td>
<td>Same as above and H. pylori</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protonix®</td>
<td>40 mg PO ID/or UGB: 90 mg IV bolus then 8 mg/h IV infusion</td>
<td>Same as above</td>
<td>Same as above and UGB</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole</td>
<td>Pantol®</td>
<td>40 mg PO OD</td>
<td>Same as above</td>
<td>Same as above and UGB</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrifil®</td>
<td>20-40 mg PO OD</td>
<td>Same as above</td>
<td>Same as above and H. pylori</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>Esomeprazole</td>
<td>Nexum®</td>
<td>20-40 mg PO OD</td>
<td>Same as above</td>
<td>Same as above and H. pylori</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Histamine H2-Receptor Antagonists</strong></td>
<td>Ranitidine</td>
<td>Zantac®</td>
<td>300 mg PO OD or 150 mg bid</td>
<td>Inhibits gastric histamine H2-receptors</td>
<td>Duodenal ulcer, gastric ulcer; NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD; not useful for acute GI bleeds</td>
<td>Hypersensitivity to drug</td>
<td>Confusion, dizziness, headache, arthralgias, constipation, nausea, agranulocytosis, pancytopenia, depression</td>
</tr>
<tr>
<td></td>
<td>Famotidine</td>
<td>Peptic®</td>
<td>Oral therapy: duodenal/gastric ulcers: 40 mg qhs</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Stool Softener</strong></td>
<td>Docusate sodium</td>
<td>Colace®</td>
<td>100-400 mg PO OD, divided in 1-4 doses</td>
<td>Promotes incorporation of water into stool</td>
<td>Relief of constipation</td>
<td>Prevention of abdominal pain, fever, N/V</td>
<td>Throat irritation, abdominal cramps, rashes</td>
</tr>
<tr>
<td><strong>Osmotic Laxatives</strong></td>
<td>Lactulose</td>
<td>Lactubase/</td>
<td>Constipation: 15-30 mL PO</td>
<td>Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid in the colon, increases osmotic colonic contents, increases stool volume</td>
<td>Chronic constipation, prevention, and treatment of portal-systemic encephalophathy</td>
<td>Patients who require a low galactose diet</td>
<td>Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constulose®</td>
<td>OD to bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enephalofil®</td>
<td>15-30 mL bid to qgd</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEG3350</td>
<td>Lax-a-day®</td>
<td>Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD</td>
<td>Osmotic agent causes water retention in stool and promotes frequency of stool</td>
<td>Relief of constipation</td>
<td>Colonicospopy prep</td>
<td>Hypersensitivity to drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Golytely®</td>
<td>5-30 mg PO OD (start at 10 mg for bowel preparation)</td>
<td>Osmotic retention of fluid which distills the colon and increases peristaltic activity</td>
<td>Relief of constipation</td>
<td>Patients with myasthenia gravis or other neuromuscular disease</td>
<td>Abdominal pain, vomiting, diarrhea</td>
</tr>
<tr>
<td></td>
<td>Magnesium hydroxide</td>
<td>Milk of Magnesia</td>
<td>Constipation (adult): 400 mg/5 mL: 30-60 mL PO qhs</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Porto-Lax®</td>
<td>5 mL: 30-60 mL PO qhs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stimulant Laxatives</strong></td>
<td>Senna</td>
<td>Sandost®</td>
<td>Tablets: 1-4 PO qhs Syrup: 10-15 mL PO qhs</td>
<td>Induces peristalsis in lower colon</td>
<td>Constipation</td>
<td>Patients with acute abdomen</td>
<td>Abdominal cramps, discoloration of breast milk, urine, feces, melanosis col and atomic colon from prolonged use (controversial)</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl</td>
<td>Bisacodyl®</td>
<td>5-30 mg PO OD (start at 10 mg for bowel preparation)</td>
<td>Enteric nerve stimulation and local contact-induced secretory effects Colonic movements</td>
<td>Constipation</td>
<td>Preparation of bowel for procedure</td>
<td>GI obstruction, Gastroenteritis</td>
</tr>
<tr>
<td><strong>Bulk Laxatives</strong></td>
<td>Polyethylene glycol</td>
<td>Mestranul®</td>
<td>2-6 tabs (1 tab = 0.52 g) PO os bid pm</td>
<td>Increases stool bulk → water retention in stool</td>
<td>Constipation</td>
<td>Hypermotility to drug</td>
<td>GI obstruction, diarrhea, constipation, abdominal cramps</td>
</tr>
<tr>
<td><strong>Antidiarrheal Agents</strong></td>
<td>Diphenoxylate</td>
<td>Lomotil®</td>
<td>5 mg PO bid to qd</td>
<td>Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time</td>
<td>Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies, and other intestinal resections</td>
<td>Children &lt;2 yr, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute ulcerative colitis or pseudomembranous colitis associated with broad-spectrum antibiotics</td>
<td>Abdominal pain or discomfort, diarrohea or distress, tiredness dry mouth, nausea and vomiting, hypersensitivity reaction</td>
</tr>
<tr>
<td></td>
<td>Atropine</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Mechanism of Action:**
- **Antidiarrheal Agents:**
  - Acts as antidiarrheal viacholinergic, noncholingeric, opiate, and nonopiate receptor-mediated mechanisms; decreases activity of myenteric plexus
  - Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time

**Indications:**
- **Proton Pump Inhibitors:**
  - Adjunctive therapy for diarrhea, as above
  - Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies, and other intestinal resections

**Contraindications:**
- **Proton Pump Inhibitors:**
  - Hypersensitivity to drug
  - Same as above and UGIB
  - Same as above and H. pylori
  - Same as above and NSAID
  - Patients who require a low galactose diet

**Side Effects:**
- **Proton Pump Inhibitors:**
  - Dizziness, headache, flatulence, abdominal pain, nausea, rash increased risk of osteoporotic fracture (secondary to impaired calcium absorption)
<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
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<th>Dosing</th>
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<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Emetics</td>
<td>dimenhydrinate</td>
<td>Gravol</td>
<td>25-50 mg PO/IM q4-6h pm</td>
<td>Competitive H1 receptor antagonist in GI tract, blood vessels, and respiratory tract. Blocks chemoenteropet trigger zone. Diminishes vestibular, suppresses labyrinthine function through central anticholinergic action.</td>
<td>Motion sickness, radiation sickness, postoperative vomiting, and drug-induced N/V</td>
<td>Hypersensitivity to drug</td>
<td>Xerostomia, sedation</td>
</tr>
<tr>
<td></td>
<td>prochlorperazine</td>
<td>Stemetil</td>
<td>10 mg PO/IV bid-tid pm</td>
<td>D1, D2 receptor antagonist in chemoenteropet trigger zone and α antagonism of α-antiadrenergic effects to depresses motilility of the vagus nerve.</td>
<td>Post-operative N/V, antipsychotic, anxiety</td>
<td>Hypersensitivity to drug</td>
<td>Dystonia, EPS, seizure, neurotoxic malignant syndrome (NMS) (rarely)</td>
</tr>
<tr>
<td></td>
<td>metoclopramide</td>
<td>Maxolon</td>
<td>10 mg IM q12 h</td>
<td>Dopamine and 5-HT receptor antagonist in chemoenteropet trigger zone. Enhances response to ACH in upper GI tract, enhancing motility and gastric emptying. Increases LES tone.</td>
<td>GERD, diabetic gastroparesis, post-operative and chemotherapy-induced N/V, migraines, constipation</td>
<td>Hypersensitivity to drug, GI obstruction, per oration, hemorrhage, pheochromocytoma, seizures, and EPS</td>
<td>Restlessness, drowsiness, diziness, fatigue, EPS, some rare serious side effects include NMS, agranulocytosis</td>
</tr>
<tr>
<td>IBD Agents</td>
<td>mesalamine</td>
<td>Pentasa, Sablex, Asacol, Mesasal</td>
<td>CD: 1 g PO tid-qid Active UC: 1 g PO qid Maintenance UC: 1.6 g PO divided doses daily also as suppositories and enemas</td>
<td>Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component.</td>
<td>Same as above.</td>
<td>N/V caused by cancer chemotherapy and radiation therapy</td>
<td>Same as above.</td>
</tr>
<tr>
<td></td>
<td>sulfasalazine</td>
<td>Salazopyrin</td>
<td>3-4 g PO in divided doses</td>
<td>Same as above.</td>
<td>Colonic disease.</td>
<td>Same as above.</td>
<td>Abdominal pain, constipation, anorexia, headache.</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>prednisone</td>
<td>Deltasone</td>
<td>20-40 mg PO OD for acute exacerbation</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>Complications of steroid therapy</td>
</tr>
<tr>
<td></td>
<td>6-mercaptopurine</td>
<td>Pu mepitol</td>
<td>CD: 1.5 mg/kg q4 PD</td>
<td>Immunomodulatory</td>
<td>Immunosuppressive.</td>
<td>Same as above.</td>
<td>Same as above.</td>
</tr>
<tr>
<td></td>
<td>azathioprine</td>
<td>Imuran</td>
<td>BID: 2 3 mg/kg PD</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>Same as above.</td>
</tr>
<tr>
<td>Biologics</td>
<td>infliximab</td>
<td>Remicade</td>
<td>5-10 mg/kg IV over 2 h</td>
<td>Monoclonal antibody to TNF-α</td>
<td>Medically refractory CD.</td>
<td>Heart failure, moderate to severe, doses &gt; 5 mg/kg</td>
<td>Reported cases of reactivated TBL, PDP, lymphoma, other infections. Other TNFα share similar serious side-effects</td>
</tr>
<tr>
<td></td>
<td>adalimumab</td>
<td>Humira</td>
<td>CD induction: 40 mg SC on day 1, then 80 mg SC on day 15 CD maintenance: 40 mg every other wk beginning day 29</td>
<td>Monoclonal antibody to TNF-α</td>
<td>Medically refractory CD or poor response to infliximab</td>
<td>Hypersensitivity to adalimumab.</td>
<td>Headaches, skin rash, upper respiratory tract infection.</td>
</tr>
<tr>
<td></td>
<td>golimumab</td>
<td>Simponi</td>
<td>RA: 2 mg/kg at wk 0, 4 and then every 8 wks thereafter (use with methotrexate) UC induction: 200 mg SC at wk 0, then 100 mg SC at wk 2 UC maintenance: 50 mg every 4 wk</td>
<td>Monoclonal antibody to TNF-α</td>
<td>Active ankylosing spondylitis. Postinfectious reactive arthritis.</td>
<td>Hypersensitivity to golimumab or latex. Moderate-to-severe RA.</td>
<td>Moderate-to-severe heart failure.</td>
</tr>
<tr>
<td></td>
<td>vedolizumab</td>
<td>Entyvio</td>
<td>CD/UC: 300 mg at 0, 2, 6 wks and then every 4 wks thereafter</td>
<td>Monoclonal antibody to α4β7 integrin.</td>
<td>Medically refractory CD/UC, including other TNF-α inhibitors and corticosteroids</td>
<td>Hypersensitivy to vedolizumab.</td>
<td>Infections, liver injury, and progressive-multifocal leukoencephalopathy</td>
</tr>
</tbody>
</table>
# Landmark Gastroenterology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score as a predictor of death in chronic liver disease</td>
<td>Gastroenterology 2003;124:91-6</td>
<td>MELD score can be applied for allocation of donor livers as it accurately predicts 3 mo mortality in patients with chronic liver failure</td>
</tr>
<tr>
<td>Infliximab, azathioprine, or combination for Crohn’s disease</td>
<td>NEJM 2010;362:1383-95</td>
<td>In moderate-severe Crohn’s disease, infliximab + azathioprine was more likely to result in corticosteroid-free remission than infliximab monotherapy. Infliximab monotherapy was more effective than azathioprine monotherapy. Similar results have been reported for ulcerative colitis (Gastroenterology 2014; 146:392-400)</td>
</tr>
<tr>
<td>Enteral versus parenteral nutrition for acute pancreatitis</td>
<td>Cochrane DB Syst Rev 2010;1:CD002837</td>
<td>For acute pancreatitis, no trial was convincing alone, but in aggregate, enteral feeds via nasogastric tube is preferable to either no feeding or parenteral nutrition</td>
</tr>
<tr>
<td>Rifaximin treatment in hepatic encephalopathy</td>
<td>NEJM 2010;362:1071-81</td>
<td>The most convincing of several articles establishing this non-absorbable antibiotic as the treatment of choice for hepatic encephalopathy for maintaining remission from hepatic encephalopathy and reducing hospitalization associated with the disease</td>
</tr>
<tr>
<td>Adenoma detection rate and risk of colorectal cancer and death</td>
<td>NEJM 2014;370:1298-1306</td>
<td>A high miss rate for colorectal cancers has been suggested, chiefly in the right colon. This study demonstrates a method of assessing the competence of endoscopists in detecting cancers using adenoma detection rate (the proportion of colonoscopic exams in which a physician detects one or more adenomas) as a surrogate marker. Adenoma detection rate was associated with lower risk of interval colorectal cancer and has launched quality assurance programs for screening colonoscopies</td>
</tr>
<tr>
<td>Prednisolone or pentoxifylline for alcoholic hepatitis</td>
<td>NEJM 2015;372:1619-28</td>
<td>For alcoholic hepatitis, prednisolone improved survival when the Maddrey’s discriminant function &gt; 32, but the benefit did not reach statistical significance and pentoxifylline was of no advantage at all. Other studies had shown some benefit with pentoxifylline, but this study was the most definitive</td>
</tr>
</tbody>
</table>
Acronyms ............................................. 2
Basic Anatomy Review .......................... 2
Differential Diagnoses of Common
Presentations .......................... 4
   Acute Abdominal Pain
   Abdominal Mass
   Gastrointestinal Bleeding
   Jaundice
Pre-Operative Preparations ................. 7
Surgical Complications ..................... 7
   Post-Operative Fever
   Wound/Incisional Complications
   Urinary and Renal Complications
   Post-Operative Dyspnea
   Respiratory Complications
   Cardiac Complications
   Intra-Abdominal Abscess
   Paralytic Ileus
   Delirium
Thoracic Surgery ............................. 13
   Hiatus Hernia
   Esophageal Perforation
   Esophageal Carcinoma
   Thymoma
   Pleura, Lung, and Mediastinum
   Tube Thoracostomy
   Lung Transplantation
   Chronic Obstructive Pulmonary Disease
Stomach and Duodenum .................. 18
   Peptic Ulcer Disease
   Gastric Carcinoma
   Gastrointestinal Stromal Tumour
   Bariatric Surgery
   Complications of Gastric Surgery
SMALL INTESTINE ........................... 21
Small Bowel Obstruction ................. 21
   Mechanical Small Bowel Obstruction
   Paralytic Ileus
   Intestinal Ischemia
   Tumours of Small Intestine
   Short Gut Syndrome
Abdominal Hernia ............................. 25
   Groin Hernias
Appendix ........................................ 27
   Appendicitis
Inflammatory Bowel Disease ............. 28
   Crohn’s Disease
   Ulcerative Colitis
LARGE INTESTINE .......................... 29
Large Bowel Obstruction ............... 29
   Mechanical Large Bowel Obstruction
   Functional LBO: Colonic Pseudo-Obstruction
   (Ogilvie’s Syndrome)
Diverticular Disease ...................... 31
   Diverticulosis
   Diverticulitis
Colorectal Neoplasms ..................... 33
   Colorectal Polyps
   Familial Colon Cancer Syndromes
   Colorectal Carcinoma
Other Conditions of the Large Intestine .. 36
   Angiodyplasia
   Volvulus
   Toxic Megacolon
   Fistula
   Stomas
Anorectum ..................................... 38
   Hemorrhoids
   Anal Fissures
   Anorectal Abscess
   Fistula-In-Ano
   Pilonidal Disease
   Rectal Prolapse
   Anal Neoplasms
Liver ............................................ 42
   Liver Cysts
   Liver Abscesses
   Neoplasms
   Liver Transplantation
Biliary Tract ................................. 46
   Cholelithiasis
   Biliary Colic
   Acute Cholecystitis
   Acalculous Cholecystitis
   Choledocholithiasis
   Acute Cholangitis
   Gallstone ileus
   Carcinoma of the Gallbladder
   Cholangiocarcinoma
Pancreas ....................................... 51
   Acute Pancreatitis
   Chronic Pancreatitis
   Pancreatic Cancer
Spleen ........................................ 54
   Splenic Trauma
   Splenectomy
   Splenic Infarct
Breast ......................................... 55
   Benign Breast Lesions
   Breast Cancer
Surgical Endocrinology .................. 60
   Thyroid and Parathyroid
   Adrenal Gland
   Pancreas
Pediatric Surgery ......................... 62
Skin Lesions ................................. 65
Common Medications ..................... 65
References .................................. 65
Acronyms

Basic Anatomy Review

Figure 1. Abdominal incisions

Lateral Abdominal Wall Layers and their Continuous Spermatic and Scrotal Structures (superficial to deep)
1. skin (epidermis, dermis, subcutaneous fat)
2. superficial fascia
   • Camper’s fascia (fatty) → Dartos muscle/fascia
   • Scarpa’s fascia (membranous) → Colles’ superficial perineal fascia
3. muscle (see Figure 2 and Figure 3)
   • external oblique → inguinal ligament → external spermatic fascia and fascia lata
   • internal oblique → cremasteric muscle/fascia
   • transversus abdominis → posterior inguinal wall
4. transversalis fascia → internal spermatic fascia
5. preperitoneal fat
6. peritoneum → tunica vaginalis

Midline Abdominal Wall Layers (superficial to deep)
1. skin
2. superficial fascia
3. rectus abdominis muscle: in rectus sheath, divided by linea alba (see Figure 3)
   • above arcuate line (midway between symphysis pubis and umbilicus)
     • anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
     • posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus abdominis aponeurosis
   • below arcuate line
     • aponeuroses of external oblique, internal oblique, transversus abdominis all pass in front of rectus abdominis
4. arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle (superficial to posterior rectus sheath above arcuate line)
5. transversalis fascia
6. peritoneum
Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord

Figure 3. Midline cross-section of abdominal wall

Figure 4. Arterial blood supply to the GI tract
Venous Flow

Portal vein (1)
Superior mesenteric vein (7)
  i) Ileal and jejunal veins (13)
  ii) Ileocolic vein (14)
  iii) Right colic vein (12)
  iv) Middle colic vein (11)
  v) Pancreaticoduodenal vein (8)
  vi) Right gastroepiploic vein (9)
Splenic vein (5)
  i) Inferior mesenteric vein (10)
  ii) Superior rectal vein until crossing
  common iliac vessels
  • Left colic veins (15)
  • Sigmoid veins (16)
  • Superior rectal veins (17)
  iii) Pancreatic veins
  iv) Left gastroepiploic vein
  iv) Short gastric veins (6)
Left gastric (coronary) vein (2)
Right gastric vein (3)
Cystic vein (4)
Paraumbilical vein – (within round ligament, not shown)

Figure 5. Venous drainage of the GI tract

Differential Diagnoses of Common Presentations

Acute Abdominal Pain

- acute abdomen = severe abdominal pain of acute onset and requires urgent medical attention
- in patients with acute abdominal pain, the first diagnoses that you should consider are those requiring potential urgent surgical intervention
- two main patterns constituting urgent general surgery referrals are peritonitis and obstruction

Table 1. Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>RUQ</th>
<th>RLQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatobiliary</strong></td>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Tuberculosis of the ileocecal junction</td>
</tr>
<tr>
<td>CBD obstruction (stone, tumour)</td>
<td>Cecal tumour</td>
</tr>
<tr>
<td>Hepatitis (includes parvovirus B19)</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>Mesenteric lymphadenitis (Yersinia)</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>Cecal diverticulitis</td>
</tr>
<tr>
<td>Hepatic abscess/mass</td>
<td>Cecal volvulus</td>
</tr>
<tr>
<td>Right subphrenic abscess</td>
<td>Hernia: femoral, inguinal obstruction, Amyand’s (and resulting cecal distention)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Gynecological</td>
</tr>
<tr>
<td>Presentation of gastric, duodenal, or pancreatic pathology</td>
<td>See ‘suprapubic’</td>
</tr>
<tr>
<td>Hepatic flexure pathology (CRC, subcostal incisional hernia)</td>
<td><strong>Genitourinary</strong></td>
</tr>
<tr>
<td>Presentation of gastric, duodenal, or pancreatic pathology</td>
<td>See ‘suprapubic’</td>
</tr>
<tr>
<td><strong>Genitourinary</strong></td>
<td>Extrapertitoneal</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>Abdominal wall hematoma/abscess</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Psoas abscess</td>
</tr>
<tr>
<td>Renal: mass, ischemia, trauma</td>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>MI</td>
</tr>
<tr>
<td>RLL pneumonia</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Effusion/empyema</td>
<td>Pleuritis</td>
</tr>
<tr>
<td>CHF (causing hepatic congestion and R pleural effusion)</td>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>MI</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Trauma</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>Costochondritis</td>
</tr>
</tbody>
</table>

In all patients presenting with an acute abdomen, order the following:

**KEY TESTS FOR SPECIFIC DIAGNOSIS**
- ALT, AST, bilirubin
- Lipase/amylase
- Urea/urea nitrogen
- HCG (in women of childbearing age)
- Troponin
- Lactate

**KEY TESTS FOR OR PREPARATION**
- CBC, electrolytes, creatinine, glucose
- INR/PTT
- CXR (if history of cardiac or pulmonary disease)
- ECG if clinically indicated by history or if >69 yr and no risk factors

**Types of Peritonitis**
- Primary peritonitis: spontaneous without clear etiology
- Secondary peritonitis: due to a perforated viscus
- Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

**Localization of Pain**
Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation; kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain

**Referred Pain**
- Biliary colic: to right shoulder or scapula
- Renal colic: to groin
- Appendicitis: periumbilical to right lower quadrant (RLQ)
- Pancreatitis: to back
- Ruptured aortic aneurysm: to back or flank
- Perforated ulcer: to RLQ (right paracolic gutter)
- Hip pain: to groin
### Differential Diagnoses of Common Presentations

#### Most Common Presentations of Surgical Pain
- Sudden onset with rigid abdomen = perforated viscus
- Pain out of proportion to physical findings = ischemic bowel
- Vague pain that subsequently localizes = appendixitis or other intra-abdominal process that irritates the parietal peritoneum
- Waves of colicky pain = bowel obstruction

#### Table 1. Differential Diagnosis of Acute Abdominal Pain (continued)

<table>
<thead>
<tr>
<th>LUQ</th>
<th>LLQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pancreatic</strong></td>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Pancreatitis (acute vs. chronic)</td>
<td>Gast intestinal</td>
</tr>
<tr>
<td>Pancreatic pseudocyst</td>
<td>Diverticulitis</td>
</tr>
<tr>
<td>Pancreatic tumours</td>
<td>Diverticulosis</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Color/sigmoid/rectal cancer</td>
</tr>
<tr>
<td>Gastritis</td>
<td>Fecal impaction</td>
</tr>
<tr>
<td>PUD</td>
<td>Preactitis (ulcerative colitis, infectious; i.e. <em>A. aerogenes</em> or <em>C. difficile</em>)</td>
</tr>
<tr>
<td>Splenic flexure pathology (e.g. CRC, ischemia)</td>
<td>Sigmoid volvulus</td>
</tr>
<tr>
<td>Splenic infarct/abscess</td>
<td>Hemia</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Extraperitoneal</td>
</tr>
<tr>
<td>Splenic rupture</td>
<td>Abdominal wall hematoma/abscess</td>
</tr>
<tr>
<td>Splenic artery aneurysm</td>
<td>Psoas abscess</td>
</tr>
<tr>
<td><strong>Cardiopulmonary (see RUQ and Epigastric)</strong></td>
<td>See ‘suprapubic’</td>
</tr>
<tr>
<td><strong>Genitourinary (see RUQ)</strong></td>
<td>See Gynecology, Urology, Respiratology, and Cardiology and Cardiac Surgery for further details regarding respective etiologies of acute abdominal pain</td>
</tr>
</tbody>
</table>

#### Table 2. Differential Diagnosis of Abdominal Mass

<table>
<thead>
<tr>
<th>Right Upper Quadrant (RUG)</th>
<th>Upper Midline</th>
<th>Left Upper Quadrant (LUQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder: cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis</td>
<td>Pancreas: pancreatic adenocarcinoma, other pancreatic neoplasm, pseudocyst</td>
<td>Spleen: splenomegaly, tumour, abscess subcapsular splenic hemorrhage, can also present as RLU mass if extreme splenomegaly</td>
</tr>
<tr>
<td>Liver: hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)</td>
<td>Abdominal aorta: AAA (pseudole)</td>
<td>Stomach: tumour</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Right Lower Quadrant (RLQ)</th>
<th>Lower Midline</th>
<th>Left Lower Quadrant (LLQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine: stool, tumour (CRC, mesenteric adenitis, appendicitis, appendiceal phelegm or other abscess, typhilitis, intussusception, Crohn’s inflammation</td>
<td>Uterus: pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra</td>
<td>Intestine: stool, tumour, abscess (see RLQ)</td>
</tr>
<tr>
<td>Ovary: ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, x ruma ovari, germ cell, Knuekenberg)</td>
<td>GU: bladder distention, tumour</td>
<td>Ovary: see RLQ</td>
</tr>
<tr>
<td>Fallopian tube: ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour</td>
<td></td>
<td>Fallopian tube: see RLQ</td>
</tr>
</tbody>
</table>

### Abdominal Mass

#### Table 2. Differential Diagnosis of Abdominal Mass

<table>
<thead>
<tr>
<th>Right Upper Quadrant (RUG)</th>
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<tr>
<td>Liver: hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)</td>
<td>Abdominal aorta: AAA (pseudole)</td>
<td>Stomach: tumour</td>
</tr>
</tbody>
</table>

#### Right Lower Quadrant (RLQ)

| Intestine: stool, tumour (CRC, mesenteric adenitis, appendicitis, appendiceal phelegm or other abscess, typhilitis, intussusception, Crohn’s inflammation | Uterus: pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra | Intestine: stool, tumour, abscess (see RLQ) |
| Ovary: ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, x ruma ovari, germ cell, Knuekenberg) | GU: bladder distention, tumour | Ovary: see RLQ |
| Fallopian tube: ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour | | Fallopian tube: see RLQ |

Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate surgical intervention.
Gastrointestinal Bleeding

- see Gastroenterology, G25

Indications for Surgery
Failure of medical management
- Exsanguinating hemorrhage: hemodynamic instability despite vigorous resuscitation
- Recurrent hemorrhage with up to two attempts of endoscopic hemostasis
- Prolonged bleeding with transfusion requirement >3 units
- Bleeding at rate >1 unit/8 h

Surgical Management of GI Bleeding
- UGIB
  - Bleeding from a source proximal to the ligament of Treitz
  - Often presents with hematemesis and melena unless very brisk (then can present with hematochezia)
  - Initial management with endoscopy; if fails, then consider surgical management appropriate to etiology
  - PUD accounts for approximately 55% of severe UGIB
- LGIB
  - Bleeding from a source distal to the ligament of Treitz
  - Often presents with BRB unless proximal to transverse colon
  - May occasionally present with melena
  - Initial management with colonoscopy to detect and potentially stop source of bleeding
  - 75% of patients will spontaneously stop bleeding, however if bleeding continues barium enema should NOT be performed
  - Angiography or RBC scan to determine source as indicated
  - Surgery indicated if bleeding is persistent - aimed at resection of area containing source of bleeding
  - Obscure bleed may require blind total colectomy if the source is not found

Table 3. Differential Diagnosis of GI Bleeding

<table>
<thead>
<tr>
<th>Anatomical Source</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Excess anticoagulation (coumadin, heparin, etc.)</td>
</tr>
<tr>
<td></td>
<td>Excess antiplatelet (clopidogrel, ASA)</td>
</tr>
<tr>
<td></td>
<td>DIC Congenital bleeding disorders</td>
</tr>
<tr>
<td></td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophageal varices</td>
</tr>
<tr>
<td></td>
<td>Mallory-Weiss tear</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastritis</td>
</tr>
<tr>
<td></td>
<td>Gastric varices</td>
</tr>
<tr>
<td></td>
<td>Dieulafoy’s lesion</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td></td>
<td>Perforated duodenal ulcer*</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Tumours*</td>
</tr>
<tr>
<td></td>
<td>Polyps</td>
</tr>
<tr>
<td>Ileum and Ileocecal Junction</td>
<td>Meckel’s diverticulum (rare surgical management)</td>
</tr>
<tr>
<td></td>
<td>Small bowel obstruction</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>Colorectal cancer*</td>
</tr>
<tr>
<td></td>
<td>Mesenteric thrombosis/ischemic bowel*</td>
</tr>
<tr>
<td></td>
<td>Ulcerative colitis* (subtotal colectomy if failure of medical management)</td>
</tr>
<tr>
<td></td>
<td>Angiodysplasia</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>Diverticulosis (*if bleeding is persistent)</td>
</tr>
<tr>
<td>Rectum and Anus</td>
<td>Hemorrhoids</td>
</tr>
<tr>
<td></td>
<td>Fissures</td>
</tr>
<tr>
<td></td>
<td>Rectal cancer*</td>
</tr>
<tr>
<td></td>
<td>Anal varices</td>
</tr>
<tr>
<td></td>
<td>Polyps (*if not amenable to colonoscopic polypectomy)</td>
</tr>
<tr>
<td></td>
<td>Crohn’s or ulcerative colitis*</td>
</tr>
<tr>
<td></td>
<td>Solitary rectal ulcer syndrome</td>
</tr>
</tbody>
</table>

*Managed surgically in most cases

Jaundice

- see Gastroenterology, G40

Indications for Urgent Operation

IHOP
- Ischemia
- Hemorrhage
- Obstruction
- Perforation

Overt bleeding: obvious hematemesis, hematochezia or melena per rectum (i.e. visible to naked eye)

Occult bleeding: bleeding per rectum is not obvious to naked eye (e.g. positive guaiac FOBT)

Obscure bleeding: bleeding with no identifiable source after colonoscopy and endoscopy (source usually in small bowel). Can be either overt or occult

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Recent study by Villanueva et al., demonstrates that a restrictive transfusion strategy (transfusion with hemoglobin below 70 g/L) significantly improves outcomes in patients with acute UGIB compared to a liberal transfusion strategy (transfusion with hemoglobin below 90 g/L). Refer to study for details.

Biochemical Signs for Differentiating Jaundice

Hepatocellular: Elevated bilirubin + elevated ALT/AST

Cholestatic: Elevated bilirubin + elevated ALP/GGT ± duct dilatation upon biliary US

Hemolysis: ↑ haptoglobin ↑ LDH

Note: cholestatic jaundice is often surgical
Pre-Operative Preparations

Considerations
- informed consent (see Ethical, Legal, and Organizational Medicine, ELOM7)
- screening questionnaire to determine risk factors e.g. age, exercise capacity, medication use, allergies
- consider pre-operative anesthesia, medicine consult as indicated to optimize patient status
- NPO according to guidelines (see Anesthesia and Perioperative Medicine, A4)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule → roughly 100-125 cc/h): normal saline or Ringer’s lactate; bolus to catch up on estimated losses including losses from bowel prep
  - appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patient’s regular medications included with the exception of hypoglycemic agents, diuretics and ACEI
- patients on steroids may require stress dose coverage, anticoagulation/antiplatelet medication must be managed to decrease surgical bleeding but not put patient at risk for increased thrombotic events (e.g. switching from warfarin to LMWH)
- prophylactic antibiotics depending on wound class (within 1 h prior to incision): usually cefazolin (Ancef®) ± metronidazole (Flagyl®)
  - consider MBP: cleans out bowel
    - oral cathartic (e.g. Fleet Phosphosoda®) starting previous day
    - in selected cases, current evidence does not support routine use
  - consider VTE prophylaxis for all inpatient surgery (LMWH or heparin)
  - do not hold anticoagulation prior to surgery unless epidural is expected
  - smoking cessation and weight loss pre-operative can significantly decrease post-operative complications
  - infection: delay elective surgery until infection controlled, including respiratory infection (particularly in asthma patients)

Investigations
- see Anesthesia and Perioperative Medicine, A4
- routine pre-operative laboratory investigations for elective procedures should be selective
  - only ASA class and surgical risk have been found to independently predict post-operative adverse effects
  - blood components: group and screen or cross and type depending on procedure
  - CBC, electrolytes, creatinine
  - INR/PT, PTT
  - CXR (PA and lateral) for patients with history of cardiac or pulmonary disease
  - ECG as indicated by history or if >69 yr and no risk factors
  - β-hCG testing in all women of reproductive age

Drains
- NGT
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding, if necessary
  - contraindications: suspected basal skull fracture, obstruction of nasal passages, esophageal strictures, esophageal varices
- Foley catheter with urometer
  - indications: to accurately monitor urinary output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  - contraindications: suspected urethral injury, and difficult insertion of catheter

Surgical Complications
- general principles in preventing complications during the post-operative period include
  - frequent examination of the patient (daily or more) and their wound
  - removal of surgical tubes as soon as possible (e.g. Foley catheters and surgical drains)
  - early ambulation
  - monitor fluid balance and electrolytes
  - analgesia - enough to adequately address pain, but not excessive
  - skillful nursing care

Post-Operative Fever
- fever does not necessarily imply infection particularly in the first 24-48 h post-operative
- fever may not be present or is blunted if patient is receiving chemotherapy, glucocorticoids, or immunosuppression
- timing of fever may help identify cause
  - hours after surgery – POD #1 (immediate)
    - inflammatory reaction in response to trauma from surgery; unlikely to be infectious
    - reaction to blood products received during surgery
    - malignant hyperthermia

Billirubin Levels

<table>
<thead>
<tr>
<th>Prophylactic</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Bilirubin</td>
<td></td>
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<tr>
<td>Indirect ↑ ↑ N</td>
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<tr>
<td>Direct N ↑ ↑</td>
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<tr>
<td>Urine Urobilinogen ↑ ↑</td>
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<tr>
<td>Bilirubin – + +</td>
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<td></td>
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<tr>
<td>Fecal Urobilinogen ↑ ↑ –</td>
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</tbody>
</table>

In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out

Surgical Emergencies: Take an AMPLE History
- Allergies
- Medications
- Past medical/surgical history (including anesthesia and bleeding disorders)
- Last meal
- Events (HPI)

Best Practice in General Surgery (BPIGS)
http://www.bpgs.ca/
BPIGS is a University of Toronto initiative with the goal of standardizing care in general surgery. This link contains EBM based guidelines which have been implemented by consensus within all Toronto teaching hospitals. This is a highly recommended source for the most up-to-date pre-operative and general treatment guidelines

Mechanical Bowel Preparation Strategies: A Clinical Practice Guideline developed by the University of Toronto’s Best Practice in Surgery
1. All open/laparoscopic colorectal procedures (excluding LARs ± diverting stoma)
   - No MBP
   - No dietary restrictions before NPO
   - Fleet enema for left colon
   - Anastomoses with transrectal stapling
2. Open/laparoscopic LAR ± diverting stoma
   - MBP
   - No dietary restrictions before MBP, clear fluids after MBP complete

Drain Size
- Measured by the unit French:
  - French = diameter (mm) x 3

Bilirubin Levels

<table>
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In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out
Surgical Complications

- POD #1-2 (acute)
  - atelectasis (most common cause of fever on POD #1)
  - early wound infection (especially Clostridium, Group A Streptococcus – feel for crepitus and ooze for “dishwasher” drainage)
  - aspiration pneumonitis
  - other: Addisonian crisis, thyroid storm, and transfusion reaction
- POD #3-7 (subacute): likely infectious
  - UTI, surgical site infection, IV site/line infection, septic thrombophlebitis, and leakage at bowel anastomosis (tachycardia, hypotension, oliguria, and abdominal pain)
- POD #8+ (delayed)
  - intra-abdominal abscess, DVT/PE (can be anytime post-operative, most commonly POD #8-10), and drug fever
  - other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, C. difficile colitis, and endocarditis

Treatment
- treat primary cause
- antipyrexia (e.g. acetaminophen)

Wound/Incisional Complications

WOUND CARE (see Plastic Surgery, PL8)
- can shower POD #2-3 after epithelialization of wound
dressings can be removed POD #2 and left uncovered if dry
- examine wound if wet dressing, signs of infection (fever, tachycardia, and pain)
skin sutures and staples can be removed POD #7-10
- exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, or immunosuppressed) removed POD #14, earlier if signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin, or ulcer)

DRAINS
- drains may be placed selectively at the time of surgery to prevent fluid accumulation (blood, pus, serum, bile, and urine)
- can be used to assess quantity of third space fluid accumulation post-operatively
- potential route of infection; to decrease risk of wound infection bring out through separate incision (vs operative wound) and remove as soon as possible
- types of drains
  - open (e.g. Penrose), higher risk of infection
  - closed: 1) Gravity drainage (e.g. Foley catheter); 2) Underwater-seal drainage system (e.g. chest tube); 3) Suction drainage (e.g. Jackson-Pratt)
  - sump (e.g. NGT)
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually <30-50 cc/24 h)
- drains do not guarantee that the patient will not form a collection of fluid
- ridged drains can erode through internal structures, and excessive suction can cause necrosis
- evidence does not support routine post-operative drainage of abdominal cavity

SURGICAL SITE INFECTION

Etiology
- *S. aureus*, *E. coli*, *Enterococcus*, *Streptococcus* spp., *Clostridium* spp.

Risk Factors

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clean</th>
<th>Clean-Contaminated</th>
<th>Contaminated</th>
<th>Dirty/Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Incision under sterile conditions; nontraumatic; no entrance of hollow organ</td>
<td>Incision under sterile conditions; ENTRANCE of hollow viscous; no evidence of active infection; minimal contamination</td>
<td>Incision under sterile conditions; MAJOR contamination of wound during procedure (i.e. gross spillage of stool, infection in biliary, respiratory, or GU systems)</td>
<td>Established infection present before wound is made in skin</td>
</tr>
<tr>
<td>Example</td>
<td>Hernia repair</td>
<td>Routine cholecystectomy; colon resection</td>
<td>Bowel obstruction with enterotomy and spillage of contents; necrotic bowel resection; fresh traumatic wounds</td>
<td>Appendiceal abscess; traumatic wound with contaminated devitalized tissue; perforated viscous</td>
</tr>
<tr>
<td>Infection Rate</td>
<td>&lt;2%</td>
<td>3-4%</td>
<td>7 10%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Wound Closure</td>
<td>Primary closure</td>
<td>Primary closure</td>
<td>Often secondary closure</td>
<td>Secondary closure</td>
</tr>
</tbody>
</table>
Surgical Complications

- patient characteristics
  - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, and chemotherapy
- other factors
  - prolonged pre-operative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts), skin preparation, hypoxemia, and hyperthermia

Prophylaxis
- pre-operative antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamycin)
- within 1 h pre-incision; can redose at 1-2 half-lives (~q4-8h) in the OR
- not required for low risk elective cholecystectomy, hemorrhoidectomy, fistulotomy, and sphincterotomy for fissure
- some evidence suggests role in breast surgery
- reserve post-operative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C during OR)
- hyperoxygenation (consider FiO₂ of 80% in OR)
- chlorhexidine alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving
- consider delayed primary closure of incision for contaminated wounds

Clinical Presentation
- typically fever POD #5-8 (Streptococcus and Clostridium can present in 24 h)
- pain, blanchable wound erythema, induration, purulent discharge, and warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, and hernia

Treatment
- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- re-open affected part of incision, drain, pack, heal by secondary intention in most cases
- for deeper infections, debride necrotic and non-ammable tissue
- antibiotics and dermal healing of erythema only if cellulitis or immunodeficiency

WOUND HEMORRHAGE/HEMATOMA
- secondary to inadequate surgical control of hemostasis

Risk Factors
- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial HTN, and severe cough
- more common with transverse incisions through muscle, due to cutting of muscle

Clinical Features
- pain, swelling, discoloration of wound edges, and leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency: consider having a suture kit at bedside in all neck surgery in the event of having to open the wound emergently

Treatment
- pressure dressing
- open drainage ± wound packing (large hematoma only)
- if significant bleeding, may need to re-operate to find source (often do not find a discrete source)

SEROMA
- fluid collection other than pus or blood
- secondary to transection of lymph vessels
- delays healing
- increased infection risk

Treatment
- consider pressure dressing ± needle drainage
- if significant may need to re-operate

WOUND DEHISCENCE
- disruption of fascial layer, abdominal contents contained by skin only
- 95% caused by intact suture tearing through fascia

Risk Factors
- local: technical failure of closure, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, patient not fully paralyzed while closing, and transverse incision

Systemic Prophylactic Antibiotics

Pre-Operative Skin Antiseptics for Preventing Surgical Wound Infections After Clean Surgery

- Cochrane DB Syst Rev 2015;6:CD003949
- Purpose: To determine if pre-operative skin antiseptics prior to clean surgery prevents surgical-site infection (SSI) and compare the effectiveness of other antiseptics.
- Methods: Systematic review of randomized-controlled trials (RCTs) of the Cochrane Wounds Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL).
- Main outcome was SSI. Secondary outcomes included quality of life, mortality, and resource use.
- Results: 13 RCTs (n=2,623 patients) were included that made 11 total comparisons between skin antiseptics. A single study found that 0.5% chlorhexidine solution in methylated spirits was significantly superior in preventing SSIs after clean surgery compared to alcohol based povidone iodine solution. No other statistically significant differences were found.
- Conclusions: Further research is warranted to determine the effectiveness of one antiseptic over the others at preventing SSI post clean surgery.

Systemic Review and Meta-Analysis of Randomized Clinical Trials Comparing Primary vs. Delayed Primary Skin Closure in Contaminated and Dirty Abdominal Incisions

- Purpose: To compare rates of surgical site infection (SSI) with delayed primary closure (DPC) vs. primary skin closure (PC).
- Results/Conclusions: 8 RCTs with 623 patients. Most common diagnosis was appendicitis (77.4%). Although there was significant heterogeneity between studies, DPC (2-5 d time to first review) was found to significantly reduce the chance of SSI (OR 0.65, 95% CI 0.40-0.90). Although current trials are poorly designed, DPC may be a simple and cost-effective way of reducing the rates of SSIs following abdominal surgery with contaminated or dirty wounds.

Pre-Operative Antibiotics

Updated Recommendations for Control of Surgical Site Infections
- Ann Surg 2011;253:1082-93
- Choice of routine prophylactic antibiotic depends on the pathogen and patient allergies.
- Vancomycin and fluoroquinolones should be administered 1-2 h prior to incision; all other antibiotics should be administered 30 min prior to incision.
- Short-acting antibiotics should be redosed —3 h after incision.
- Antibiotic administration >24 h after surgery does not appear to add benefits.
- Antibiotics should no longer be routinely administered in three doses.
- The majority of antibiotics are renally excreted hence renal function must be considered in antibiotic administration.
- Obese patients need higher antibiotic doses to achieve therapeutic concentrations.
- Drug half-life and length of operation need to be considered in antibiotic administration.
Surgical Complications

- systemic: male, smoking, malnutrition (hypalbuminemia, vitamin C deficiency), connective tissue
diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy,
obesity, and other (e.g. age, sepsis, and uremia)
- DM alone is not a risk factor

Clinical Features
- typically POD #1-3; most common presentation sign is serosanguinous drainage from wound
- ± evisceration
- palpation of wound edge: should normally feel a "healing ridge" from abdominal wall closure (raised
area of tissue under incision)

Treatment
- place moist dressing over wound with binder around abdomen and transfer to OR
- may consider conservative management with debridement of fascial and/or skin margins
- evisceration (also known as 'burst abdomen') is a surgical emergency: take patient for operative re-
closure without abdomen binder

Urinary and Renal Complications

Urinary Retention
- may occur after any operation with general anesthesia or more commonly spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia, and patients on anticholinergics

Clinical Presentation
- abdominal discomfort, palpable bladderoverflow incontinence, post-void residual urine volume >100 mL

Treatment
- Foley catheter to rest bladder, then trial of voiding

Oliguria/Anuria (see Nephrology, NP18)

Etiology
- prerenal vs. renal vs. postrenal
- most common post-operative cause is prerenal ± ischemic ATN
  - external fluid loss: hemorrhage, dehydration, and diarrhea
  - internal fluid loss: third-spacing due to bowel obstruction, and pancreatitis

Clinical Presentation
- urine output <0.5 cc/kg/h, increasing Cr, and increasing BUN

Treatment
- according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

Post-Operative Dyspnea

- see Respiratory Complications next and Cardiac Complications, GS12

Etiology
- respiratory: atelectasis, pneumonia/pneumonitis, pulmonary embolus (PE), ARDS, asthma, and pleural
  effusion
- cardiac: MI arrhythmia, and CHF
- inadequate pain control

Respiratory Complications

Atelectasis
- comprises 90% of post-operative pulmonary complications

Risk Factors
- COPD, smoking, obesity, and elderly persons
- upper abdominal/thoracic surgery, oversedation, significant post-operative pain, and poor inspiratory
  effort

Clinical Features
- low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, and
tachypnea
Treatment
- pre-operative prophylaxis
  - smoking cessation (best if >8 wk pre-operative)
- post-operative prophylaxis
  - incentive spirometry, deep breathing exercise, chest physiotherapy, and intermittent positive-pressure breathing
  - selective NGT decompression after abdominal surgery
  - short-acting neuromuscular blocking agents
  - minimize use of respiratory depressant drugs, appropriate pain control, and early ambulation

PNEUMONIA/PNEUMONITIS
- may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

Risk Factors
- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NGT, pregnancy, and seizure disorder
- non-aspiration: atelectasis, immobility, and pre-existing respiratory disease

Clinical Features
- productive cough, and fever
- tachycardia, cyanosis, respiratory failure, and decreased LOC
- CXR: pulmonary infiltrate

Treatment
- prophylaxis: see atelectasis prophylaxis, pre-operative NPO/NGT, and rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- empiric IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. piperacillin-tazobactam, cefepimemetronidazole)

PULMONARY EMBOLUS (see Respirology, R18)

Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset dyspnea, pleuritic chest pain, tachycardia, and fever
- most commonly POD #8-10, but can occur anytime post-operatively, even after discharge
- diagnosis made by Chest CT scan usually

Treatment
- initial treatment: IV heparin or subcutaneous LMWH, bridging to therapeutic anticoagulation is required for a minimum of 3 mo; for patients with cancer, or other risk factors for hypercoagulability, the duration of anticoagulation may be longer
- Greenfield (IVC) filter if contraindications to anticoagulation
- prophylaxis: subcutaneous heparin (5,000 U bid) or LMWH, compression stockings (TED™ Hose), and sequential compression devices

PULMONARY EDEMA

Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, and alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anesthesia

Clinical Features
- shortness of breath, crackles at lung bases, and CXR abnormal

Treatment (LMNOP)
- Lasix
- Morphine (decreases symptoms of dyspnea, venodilator, and afterload reduction)
- Nitrates (venodilator)
- Oxygen + non-invasive ventilation
- Position (sit patient up)
**RESPIRATORY FAILURE**

**Clinical Features**
- dyspnea, cyanosis, and evidence of obstructive lung disease
- earliest manifestations - tachypnea and hypoxemia (RR >25, pO2 <60)
- pulmonary edema, and unexplained decrease in SaO2

**Treatment**
- ABCs, O2, ± positive pressure ventilation, and intubation
- bronchodilators, and diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO2 >60, consider ARDS (see Respilology, R27)

**Cardiac Complications**
- abnormal ECGs common in post-operative period (compare to pre-operative ECG)
- common arrhythmias: supraventricular tachycardia, atrial fibrillation (secondary to fluid overload, PE, and MI)

**MYOCARDIAL INFARCTION**
- see Cardiology and Cardiac Surgery, C27
- surgery increases risk of MI
- incidence
  - 0.5% in previously asymptomatic men >50 yr old
  - 40-fold increase in men >50 yr old with previous MI

**Risk Factors**
- pre-operative HTN, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intra-operative hypotension
- operations >3 h
- angina

**Clinical Features**
- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, and hypotension

**Intra-Abdominal Abscess**

**Definition**
- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

**Etiology**
- usually polymicrobial: Gram-negative bacteria, and anaerobes
  - consider Gram-positives if coexisting cellulitis

**Risk Factors**
- emergency surgery, and contaminated OR
- GI surgery with anastomoses
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid re-distribution occurs

**Clinical Features**
- persistent spiking fever, dull pain, and weight loss
- mass difficult to palpate
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised, and elderly)
- co-existing effusion (pleural effusion with subphrenic abscess)
- common sites: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, and psoas

**Investigations**
- CBC, blood cultures x2
- CT ± IV and water-soluble contrast
- DRE (pelvic abscess)
**Treatment**
- drain placement by interventional radiology (preferred), laparoscopy, and open drainage
- subsequent antibiotic coverage; ceftriaxone + metronidazole or piperacillin-tazobactam (Pip-Tazo)

**Paralytic Ileus**
- see Bowel Obstruction, GS23

**Delirium**
- see Psychiatry, PS19 and Neurology, N20

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**Thoracic Surgery**

**Hiatus Hernia**

![Image of hiatus hernia types](image)

**Figure 6. Types of hiatus hernia**

**SLIDING HIATUS HERNIA (TYPE I)**
- see Figure 6
- herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

**Risk Factors**
- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, and heavy lifting)
- smoking

**Clinical Features**
- majority are asymptomatic
- hernias frequently associated with GERD due to decreased competence of LES

**Complications**
- most common complication is GERD
- other complications are rare and are related to reflux
- esophagitis (dysphagia, and heartburn)
- consequences of esophagitis (peptic stricture, Barrett's esophagus, and esophageal carcinoma)
- extra-esophageal complications (aspiration pneumonitis/pneumonia, asthma type bronchospasm, cough, and laryngitis)

**Investigations**
- barium swallow, endoscopy (esophago-gastroscopy), or esophageal manometry (technique for measuring LES pressure)
- 24 h esophageal pH monitoring to quantify reflux
- endoscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett's esophagus, and cancer

<table>
<thead>
<tr>
<th>Differential Diagnosis of Hiatus Hernia</th>
<th>GI Causes</th>
<th>Non-GI Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis</td>
<td>MI</td>
<td>Angina</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td></td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achalasia</td>
<td></td>
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<tr>
<td>Pancreatitis</td>
<td></td>
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<tr>
<td>GERD</td>
<td></td>
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<tr>
<td>Gastritis</td>
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</tbody>
</table>

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Treatment
• lifestyle modification
  ■ stop smoking, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint, and fat
  ■ medical
    ▲ antacid, H2-antagonist, PPI, prokinetic agent
  ■ surgical (<15%)
    ● if failure of medical therapy, complications of GERD such as esophageal stricture, severe nocturnal aspiration, Barrett’s esophagus
    ■ anti-reflux procedure (usually laparoscopic) e.g. Nissen fundoplication
      ● fundus of stomach is wrapped around the lower esophagus and sutured in place
      ● 90% success rate

Paraesophageal Hiatus Hernia (Type II)
• see Figure 6
  ● herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
  ● least common esophageal hernia (<10%)

Clinical Features
• usually asymptomatic due to normal GE junction
• pressure sensation in lower chest, dysphagia

Complications
• hemorrhage, incarceration, strangulation (gastric volvulus), obstruction, gastric stasis ulcer (Cameron’s lesion – causes Fe-deficiency anemia)

Treatment
• surgery to address symptoms or treat/prevent complications
• reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
• may consider suturing stomach to anterior abdominal wall (gastroscopy)
• in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy) to anchor the stomach in the abdomen

Mixed Hiatus Hernia (Type III)
• see Figure 6
• combination of Types I and II

Type IV Hernia
• herniation of stomach and other abdominal organs into thorax: colon, spleen, small bowel
• Fe-deficiency anemia is common

Esophageal Perforation

Etiology
• iatrogenic (most common)
  ■ endoscopic, dilatation, biopsy, intubation, operative, and NGT placement (rare)
  ■ barogenic
  ■ trauma
  ■ repeated forceful vomiting (Boerhaave’s syndrome)
  ■ other: convulsions, defecation, or labour (rare)
  ■ ingestion injury
  ■ foreign body, or corrosive substance
  ■ carcinoma

Clinical Features
• neck or chest pain
• fever, tachycardia, hypotension, dyspnea, and respiratory compromise
• subcutaneous emphysema, pneumothorax, pleural effusion, and hematemesis

Investigations
• CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air, and widened mediastinum
• CT chest: pneumomediastinum, pleural effusion, pneumothorax, contrast in the chest, and subcutaneous emphysema
• upper GI swallow study with water soluble contrast
  ● if negative then perform with diluted barium: contrast extravasation

Boerhaave’s syndrome: transmural esophageal perforation
Mallory-Weiss tear: non-transmural esophageal tear (partial thickness tear)
Both are associated with forceful emesis
6Ss of SCC
$ Smoking
$ Spirits (alcohol)
$ Seeds (betel nut)
$ Scalding (hot liquid)
$ Strictures
$ Sack (diverticula)
Treatment
- support if rupture is contained
  - NPO, fluid resuscitation, broad-spectrum antibiotics, and possible percutaneous drainage of mediastinum or pleura
- surgical
  - <24 h from perforation
    - primary closure of a healthy esophagus or resection of diseased esophagus
  - >24 h from perforation or non-viable wound edges
    - diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, and gastrostomy/jejunostomy for decompression/feeding)

Complications
- sepsis, abscess, fistula, empyema, mediastinitis, and death
- post-operative esophageal leak
- mortality 10-50% dependent on timing of diagnosis

Esophageal Carcinoma

Epidemiology
- M:F = 3:1
- onset 50-60 yr of age
- upper (20-33%), middle (33%), and lower (33-50%)
- main types
  - most common worldwide: SCC in upper 2/3 of esophagus
  - most common in Western countries: adenocarcinoma in distal 1/3 of esophagus

Risk Factors
- SCC
  - underlying esophageal disease such as strictures, diverticula, and achalasia
  - smoking, alcohol, hot liquids
  - more common in black and Asian populations
- adenocarcinoma
  - Barrett's esophagus (most important), smoking, obesity (increased reflux), and GERD
  - more common in Caucasian populations

Clinical Features
- progressive dysphagia (mechanical): first solids then liquids
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis, and anemia
- direct, hematogenous, or lymphatic spread
- trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac and mediastinal nodes

Investigations and Staging
- barium swallow: shows narrowing - suggestive but not diagnostic
- endoscopic biopsy and assess resectability
- both SCC and adenocarcinoma use TNM staging system but have separate stage groupings according to histology
- endoscopic U/S (EUS)
  - visualize local disease
  - regional nodal involvement (number of nodes may be more important than location)
- bronchoscopy ± thoracotomy
  - rule out airway invasion in tumours of the upper and mid esophagus
- full metastatic workup (CXR, bone scan, CT head, CT chest/abdomen/pelvis, and LFTs, etc.)
- PET scan more sensitive than CT in detecting metastatic disease

Treatment
- if present with distant metastatic disease
- treat with systemic therapy and treat symptoms (esophageal stent)
  - if locally advanced (locally invasive disease or nodal disease on CT or EUS)
  - multimodal therapy
    - concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
    - possibility of curative esophagectomy after chemoradiation if disease responds well
  - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilatation/stent/laser ablation for palliation
  - if present with distant metastatic disease
   - palliative if rupture is contained
   - supportive if rupture is contained
   - >24 h from perforation
     - primary closure of a healthy esophagus or resection of diseased esophagus
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Complications
- sepsis, abscess, fistula, empyema, mediastinitis, and death
- post-operative esophageal leak
- mortality 10-50% dependent on timing of diagnosis
• if early stage (non-transmural and without evidence of nodal disease)
  • endoscopic mucosal resection can be considered for early mucosal cancer or high grade dysplasia
  • esophagectomy (transhiatal or trans-thoracic approach) and lymphadenectomy
  • anastomosis in chest or neck
  • stomach most often used for reconstruction; may also use colon
  • neoadjuvant chemotherapy and radiation are controversial
  • adjuvant chemotherapy ± radiation usually recommended for post-operative node-positive disease

Prognosis
• TNM status - usually poor because presentation is usually at advanced stage.

OTHER DISORDERS
• esophageal motor disorders (see Gastroenterology, G8)
• esophageal varices (see Gastroenterology, G26)
• Mallory-Weiss tear (see Gastroenterology, G26)

Thymoma

Epidemiology
• rare neoplasms in thymus including both thymoma and thymic carcinoma
• patients between 40 and 60 yr
• M = F

Risk Factors
• no known risk factors, strong association with myasthenia gravis and other paraneoplastic syndromes

Clinical Presentation
• frequently asymptomatic: incidental finding on imaging
• symptoms related to tumour size and location or myasthenia gravis: chest pain, SOB, cough, and phrenic nerve palsy
• ddx includes lymphoma, other anterior mediastinal tumours (see Respirology, R21)

Investigations
• CT chest (and/or MRI)
• Germ cell tumour markers (β-hCG, alpha fetoprotein), thyroid function, and PFTs

Treatment
• for patients with resectable disease
  • surgical resection of thymus via median sternotomy or VATS depending on the size
  • ± post-operative radiation based on Masaoka staging
• for non-surgical patients
  • multimodal therapy including neoadjuvant or palliative chemotherapy and post-operative chemoradiotherapy if de-bulking procedure feasible

Prognosis
• depends upon stage of disease and resectability
• generally slow growing tumours and have good prognosis, however thymic carcinomas more aggressive and have poorer prognosis

Pleura, Lung, and Mediastinum
• see Respirology, R22

Tube Thoracostomy

Indications
• to drain abnormal large-volume air or fluid collections in the pleural space
  • hemothorax, pleural effusion, chylothorax, and empyema
  • pneumothorax, if:
    • large or progressive
    • patient is on mechanical ventilation
    • bronchopleural fistula
    • tension pneumothorax
  • to treat symptomatic and/or recurrent pleural effusion
  • see Respirology, R22
  • for long-term drainage of malignant effusions use: 1. Tunneled pleural catheter; 2. Pleural drainage and chemical pleurodesis
  • via facilitation of pleurodesis (obliteration of the pleural space by instilling talc or doxycycline to cause fibrosis and adherence of parietal and visceral pleura)
Complications
- overall complications are rare (1-3%)
  - malposition (most common complication), especially by inexperienced operators
    - tubes may dissect along the external chest wall, or may be placed below the diaphragm
  - bleeding (anticoagulation is a relative contraindication)
  - local infection, empyema
  - perforation of lung parenchyma or vasculature
  - risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0-1.5 L)

Lung Transplantation

Conditions Leading to Transplantation
- chronic acquired lung disease: COPD
- genetic: CF, and emphysema due to α-1 antitrypsin deficiency
- idiopathic interstitial pneumonias: IPF, and nonspecific interstitial pneumonitis
- HTN-related: IPAH, secondary pulmonary HTN, and Eisenmenger's syndrome
- other: sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis

Clinical Indications
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and have risk of death >50% over the next 2 yr

Criteria for Transplantation
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
  - transplant benefit = post-transplant survival (days) – waitlist survival (days)

Contraindications
- uncontrolled or untreatable pulmonary, or extrapulmonary infection
- malignancy in the last 2 yr
- advanced cardiopulmonary disease
- significant chest wall/spinal deformity
- active cigarette smoking, and BMI ≥ 35
- HIV infection, ongoing HBV, HCV, or TB infections

Post-Operative Complications
- primary graft dysfunction: main cause is ischemia reperfusion injury, graded by PaO2/FiO2 ratio and CXR findings
- airway anastomotic complications (focal infection, bronchial necrosis and dehiscence, excess granulation tissue, tracheobronchomalacia, stenosis, and fistula)
- chronic graft dysfunction: bronchiolitis obliterans syndrome, and restrictive allograft syndrome
- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, and mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disease, colon, breast, Kaposi's sarcoma, and bladder)

Prognosis
- median survival for all adult recipients: 5.7 yr
- 1 yr survival: COPD > IPF > IPAH
- 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD > IPF

Chronic Obstructive Pulmonary Disease
- see Respirology, R9

Treatment
- indications for surgical management
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation
- contraindications
  - age >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - diffusing capacity of lung for carbon monoxide <20% of predicted, PaCO2: >60 mmHg, PaO2: <45 mmHg
- surgical procedures
  - lung volume reduction surgery: wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS

---

Long-Term Survival Analysis of the Canadian Lung Volume Reduction Surgery Trial

Study: Retrospective observational study assessing the long-term survival of patients enrolled in the CLVRS at 8-10 yr follow-up.

Results/Conclusions: Compared with the best medical care group, patients in the LVRS group showed a 16-mo survival advantage and a 20% reduction in mortality. Although not statistically significant, LVRS may provide long-term benefits in the treatment of end-stage emphysema.
Complications of Treatment
- air leak; may require reintubation and mechanical ventilation
- arrhythmias, pneumonia

Prognosis
- total mortality at 2 yr same as with maximal medical therapy, but better exercise capacity and quality of life with LVRS

Stomach and Duodenum

Peptic Ulcer Disease

GASTRIC ULCERS
- see Gastroenterology, G11

Indications for Surgery
- refractory to medical management
- suspicion of malignancy (even if biopsy benign)
- complications of PUD: obstruction, perforation, and bleeding (3x greater risk compared to duodenal ulcers)
- surgical treatment is increasingly rare due to H. pylori eradication and medical treatment

Procedures
- ligation of bleeding vessels
- distal gastrectomy with ulcer excision: Billroth II, Roux-en-Y gastrojejunostomy or Billroth I (rarely) reconstruction
- vagotomy and pyloroplasty only if acid hypersecretion (rare)
- wedge resection if possible or biopsy with primary repair

DUODENAL ULCERS
- see Gastroenterology, Bleeding Peptic Ulcer, G12, and Peptic Ulcer Disease, G11
- most within 2 cm of pylorus (duodenal bulb)

Indications for Surgery
- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
- refractory to medical and endoscopic management

Procedures
- omental (Graham) patch: plication of ulcer supported by overlying omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- treat with H pylori eradication protocol post operatively

Complications of Gastric Surgery
- retained antrum
- fistula (gastrocolic/gastrojejunual)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome (see Complications of Gastric Surgery, GS21)

Table 5. Complications of Duodenal Ulceration

<table>
<thead>
<tr>
<th>Complication</th>
<th>Clinical Features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforated Ulcer (typically on anterior surface)</td>
<td>Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter) Acute abdomen: rigid, diffuse guarding Heus Initial chemical peritonitis followed by bacterial peritonitis</td>
<td>In-estigation CXR - free air under diaphragm (70% of patients) Treatment Oversew ulcer (plication) and omental (Graham) patch – most common treatment</td>
</tr>
<tr>
<td>Posterior Penetration</td>
<td>Elevated amylase/lipase if penetration into pancreas Constant mid-epigastric pain burrowing into back, unrelated to meals</td>
<td>Resuscitation initially with crystalloids; blood transfusion if necessary Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope Consider interventional radiology: angiography with embolization/ coiling Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and I&amp;d: oversewing of ulcer, pyloroplasty</td>
</tr>
<tr>
<td>Hemorrhage (typically on posterior surface)</td>
<td>Gastroduodenal artery involvement</td>
<td>NGT decompression and correction of hypochloremic, hypokalemic metabolic alkalosis Medical management initially: high dose PPI therapy Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty, or gastrojejunostomy</td>
</tr>
<tr>
<td>Gastric Outlet Obstruction</td>
<td>Ucer can lead to edema, fibrosis of pyloric channel, and neoplasia N/V (undigested food, non-bilious), dilated stomach, and crampy abdominal pain Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken) Auscultate gas and fluid movement in obstructed organ</td>
<td>Figure 9. Billroth I and Billroth II with Roux-en-Y reconstruction (gastrojejunostomy)</td>
</tr>
</tbody>
</table>

Kissing Ulcer: combination of perforation and bleeding
Gastric Carcinoma

Epidemiology
- 5th most common cancer in the world
- M:F = 3:2
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr
- incidence of adenocarcinoma <10 (US) vs. 40 (Japan, Korea) per 100,000 (incidence highest in Asia, Latin America, and Caribbean)

Risk Factors
- compensatory epithelial cell proliferation via gastric atrophy from:
  - *H. pylori*, causing chronic atrophic gastritis
  - pernicious anemia associated with achlorhydria and chronic atrophic gastritis
  - previous partial gastrectomy (>10 yr post-gastrectomy)
- host-related factors
  - blood type A
  - hereditary nonpolyposis colorectal cancer (HNPCC), hereditary diffuse gastric carcinoma (HDGC)
  - gastric adenomatous polyps
  - hypertrophic gastropathy
  - genetic syndromes: hereditary diffuse gastric cancer E-cadherin (CDH-1) gene
- environmental factors: smoking, alcohol, smoked food, and nitrosamines

Clinical Features
- clinical suspicion
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious, or late onset of symptoms
  - postprandial abdominal fullness, vague epigastric pain
  - anorexia, or weight loss
  - burping, N/V, dyspepsia, and dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis fecal occult blood, melena, and iron-deficiency anemia
- metastasis
  - peritoneum, ovarian, liver, lung, and brain

Investigations
- OGD and biopsy; consider EUS to assess pre-operative T-stage and N-stage
- CT chest/abdomen/pelvis (for metastatic workup see Table 7)

Table 6. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>NX</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>N0</td>
<td>No regional node metastasis</td>
</tr>
<tr>
<td>T1a</td>
<td>N1</td>
<td>Metastasis in 1-2 regional nodes</td>
</tr>
<tr>
<td>T1b</td>
<td>N2</td>
<td>Metastasis in 3-6 regional nodes</td>
</tr>
<tr>
<td>T2</td>
<td>N3a</td>
<td>Metastasis in 7-15 regional nodes</td>
</tr>
<tr>
<td>T3</td>
<td>N3b</td>
<td>Metastasis in ≥16 regional nodes</td>
</tr>
<tr>
<td>T4a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Staging and 5 Yr Survival Rates for Gastric Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T/N/M</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>71%</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td>57%</td>
</tr>
<tr>
<td>IIA</td>
<td>T3N0M0</td>
<td>45%</td>
</tr>
<tr>
<td>IIB</td>
<td>T4N0M0</td>
<td>33%</td>
</tr>
<tr>
<td>IIA</td>
<td>T4N1M0</td>
<td>20%</td>
</tr>
<tr>
<td>IIB</td>
<td>T4N2M0</td>
<td>14%</td>
</tr>
<tr>
<td>IIC</td>
<td>T4N2M0</td>
<td>9%</td>
</tr>
<tr>
<td>IV</td>
<td>T4N3M0</td>
<td>4%</td>
</tr>
</tbody>
</table>

Signs of Metastatic Gastric Carcinoma
- Virchow’s node: left supraclavicular node
- Blumer’s shelf: mass in pouch of Douglas
- Krukenberg tumour: metastases to ovary
- Sister Mary Joseph node: umbilical metastases
- Irish’s node: left axillary nodes

Treatment
- adenocarcinoma
  - proximal lesions
    - total gastrectomy and Roux-en-Y esophagojejunostomy
  - distal lesions
    - distal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes with Roux-en-Y or Billroth II reconstruction
  - palliation
    - limited gastric resection or endoscopic stenting to decrease bleeding and relieve obstruction, enables the patient to eat
    - radiation therapy
    - studies are showing larger role for adjuvant/ neoadjuvant and palliative chemotherapy
- lymphoma
  - *H. pylori* eradication, chemotherapy ± radiation, and surgery in limited cases (perforation, bleeding, and obstruction)
Gastrointestinal Stromal Tumour

Epidemiology
- Most common mesenchymal neoplasm of GI tract
- Derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- Most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- Typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anaemia
- Often discovered incidentally on CT, laparotomy, or endoscopy

Risk Factors
- Carney's triad: GISTs, paraganglioma, and pulmonary chondroma
- Type IA neurofibromatosis

Investigations
- Pre-operative biopsy (endoscopic ultrasound): controversial, but useful for indeterminate lesions
- Not recommended if index of suspicion for GIST is high
- Percutaneous biopsy is NOT recommended due to high friability and risk of peritoneal spread

Treatment
- Surgical resection if >2 cm; follow with serial endoscopy if <2 cm and resect if growing or symptomatic
- Localized GIST
- Surgical resection with preservation of intact pseudocapsule
- Lymphadenectomy NOT required, as GISTs rarely metastasize to lymph nodes
- Consider adjuvant treatment with imatinib (Gleevec) or high-risk GIST (large, >4 cm with significant mitotic activity)
- Advanced disease (i.e. metastases to liver and/or peritoneal cavity)
- Palliative intent chemotherapy with imatinib
- Metastectomy may be considered for liver limited disease

Prognosis
- Risk of metastatic potential depends on
  - Tumour size (worse if >10 cm)
  - Mitotic activity (worse if >5 mitotic figures or 50/hpf)
  - Degree of nuclear pleomorphism
  - Location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- Metastases to liver, omentum, peritoneum; nodal metastases rare

Bariatric Surgery

- Weight reduction surgery for morbid obesity
- Indications: BMI ≥40 without illness or BMI ≥35 with 1+ serious comorbidity (e.g. DM, CAD, sleep apnea, or severe joint disease)

Surgical Options
- Malabsorptive/restrictive
  - Laparoscopic Roux-en-Y gastric bypass (most common)
  - Staple off small gastric pouch (restrictive) with Roux-en-Y limb to pouch (malabsorptive) with dumping syndrome physiology most effective, higher complication rates
- Restrictive
  - Laparoscopic adjustable gastric banding
  - Silicone band around fundus creates pouch, adjustable through port under skin
  - Laparoscopic vertical sleeve gastrectomy
  - Vertical stapled small gastric pouch
- Malabsorptive
  - Bilipancreatic diversion with duodenal switch
  - Gastrectomy, enterointerostomy, duodenal division closure, and duodenoenterostomy

Complications
- Perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
- Obstruction at enterointerostomy (see Complications of Gastric Surgery)
- Staple line dehiscence
- Dumping syndrome
- Cholelithiasis due to rapid weight loss (20-30%)
- Band abscess (if long-term)
Complications of Gastric Surgery

- most resolve within 1 yr

Alkaline Reflux Gastritis
- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment
  - medical: H2-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  - surgical: conversion of Billroth I or II to Roux-en-Y

Afferent Loop Syndrome
- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features
  - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
- treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Dumping Syndrome
- early: 15 min post-prandial
  - etiology
    - hyperosmotic chyme released into small bowel (fluid accumulation and jejunal distention)
  - clinical features
    - post-prandial symptoms
    - epigastric fulness or pain, emesis, nausea, diarrhea, palpitations, dizziness, tachycardia, diaphoresis
  - treatment
    - small multiple low carbohydrate, low fat, and high protein meals and avoidance of liquids with meals
    - last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late: 3 h post-prandial
  - etiology: large glucose load leads to large insulin release and hypoglycemia
  - treatment: small snack 2 h after meals

Blind-Loop Syndrome
- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features
  - anemia/weakness, diarrhea, malnutrition, abdominal pain, and hypocalcemia
- treatment: broad-spectrum antibiotics, and surgery (conversion to Billroth I)

Postvagotomy Diarrhea
- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine), and surgical (reversed interposition jejunal segment)

SMALL INTESTINE

Small Bowel Obstruction

Mechanical Small Bowel Obstruction

Pathophysiology
- obstruction → gas and fluid (swallowed or GI secretions) accumulate proximal to site of obstruction and distal decompression → intestinal activity increases to overcome obstruction → colicky pain and diarrhea (initially)
- bowel wall edema and disruption of normal bowel absorptive function can lead to increased intraluminal fluid and transudative fluid loss into peritoneal cavity, electrolyte disturbances
- increase intramural pressure can lead to impaired microvascular perfusion leading to intestinal ischemia and necrosis (strangulated bowel obstruction)
Etiology

Table 7. Common Causes of SBO

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Intraluminal</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intussusception</td>
<td>Crohn’s</td>
<td>Adhesions from previous surgeries (75% SBO)</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Radiation stricture</td>
<td>Incarcerated hernia</td>
</tr>
<tr>
<td>Bezoars</td>
<td>Adenocarcinoma</td>
<td>Peritoneal carcinomatosis</td>
</tr>
</tbody>
</table>

- **three types**
  - partial SBO: only a portion of intestinal lumen is occluded, allows passage of some gas & fluid, low risk of strangulation
  - complete SBO: the lumen of the intestine is occluded, no passage of gas or stool, at higher risk of strangulation
  - closed-loop obstruction: segment of intestine is obstructed both proximally and distally (e.g. volvulus), leading to rapid rise in intraluminal pressure from gas and fluid that cannot escape, high risk of strangulation due to bowel wall ischemia

**Risk Factors**
- prior abdominal or pelvic surgery
  - abdominal wall or groin hernia
  - history of malignancy
  - prior radiation

**Clinical Features**
- 1) distinguish mechanical obstruction from ileus; 2) determine etiology of obstruction; 3) recognize partial from complete SBO; 4) differentiate simple from complicated (e.g. strangulated) obstruction
- symptoms: colicky abdominal pain, nausea/vomiting, obstipation
  - vomiting is more prominent with proximal than distal
  - more feculent vomitus suggests more established obstruction because of bacterial overgrowth
  - continue passage of gas and/or stool 6-12 h after onset of symptoms suggest partial than complete obstruction
- signs: abdominal distention (most prominent if obstruction at distal ileum), hyperactive proceeding to minimal bowel sound
- strangulated obstruction: abdominal pain disproportionate to physical exam findings suggest intestinal ischemia
  - may have tachycardia, localized abdominal tenderness
  - fever, marked leukocytosis, and lactate acidosis

**Investigations**
- radiological
  - abdominal x-ray (3 views): triad of dilated small bowel (>3 cm in diameter), air-fluid levels on upright film, paucity of air in colon (high sensitivity, low specificity as ileus and LBO can present similarly)
  - CT: discrete transition zone with proximal bowel dilation, distal bowel decompression, and intraluminal contrast does not pass the transition zone
    - most importantly to rule out ischemic bowel/strangulation: pneumatosis intestinalis (free air in bowel wall) and thickened bowel wall, air in portal vein, free intraperitoneal fluids, and differential wall enhancements (poor uptake of IV contrast into the wall of the affected bowel)
  - other
    - less used: upper GI series/small bowel series (if no cause apparent, i.e. no hernias, and no previous surgeries)
    - may consider U/S or MRI in pregnant patients
- laboratory
  - may be normal early in disease course
  - creatinine, and hematocrit to assess degree of dehydration
  - fluid, and electrolyte abnormalities; metabolic alkalosis due to frequent emesis; amylase elevated
  - if strangulation: leukocytosis with left shift, elevated lactate (late signs)

**Treatment**
- IV isotonic fluid resuscitation + urine output monitoring with catheter
  - SBO related vomiting and decrease PO intake leads to volume depletion
  - NG tube in the stomach for gastric decompression; decrease nausea, distention, and risk of aspiration from vomiting
- Partial SBO/Crohn’s/Carcinomatosis: conservative management with fluid resuscitation and NG tube decompression
  - 48 h of watchful waiting; if no improvement or develops complications, surgery
- Complete SBO, if no clinical features of strangulation, short course of conservative management with fluid resuscitation and NG tube decompression with frequent re-examination by surgical team
  - duration of observation varies from hours to a few days
  - if SBO fails to resolve, or if symptoms of strangulation develop, then surgery

**MUST DO**
- Rule out CRC in constipated patient
- Send for TURP in patient with BPH (treat intra-abdominal HTN)

**Increased Risk of Perforation with Distention as seen on Abdomen Imaging**
- Small bowel ≥3 cm
  - Distal colon ≥6 cm
  - Proximal colon ≥3 cm
  - Cecum ≥12 cm

**Patients presenting with a SBO in setting of “virgin” abdomen should have surgery ASAP**
  - EXCEPTION: malignant obstruction from history and imaging

**In a non-virgin abdomen – adhesional SBOs resolve spontaneously with NGT decompression 70% of time**

**Top 3 Causes of SBO (in order)**
- ABC
  - Adhesions
  - Bulge (hernias)
  - Cancer (neoplasms)

**Causes of SBO**
- SHAHING
  - Stricture
  - Hernia
  - Adhesions
  - Volvulus
  - Intussusception/BDO
  - Neoplasm
  - Gallstones
• High risk for strangulation based on clinical symptoms: urgent surgery to prevent irreversible ischemia
  • early post operative SBO: if bowel function does not return within 3-5 d after surgery; usually partial, extended conservative therapy (2-3 wk) with bowel rest, fluids, and TPN is appropriate surgery if presence of peritonitis or complete SBO demonstrated

Prognosis
• related to etiology; mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%

Prevention
• open surgery has four fold increase in risk of SBO in 5 yr compared to laparoscopic surgery

**Paralytic Ileus**

Pathogenesis
• temporary, reversible impairment of intestinal motility; mostly frequently caused by:
  • abdominal operations, infections and inflammation, medications (opiates, anesthetics, psychotropics), and electrolyte abnormalities
  • passing gas is the most useful indicator
• NOT the same as intestinal pseudo-obstruction
  • chronic pseudo-obstruction refers to specific disorders that affect the smooth muscle and myenteric plexus, leading to irreversible intestinal dysmotility

Clinical Features
• symptoms and signs of intestinal obstruction without mechanical obstruction
  • bowel sounds are diminished or absent (in contrast to initial hyperactive bowel sounds in SBO)

Investigations
• routine post-operative ileus: expected, no investigation needed
• if ileus persists or occurs without abdominal surgery
  • review patient medications (especially opiates)
  • measure serum electrolyte to monitor for electrolyte abnormalities (including extended electrolytes like Mg, Calabour, PO4)
  • CT scan to rule out abscess or peritoneal sepsis, or to exclude complete mechanical obstruction

Treatment
• most important: NPO + fluid resuscitation
• NGT decompression, correct causative abnormalities (e.g. sepsis, medications, electrolytes), consider TPN for prolonged ileus
• post-operative: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d
• current interest in novel therapies such as gum chewing and pharmacologic therapy (e.g. alvimopan, an opioid antagonists)

**Intestinal Ischemia**

Etiology
• acute
  • arterio-occlusive mesenteric ischemia (AOMI)
    • thrombotic, embolic, and extrinsic compression (e.g. strangulating hernia)
  • non-occlusive mesenteric ischemia (NOMI)
    • mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  • mesenteric venous thrombosis (MVT)
    • consider hypercoagulable state (i.e. rule out malignancy), and DVT (prevents venous outflow)
• chronic: usually due to atherosclerotic disease – look for CVD risk factors
• can lead to occlusion in vessels that supplies the small intestine and the large intestine

Clinical Features
• acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, and sepsis
• chronic: postprandial pain (from mesenteric angina), fear of eating, and weight loss
• common sites: SMA supplied territory, "watershed" areas of colon – splenic flexure, left colon, and sigmoid colon

Pain "out of keeping with physical findings" is the hallmark of early intestinal ischemia
Investigations
- laboratory: leukocytosis (non-specific), and lactic acidosis (late finding)
- amylase, lactate, CK, and ALP can be used to observe progress
- hypercoagulability workup if suspect venous thrombosis
- AXR: portal venous gas, intestinal pneumatosis, and free air if perforation
- contrast CT: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, and pneumatosis
CT angiography is the gold standard for acute arterial ischemia

Treatment
- fluid resuscitation, correct metabolic acidosis, NPO, NGT decompression of stomach, and prophylactic broad-spectrum antibiotics; avoid vasoconstrictors and digitalis
- exploratory laparotomy
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, and percutaneous transluminal angioplasty ± stent
- segmental resection of necrotic intestine
- assess extent of viability; if extent of bowel viability is uncertain, a second look laparotomy 12-24 h later is mandatory

Tumours of Small Intestine

BENIGN TUMOURS
- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum, and proximal jejunum
- polyps
  - adenomas
  - hamartomas
  - FAP (see Familial Colon Cancer Syndromes, GS33)
- juvenile polyps
- other: leiomyomas, lipomas, and hemangiomas

Table 8. Malignant Tumours of the Small Intestine

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Lymphoma</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Usually 50-70 yr M&gt;F</td>
<td>Increased incidence 50-80 yr</td>
<td>Highest incidence in 70s M&gt;F Usually non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Crohn’s, FAP, history of CRC, HNPCC</td>
<td>Classified based on embryological origin (foregut, midgut, and hindgut)</td>
<td>Crohn’s, colic disease, autoimmune disease, immunosuppression, radiation therapy, and nodular lymphoid hyperplasia</td>
</tr>
<tr>
<td>Origin/ Location</td>
<td>Usually in proximal small bowel, incidence decreases distally</td>
<td>Usually distal ileum Proximal jejunum in patients with celiac disease</td>
<td></td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Early metastasis to lymph n des 80% metastatic at time of operation Abdominal pain (common)</td>
<td>N/V, anemia, GI bleeding, jaundice, and weight loss (less common) Often slow-growing Usually asymptomatic, incidental finding Obstruction, bleeding, crampy abdominal pain, and intussusception Carcinoid syndrome (&lt;10%) Not flatus, hypotension, diarrhea, bronchoconstriction, and right heart failure Requires liver involvement: lesion secretes serotonin, kinins, and vasoactive peptides directly to systemic circulation (normally inactivated by liver)</td>
<td>Fatigue, weight loss, fever, malabsorption, abdominal pain, anorexia, vomiting, constipation, and mass Rarely – perforation, obstruction, bleeding, and intussusception</td>
</tr>
<tr>
<td>Investigations</td>
<td>CT abdomen/pelvis</td>
<td>Most found incidentally at surgery for obstruction or appendectomy Chest thorax/abdomen/pelvis Consider small bowel enteroclysis to look for primary</td>
<td>CT abdomen/pelvis</td>
</tr>
</tbody>
</table>
Table 8. Malignant Tumours of the Small Intestine (continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Lymphoma</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Surgical resection ± chemotherapy</td>
<td>Surgical resection ± chemotherapy</td>
<td>Low grade: chemotherapy with cyclophosphamide</td>
<td>Palliation</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>Carcinoid syndrome treated with steroids, histamine, and octreotide</td>
<td>High grade: surgical resection, and radiation</td>
<td>Palliative: somatostatin, doxorubicin</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>Metastatic risk 2% if size &lt; 1 cm, 90% if &gt;2 cm</td>
<td>Metastatic risk 2% if size &lt; 1 cm, 90% if &gt;2 cm</td>
<td>Metastatic risk 2% if size &lt; 1 cm, 90% if &gt;2 cm</td>
<td></td>
</tr>
</tbody>
</table>

| Prognosis          | 5 yr survival 25% (if node positive) | 5 yr survival 70%; 20% with liver metastases | 5 yr survival 40% | Poor |

| Staging System     | TNM | TNM | Ann Arbor |

### Short Gut Syndrome

**Definition**
- reduced surface area (length) of small bowel causing insufficient intestinal absorption leading to diarrhea, malnutrition, and dehydration

**Etiology**
- acute mesenteric ischemia: resection of large amount of bowel at once
- Crohn's disease: cumulative resections
- malignancies

**Prognostic Factors**
- residual small bowel length, residual colon length (reabsorption of water and electrolytes and some reabsorption of nutrients), condition of the remnant small bowel (healthier bowel facilitate better reabsorption), presence of ileocecal valve (delay transition into colon leading to more reabsorption)
- resection of ileum is less tolerated than resection of jejunum (ileum reabsorbs bile salt and vitamin B12)

**Therapy**
- medical
  - TPN: replenish lost fluid and electrolytes in diarrhea
  - HT2R antagonist or PPI to prevent gastric acid secretion
  - antimitoty agent to prolong transit time in the small intestine
  - consider octreotide to decrease GI secretion and cholestyramine for bile acid absorption
- surgical: non-transplant
  - to slow transit time: small bowel segmental reversal, intestinal valve construction, or electrical pacing of small bowel
  - to increase intestinal length:
    - LITT (longitudinal intestinal lengthening and tailoring) procedure
    - STEP (serial transverse enteroplasty procedure) in dilated small bowels
- surgical: transplant
  - indication: life-threatening complication from intestinal failure or long-term TPN
  - liver failure, thrombosis of major central veins, recurrent catheter-related sepsis, recurrent severe dehydration

### Abdominal Hernia

- see Hiatus Hernia, GS13

**Definition**
- defect in abdominal wall causing abnormal protrusion of intra-abdominal contents

**Epidemiology**
- M:F = 9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- frequency of occurrence: 50% indirect inguinal, 25% direct inguinal, 8-10% incisional (ventral), 5% femoral, and 3-8% umbilical
- most common surgical disease of males

**Risk Factors**
- activities which increase intra-abdominal pressure
  - obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, and heavy lifting
  - congenital abnormality (e.g. patent processus vaginalis, and indirect inguinal hernia)
  - previous hernia repair, especially if complicated by wound infection
  - loss of tissue strength and elasticity (e.g. hiatus hernia, aging, and repetitive stress)
Abdominal Hernia

Clinical Features
- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

Investigations
- physical examination usually sufficient
- U/S ± CT (CT required for obturator hernias, internal abdominal hernias, and Spigelian and/or femoral hernias in obese patients)

Classification
- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
- requires emergency repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter’s hernia: only part of bowel circumference (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
- a strangulated Richter’s hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation in the absence of obstructive symptoms
- sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)

Anatomical Types
- groin
- indirect and direct inguinal, femoral
- pantalloen: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre’s (involving Meckel’s), Amyand’s (containing appendix), lumbar, obturator, peristomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

Complications
- incarceration
- strangulation
- small, new hernias more likely to strangulate
- femoral >> indirect inguinal > direct inguinal
- intense pain followed by tenderness
- intestinal obstruction, gangrenous bowel, sepsis
- surgical emergency
- DO NOT attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous
- will cause closed loop SBO – and EMERGENCY

Treatment
- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, for cosmesis, if asymptomatic can delay surgery
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

Post-Operative Complications
- recurrence (15–20%)
  - risk factors: recurrent hernia, age >50, smoking, BMI >25, poor pre-operative functional status (ASA ≥3 – see Anesthesia and Perioperative Medicine, A4), associated medical conditions: type 2 DM, hyperlipidemia, immunosuppression, and any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/"tension-free" repair
  - scrotal hematoma (3%)
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
  - nerve entrapment
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
  - stenosis/occlusion of femoral vein
  - acute leg swelling
  - ischemic colitis

Shouldice Technique vs. Other Open Techniques for Inguinal Hernia Repair
Cochrane DB Syst Rev 2012;4:CD001543
Purpose: To evaluate the efficacy and safety of the Shouldice technique to other non-laparoscopic techniques.
Results/Conclusions: 16 RCTs or quasi-randomized RCTs with 2,568 hernias (1,121 mesh, 1,488 non-mesh). The recurrence rate with Shouldice was higher than mesh (OR 3.80, 95% CI 1.69-7.26) but lower than non-mesh (OR 0.62, 95% CI 0.45-0.85). There was no difference in chronic pain or complications. In conclusion, with respect to recurrence rates, Shouldice hernorrhaphy is the best non-mesh technique, although inferior to mesh. However, it is also more time consuming and results in slightly longer post-operative hospital stays.

Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men: A Randomized Controlled Trial
JAMA 2006;295:295-292
Purpose: To compare pain and the physical component score (PCS) of the Short Form 36 Version 2 survey at 2 yr in men with minimally symptomatic inguinal hernias treated with watchful waiting or surgical repair.
Methods: RCT of 1275 men in (n=384 watchful waiting, n=891 surgical repair) followed up for 2-4.5 yr. Watchful-waiting patients were followed up at 6 mo and annually and watchful for hernia symptoms; repair patients received standard open tension-free repair and were followed up at 3 and 6 mo and annually. The main outcome was pain and discomfort interfering with usual activities at 2 yr and change in PCS from baseline to 2 yr. Secondary outcomes were complications, patient-reported pain, functional status, as well as levels, and satisfaction with care.
Results: Primary intention-to-treat outcomes were similar a 2 yr for watchful waiting vs. surgical repair; pain limiting activities (5.1% vs. 2.2%, respectively), p=0.04 (corrected); PCS (improvement over baseline, 0.29 points vs. 0.13 points, p=0.05). Twenty-three percent of patients assigned to watchful waiting crossed over to receive surgical repair (increase in hernia-related pain was the most common reason offered). 1% assigned to receive repair crossed over to watchful waiting. Self-reported pain in watchful-waiting patients crossed over improved after repair. Occurrence of post-operative hernia-related complications was similar in patients who received repair as assigned and in watchful-waiting patients who crossed over. One watchful-waiting patient (0.3%) experienced acute hernia incarceration without strangulation within 2 yr; a second had acute incarceration with bowel obstruction at 4 yr; with a frequency of 1.8/1,000 patients/year of patients to bowel up for as long as 4.5 yr.
Conclusion: Watchful waiting is an acceptable option for men with minimally symptomatic inguinal hernias. Delaying surgical repair until symptoms increase is safe because acute hernia incarcerations occur rarely.

Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias
Purpose: To compare outcomes (surgical site infection (SSI), hernia recurrence and bulging) of patients undergoing laparoscopic ventral hernia repair (LVRH) versus open ventral hernia repair (OVHR).
Results/Conclusions: 79 patients with LVRH matched to 79 patients with OVHR with mesh with a median follow-up of 56 mo. LVRH was associated with fewer SSS (7.6% vs. 34.4%) but more cases of bulging (21.3% vs. 1.3%) and post-surgery hernia (2.5% vs. 0.0%). No differences in recurrence were observed.
Groin Hernias

Table 9. Groin Hernias

<table>
<thead>
<tr>
<th></th>
<th>Direct Inguinal</th>
<th>Indirect Inguinal</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>1% of all men</td>
<td>Most common hernia in men and women M&gt;F</td>
<td>Affects mostly females</td>
</tr>
<tr>
<td>Etiology</td>
<td>Acquired weakness of transversalis fascia “Wear and tear” Increased intra-abdominal pressure</td>
<td>Congenital persistence of processus vaginalis in 20% of adults</td>
<td>Pregnancy – weakness of pelvic floor musculature Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Through Hesselbach’s triangle Medial to infra epigastric artery Usually does not descend into scrotal sac</td>
<td>Originates in deep inguinal ring Lateral to inferior epigastric artery Often descends into scrotal sac (or labia majora)</td>
<td>Into femoral canal, below inguinal ligament but may override it Medial to femoral vein within femoral canal</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgical repair</td>
<td>Surgical repair</td>
<td>Surgical repair</td>
</tr>
<tr>
<td>Prognosis</td>
<td>3-4% risk of recurrence</td>
<td>&lt;1% risk of recurrence</td>
<td></td>
</tr>
</tbody>
</table>

Table 10. Superficial Inguinal Ring vs. Deep Inguinal Ring*

<table>
<thead>
<tr>
<th>Superficial Inguinal Ring</th>
<th>Deep Inguinal Ring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening in external abdominal aponeurosis; palpable superior and lateral to pubic tubercle</td>
<td>Opening in transversalis fascia: palpable superior to mid-inguinal ligament</td>
</tr>
<tr>
<td>Medial border: medial crus of external abdominal aponeurosis</td>
<td>Medial border: inferior epigastric vessels</td>
</tr>
<tr>
<td>Lateral border: lateral crus of external oblique aponeurosis</td>
<td>Superior-lateral border: internal oblique and transversus abdominis muscles</td>
</tr>
<tr>
<td>Roof: intercrural fibres</td>
<td>Inferior border: inguinal ligament</td>
</tr>
</tbody>
</table>

*see Basic Anatomy Review, Figure 2, GS3

Appendix

Appendicitis

Epidemiology
- 6% of population, M>F
- 80% between 5-35 yr of age

Pathogenesis
- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecolith, or obstructing neoplasm
  - other causes: parasites, or foreign body

Clinical Features
- most reliable feature is progression of signs and symptoms
- low grade fever (38°C), rises if perforation
- abdominal pain then anorexia, N/V
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney’s point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
  - McBurney’s sign
- signs
  - inferior appendix: McBurney’s sign (see sidebar), Rovsing’s sign (palpation pressure to left abdomen causes McBurney’s point tenderness). McBurney’s sign is present whenever the opening of the appendix at the cecum is directly under McBurney’s point; therefore McBurney’s sign is present even when the appendix x is in different locations
  - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
  - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)
- complications
  - perforation (especially if >24 h duration)
  - abscess, phlegmon
  - sepsis

Figure 12. Schematic of inguinal (direct and indirect) and femoral hernias

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Investigations
- Laboratory
  - mild leukocytosis with left shift (may have normal WBC counts)
  - higher leukocyte count with perforation
  - β-hCG to rule out ectopic pregnancy
- Imaging
  - U/S: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/PPV/PV 98%)
  - CT scan: thick wall, enlarged (>6 mm), wall enhancement, appendicolith, and inflammatory changes – overall accuracy 94-100%, optimal investigation

Treatment
- Hydrate, correct electrolyte abnormalities
- Appendectomy (gold standard)
  - laparoscopic vs. open (see sidebar)
- Complications: intra-abdominal abscess, appendiceal stump leak
- Perioperative antibiotics:
  - cefazolin + metronidazole if uncomplicated peri-operative dose is adequate
  - Consider treatment with post-operative antibiotics for perforated appendicitis
  - For patients who present with an abscess (palpable mass or phlegmon on imaging and often delayed diagnosis with symptoms for >4-5 d), consider radiologic drainage + antibiotics x 14 d ± interval appendectomy once inflammation has resolved (controversial)
  - Recent research supports antibiotic only treatment as reasonable for uncomplicated appendicitis, with 10-20% recurrence rates
  - Colonoscopy in the elderly to rule out other etiology (neoplasm)

Prognosis
- Mortality rate: 0.08% (non-perforated), 0.5% (perforated appendicitis)

Inflammatory Bowel Disease

- See Gastroenterology, G19

Principles of Surgical Management
- Can alleviate symptoms, address complications, and improve quality of life
- Conserve bowel: resect as little as possible to avoid short gut syndrome
- Perioperative management
  - Optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  - Hold immunosuppressive therapy pre-operative, provide pre-operative stress dose of corticosteroid if patient had recent steroid therapy, taper steroids post-operative
  - VTE prophylaxis: LMWH or heparin in the elderly
- See Gastroenterology, G19

Crohn’s Disease

- See Gastroenterology, G20

Treatment
- Surgery is for symptom management, it is NOT curative, but over lifetime ~70% of Crohn’s patients will have surgery
- Indications for surgical management
  - Failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - Abscess, fistula (enterocolic, vesiculovaginal, ileal cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), and perianal disease
  - Surgical procedures
    - Resection and anastomosis/stoma if active or subacute inflammation, perforation, or fistula
    - Resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
    - Strictureplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

Complications of Treatment
- Short gut syndrome (diarrhea, steatorrhea, malnutrition)
- Fistulas
- Gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- Kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

Effect of Delay to Operation on Outcomes in Adults with Acute Appendicitis
- Arch Surg 2010;145:886-892
- Purpose: To examine the effect of delay to appendectomy on morbidity and mortality among adults with appendicitis
- Method: Retrospective cohort study with the main exposure being time to operation, and main outcomes being 30 d overall morbidity and serious morbidity/mortality
- Results: Of 32,782 patients in the study, 75.2%, 15.1%, and 9.8% underwent surgeries within 6 h, 6-12 h, and >12 h of admission, respectively
  - Differences in operative duration and length of post-operative stay were statistically significant but not clinically meaningful. No significant differences were observed in adjusted overall morbidity or serious morbidity/mortality. Duration from surgical admission to anesthetic induction was not predictive in regression models for either outcomes.
- Conclusions: Delay of appendectomy for acute appendicitis among adults does not adversely affect outcomes.

Antibiotics vs. Placebo for Prevention of Post-Operative Infection After Appendectomy
- Purpose: To determine the effectiveness of antibiotics against post operative infections after appendectomy
- Method: Meta-analysis of randomized controlled trials (RCTs) and controlled clinical trials (CCTs), on both adults and children, in which any antibiotic regime was compared to placebo in patients undergoing appendectomy for suspected appendicitis. The main outcomes of interest were wound infection, intra-abdominal abscess, length of hospital stay, and mortality.
- Results: 45 studies (n = 9,576) were included
  - Treatment with antibiotics decreased wound infection and abscess rates
- Conclusion: Various prophylactic antibiotic regimens are effective in preventing post-operative complications after appendectomy.

Laparoscopic vs. Open Appendectomy
- Cochrane DB Syst Rev 2010;10:CD001546
- Laparoscopic Surgery
  - Wound infection less likely
  - Intra-abdominal abscesses 2x more likely
  - Reduced pain on POD #1
  - Reduced hospital stay by 1.1 d
  - Sooner return to normal activity, work, and sport
  - Costs outside hospital are reduced
- Open Surgery
  - Shorter duration of surgery
  - Lower operation costs
- Overview
  - Diagnostic laparoscopy and laparoscopic appendectomy appear to be advantageous over open appendectomy, particularly for young female patients and obese patients.

Laparoscopic Surgery
- Reduced duration of hospital stay
- Reduced post-operative pain
- Reduced wound infection
- Reduced abscess and sepsis
- Reduced morbidity and mortality
- Sooner return to normal activity, work, and sport
- Reduced costs outside hospital
- Reduced length of hospital stay
- Reduced incidence of wound infection and abscess
- Reduced mortality

Open Surgery
- Increased duration of hospital stay
- Increased post-operative pain
- Increased wound infection
- Increased abscess and sepsis
- Increased morbidity and mortality
- Delayed return to normal activity, work, and sport
- Increased costs outside hospital
- Increased length of hospital stay
- Increased incidence of wound infection and abscess
- Increased mortality

Antibiotics
- Reduced duration of hospital stay
- Reduced post-operative pain
- Reduced wound infection
- Reduced abscess and sepsis
- Reduced morbidity and mortality
- Sooner return to normal activity, work, and sport
- Reduced costs outside hospital
- Reduced length of hospital stay
- Reduced incidence of wound infection and abscess
- Reduced mortality

Placebo
- Increased duration of hospital stay
- Increased post-operative pain
- Increased wound infection
- Increased abscess and sepsis
- Increased morbidity and mortality
- Delayed return to normal activity, work, and sport
- Increased costs outside hospital
- Increased length of hospital stay
- Increased incidence of wound infection and abscess
- Increased mortality
Prognosis
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), strictureplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr

Ulcerative Colitis
- see Gastroenterology, G21

Treatment
- indications for surgical management
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per yr after 10 yr of disease)
- surgical procedures
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
  - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

Complications of Treatment
- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

Prognosis
- mortality: 5% over 10 yr
- total proctocolectomy will eliminate risk of cancer
- perforation of the colon is the leading cause of death from ulcerative colitis

LARGE INTESTINE

Large Bowel Obstruction

Mechanical Large Bowel Obstruction

Etiology

Table 11. Common Causes of LBO

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Intramural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Adenocarcinoma</td>
<td>Volvulus</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>Diverticulitis</td>
<td>Adhesions</td>
</tr>
<tr>
<td></td>
<td>IBD stricture</td>
<td>Hernias (sigmoid colon in a large groin hernia)</td>
</tr>
<tr>
<td></td>
<td>Radiation stricture</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features (unique to LBO)
- open loop (10-20%)
  - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical presentation similar to SBO
- closed loop (80-90%) (dangerous)
  - competent ileocecal valve, resulting in proximal and distal occlusions
  - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

Treatment
- surgical correction of obstruction (usually requires resection + temporary diverting colostomy)
- volvulus requires sigmoidoscopic or endoscopic decompression followed by operative reduction if unsuccessful
  - if successful, consider interval sigmoid resection on same admission
- cecal volvulus can be a true volvulus or a cecal ‘basicle’ (cecum folds anteriorly to the ascending colon producing a flap valve occlusion to cecal emptying) – both need surgical treatment

Findings in Crohn’s
- “Cobblestoning” on mucosal surface due to edema and linear ulcerations
- “Skip lesions”: normal mucosa in between
- “Creeping fat”: mesentery infiltrated by fat
- Granulomas: 25-30%

Findings in Ulcerative Colitis
- Patients usually present with diarrhea (± blood in their stool)
- Associated symptoms include colicky abdominal pain, urgency, tenesmus, and incontinence
- Presence of extra-intestinal manifestations
  - Endoscopically, there is loss of vascular markings, erythema, granularity of mucosa, petechiae, exudates, edema, erosions, and spontaneous bleeding
  - Biopsy features included crypt abscesses, crypt branching, shortening and disarray, and crypt atrophy
- Inflammation is continuous and usually involves rectum

Top 3 Causes of LBO (in order)
- Cancer
- Diverticulitis
- Volvulus

In a patient with clinical LBO consider impending perforation when:
- Cecum ≥ 12 cm in diameter
- Tenderness present over cecum
**Prognosis**
- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality

**Table 12. Bowel Obstruction vs. Paralytic Ileus**

<table>
<thead>
<tr>
<th></th>
<th>SBO</th>
<th>LBO</th>
<th>Paralytic Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/V</td>
<td>Early, may be bilious</td>
<td>Late, may be feculent</td>
<td>Present</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Colicky</td>
<td>Colicky</td>
<td>Minimal or absent</td>
</tr>
<tr>
<td>Abdominal Distention</td>
<td>+ (prox SBO), ++ (distal SBO)</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bowel Sounds</td>
<td>Normal, increased</td>
<td>Normal, increased (borborygmi)</td>
<td>Decreased, absent</td>
</tr>
<tr>
<td></td>
<td>Absent if secondary ileus</td>
<td>Absent if secondary ileus (delayed presentation)</td>
<td></td>
</tr>
<tr>
<td>AXR Findings</td>
<td>Air-fluid levels</td>
<td>Air-fluid levels</td>
<td>Air throughout small bowel and colon</td>
</tr>
<tr>
<td></td>
<td>“Ladder” pattern (plicae circularis)</td>
<td>“Picture frame” appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proximal distention (&gt;3 cm)</td>
<td>Proximal distention + distal decompression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ no colonic gas</td>
<td>No small bowel air if competent ileocecal valve</td>
<td></td>
</tr>
</tbody>
</table>

**Functional LBO: Colonic Pseudo-Obstruction (Ogilvie’s Syndrome)**

**Definition**
- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic deprivation to colon, unopposed parasympathetic tone, and interruption of sacral parasympathetic tone to distal bowel

**Associations**
- most common: trauma, infection, and cardiac (MI, CHF)
- disability (long-term debilitation, chronic disease bed-bound nursing home patients, and paraplegia), drugs (narcotic use, laxative abuse, and polypharmacy), other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, and diffuse carcinomatosis)

**Clinical Features**
- most prominent is abdominal distention (acute or graduate over 3-7 days)
- abdominal pain, nausea and vomiting, constipation/diarrhea
- watch out for fever, leukocytosis, and presence of peritoneal signs

**Investigations**
- AXR: cecal dilatation – if diameter ≥12 cm, increased risk of perforation

**Treatment**
- treat underlying cause
- NPO, NGT
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical decompression (ostomy/resection) uncommon
- surgery (extremely rare): if perforation, ischemia, or failure of conservative management

**Prognosis**
- most resolve with conservative management
Diverticular Disease

Definitions
- diverticulum: abnormal sac-like protrusion from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

Figure 13. Diverticular disease – cross-sections of true and false diverticuli

Diverticulosis

Epidemiology
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

Pathogenesis
- risk factors:
  - lifestyle: low-fibre diet (predispose to motility abnormalities and higher intraluminal pressure),
    inactivity, and obesity
  - muscle wall weakness from aging and illness (e.g. Ehler-Danlos, Marfan’s)
- high intraluminal pressures cause outpouching to occur at point of greatest weakness, most commonly
  where vasa recta penetrate the circular muscle layer, therefore increased risk of hemorrhage

Clinical Features
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications:
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive LGIB
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, and abdominal pain

Treatment
- uncomplicated diverticulosis: high fibre, education
- diverticular bleed
  - initially workup and treat as any LGIB
  - if hemorrhage does not stop, resect involved region

Diverticulitis

Epidemiology
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

Pathogenesis
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and
  focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula, or
  obstruction can ensue
- poor containment results in free perforation and peritonitis
**Clinical Features**

- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, N/V, and urinary symptoms (with adjacent inflammation)
- low grade fever, mild leukocytosis common, and occult or gross blood in stool rarely coexist with acute diverticulitis complications (25% of cases)
  - abscess: palpable, tender abdominal mass
  - fistula: colovesical (most common), coloenteric, colovaginal, c and olocutaneous
  - colonic obstruction: due to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
  - recurrent attacks rarely lead to peritonitis

**Investigations**

- AXR, upright CXR
  - localized diverticulitis (ileus, thickened wall, SBO, and partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- CT scan (test of choice): very useful for assessment of severity and prognosis; usually done with rectal contrast
  - 97% sensitive, 99% specific
  - increased soft tissue density within pericolic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), and fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- elective evaluation: establish extent of disease and rule out other diagnoses (polyps, and malignancy) AFTER resolution of acute episode
  - colonoscopy or barium enema and flexible sigmoidoscopy

**Treatment**

- uncomplicated: conservative management
- outpatient: clear fluids only until improvement and antibiotics (e.g. cefazolin and metronidazole) 7-10 d to cover gram negative rods and anaerobes (e.g. B. fragilis)
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, or fail to improve outpatient management
- treat with NPO, IVF, and IV antibiotics (e.g. IV ceftriaxone + metronidazole)
- indications for surgery
  - unstable patient with peritonitis
  - Hinchey stage 3-4
  - after 1 attack if immunosuppressed
  - consider if recurrent episodes of diverticulitis (3 or more), recent trend is toward conservative management of recurrent mild/moderate attacks
  - complications: perforation, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
- surgical procedures
  - for unstable patient or complex cases: Hartmann procedure
  - colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo
  - for more stable patients with Hinchey stage III and IV acute diverticulitis, colonic resection, primary anastomosis + diverting loop ileostomy is becoming more common, with benefits for mortality and morbidity
  - laparoscopic peritoneal lavage with drain placement near the affected colon, in addition to IV antibiotics (NO resection) has been proposed for Hinchey stage III

**Prognosis**

- mortality rates: 6% for purulent peritonitis, 35% for feculent peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

**Table 13. Hinchey Staging and Treatment for Diverticulitis**

<table>
<thead>
<tr>
<th>Hinchey Stage</th>
<th>Description</th>
<th>Acute Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phlegmon/small pericolic abscess</td>
<td>Medical</td>
</tr>
<tr>
<td>2</td>
<td>Large abscess/fistula</td>
<td>Medical, abscess drainage ± resection with primary anastomosis</td>
</tr>
<tr>
<td>3</td>
<td>Purulent peritonitis (ruptured abscess)</td>
<td>Resection or Hartmann procedure</td>
</tr>
<tr>
<td>4</td>
<td>Feculent peritonitis</td>
<td>Hartmann procedure</td>
</tr>
</tbody>
</table>
Colorectal Neoplasms

Colorectal Polyps

Definition
- polyp: protuberance into the lumen of normally flat colonic mucosa
- sessile (flat) or pedunculated (on a stalk)

Epidemiology
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70

Clinical Features
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, and mucus
- usually detected during routine endoscopy or familial/high risk screening

Pathology
- non-neoplastic
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, and carcinoids
- neoplastic
  - lipomas, leiomyomas, carcinoids
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
    - malignant risk due to associated adenomas (large bowel)
  - low malignant potential → most spontaneously regress or autoamputate
  - adenomas: premalignant, considered carcinoma in situ IF high grade dysplasia
  - some may contain invasive carcinoma (“malignant polyp” – 3-9%): invasion into submucosa
    - malignant potential: villous > tubulovillous > tubular

<table>
<thead>
<tr>
<th>Table 14. Characteristics of Tubular vs. Villous Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Incidence</td>
</tr>
<tr>
<td>Size</td>
</tr>
<tr>
<td>Attachment</td>
</tr>
<tr>
<td>Malignant Potential</td>
</tr>
<tr>
<td>Distribution</td>
</tr>
</tbody>
</table>

Investigations
- colonoscopy is the gold standard for diagnosis and treatment of colonic polyps
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscopy if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy

Treatment
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- indications for segmental resection for malignant polyps: 1) lymphovascular invasion; 2) tumour budding; 3) positive resection margin; 4) poorly differentiated cells; 5) evidence of regional or distant metastases on staging. Most of these cases are usually discussed at multi-disciplinary tumour boards
- follow-up endoscopy 1 yr later, then every 3–5 yr

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSI

Pathogenesis
- autosomal dominant inheritance, mutation in adenomatous polyposis coli (APC) gene on chromosome 5q21
Clinical Features
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40s in attenuated FAP)
- extracolonic manifestations
  - carcinoma of large bowel (i.e. polyps in colon), bile duct, pancreas, stomach, thyroid, adrenal, and small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
  - virtually 100% lifetime risk of colon cancer (because of number of polyps)
- variants
  - Gardner's syndrome: FAP + extra-intestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
  - Turcot syndrome: FAP + CNS tumours (childhood cerebellar medulloblastoma)

Investigations
- genetic testing (80-95% sensitive, 99-100% specific)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy and consider surgery (see Figure 15); consider upper endoscopy to evaluate for peripapillary tumours

Treatment
- surgery indicated by age 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

HEREDITARY NON-POLYPsis COLORECTAL CANCER – LYNCH SYNDROME

Pathogenesis
- autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1)
- resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all colorectal cancers

Clinical Features
- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr; lifetime risk 70-80% (M>F)
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

Diagnosis
- Amsterdam Criteria
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr old
  - FAP is excluded
  - genetic testing (80% sensitive) – colonoscopy mandatory even if negative
  - refer for genetic screening individuals who fulfill EITHER the Amsterdam Criteria OR the revised Bethesda Criteria
  - colonoscopy (starting age 20) annually
  - surveillance for extracolonic lesions

Referral Criteria for Genetic Screening
- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 yr old)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)

Treatment
- total colectomy and ileorectal anastomosis with annual proctoscopy

Colorectal Carcinoma

Epidemiology
- 4th most common cancer (after lung, prostate, and breast), 2nd most common cause of cancer death

Risk Factors
- most patients have no specific risk factors
- age ≥50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, or family history of CRC
- colonic conditions
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC; risk is 1-2%/yr if UC ≥10 yr)
  - previous colorectal cancer (also gonadal or breast)
  - diet (increased fat, red meat, and decreased fibre) and smoking
  - DM and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

Staging for CRC
- I T1,N0,M0
- II T2,N0,M0
- III T3-4,N0,M0
- IV T4,Nx,M1

APR removes distal sigmoid colon, rectum, and anus; permanent end colostomy required
LAR removes distal sigmoid and rectum with anastomosis of distal colon to anus

Pathogenesis
- adenoma-carcinoma sequence; rarely arise de novo

Clinical Features
- often asymptomatic
- hematochezia/melena, abdominal pain, and change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, and obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread
  - direct extension, lymphatic, and hematogenous (liver most common, lung, bone, and brain; tumour of distal rectum → IVC → lungs)
  - peritoneal seeding: oarry, and Blumer's shelf (pelvic cul-de-sac)

Table 15. Clinical Presentation of CRC

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
<th>Pathology</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>25%</td>
<td>Exophytic lesions with occult bleeding</td>
<td>Fe-deficiency anemia, RLQ mass (10%)</td>
</tr>
<tr>
<td>Weakness</td>
<td>35%</td>
<td>Annular, invasive lesions</td>
<td>BRBPR, LBO</td>
</tr>
<tr>
<td>Rarely obstruction</td>
<td></td>
<td>Ulcerating</td>
<td>Palpable mass on DRE</td>
</tr>
</tbody>
</table>

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Classification</th>
<th>N Classification</th>
<th>M Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T0 No primary tumour found</td>
<td>N0 No regional node involvement</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>II</td>
<td>Tis Carcinoma in situ</td>
<td>N1 Metastasis in 1-3 regional nodes</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>III</td>
<td>T1 Invasion into submucosa</td>
<td>N2 Metastasis in 4 or more regional nodes</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T2 Invasion into muscularis propria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>T3 Invasion through muscularis propria and into serosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>T4 Invasion into adjacent structures or organs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigations
- colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema (“apple core” lesion) + sigmoidoscopy
- if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy
- laboratory: CBC, urinalysis, liver enzymes, liver function tests, carcinogenic embryonic antigen (CEA) (pre-operative for baseline, > 5 ng/mL have worse prognosis)
- staging: CT chest/abdo; laboratory: CBC, urinalysis; if a patient is FOBT +ve, or has microcytic anemia, do colonoscopy
- colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema (“apple core” lesion) + sigmoidoscopy
- if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy

Treatment
- colon cancer
  - wide surgical resection of lesion and regional lymphatic drainage; usually colectomy with primary anastomosis
  - curative: wide resection of lesion (5 cm margins) with nodes (>12) and mesentery
  - metastatic lesions confined to the liver can be resected with curative intent
  - palliative: if distant spread, local control for hemorrhage or obstruction
  - care is taken to not spread tumour by unnecessary palpation
  - cancer-bearing portion of colon is removed according to vascular distribution of segment
  - adjuvant chemotherapy (5-FU or oral capecitabine with oxaliplatin) for stage III and is considered in select stage II patients

- rectal cancer
  - choice of operation depends on individual case; types of operations
    - low anterior resection of rectum (LAR): curative procedure of choice if adequate distal margins (~2 cm); uses technique of total mesorectal excision
    - abdominoperineal resection of rectum (APR): if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus – permanent end colostomy required
    - transanal minimally invasive surgery (TAMIS): local excision for select T1 lesions only
    - palliative procedures involve proximal diversion with an ostomy for obstruction and radiation for bleeding or pain
    - adjuvant therapy
      - combined neoadjuvant chemoradiation therapy followed by post-operative adjuvant chemotherapy for stages II and III
      - adjuvant therapy

Follow-Up
- currently there are no data suggesting optimal follow-up
- combination of periodic CT chest/abdomen/pelvis, CEA, and colonoscopy is recommended
- CEA to monitor for initial response to treatment, and for surveillance (q6mo)

Other Conditions of the Large Intestine

Angiodysplasia

Definition
- vascular malformation: focal submucosal venous dilatation and tortuosity

Clinical Features
- most frequently in right colon of patients >60 yr old
- bleeding typically intermittent, rarely massive, and not usually hypotensive (melena, anemia, and occult blood positive stools)

Investigations
- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, and delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

Treatment
- none if asymptomatic
- cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

Volvulus

Definition
- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), and splenic flexure (2%)
- 5-10% of large bowel obstruction; 25% of intestinal obstruction during pregnancy

Risk Factors
- age (50% of patients >70 yr: stretching/elongation of bowel with age is a predisposing factor)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, and institutionalization (less frequent evacuation of bowels)

Clinical Features
- symptoms due to bowel obstruction (see Large Bowel Obstruction, GS29) or intestinal ischemia (see Intestinal Ischemia, GS23)
- colicky abdominal pain, persistence of pain between spasms, abdominal distention, and vomiting

Investigations
- AXR (classic findings): "omega", "bent inner-tube", "coffee-bean" signs
- barium/Gastrografin® enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT: "whirl pattern" of mesenteric vessels twisting about the volvulus axis

Treatment
- initial supportive management (same as initial management for bowel obstruction (see Large Bowel Obstruction, GS29)
- cecum
  - nonsurgical
    - may attempt colonoscopic detorsion and decompression; successful 15-20% of cases
  - surgical
    - right colectomy + ileotransverse colonic anastomosis
- sigmoid
  - nonsurgical
    - decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
    - subsequent elective surgery recommended (50-70% recurrence)
  - surgical
    - surgical resection with or without primary anastomosis
    - indications: strangulation, perforation, or unsuccessful endoscopic decompression
**Toxic Megacolon**

**Pathogenesis**
- extension of inflammation into smooth muscle layer causing paralysis
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

**Etiology**
- inflammatory bowel disease (ulcerative colitis > Crohn's disease)
- infectious colitis: bacterial (*C. difficile*, *Salmonella*, *Shigella*, and *Campylobacter*), viral (cytomegalovirus), and parasitic (*E. histolytica*)

**Clinical Features**
- infectious colitis usually presents for >1 wk before colonic dilatation
- diarrhea ± blood (sudden improvement of diarrhea may signify onset of megacolon)
- abdominal distention, tenderness, ± local/general peritoneal signs (suggest perforation)
- triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, and anticholinergics), barium enema, and colonoscopy

**Diagnostic Criteria**
- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon
- three of: fever, HR >120, WBC >10.5, and anemia
- one of: fluid and electrolyte disturbances, hypotension, or altered LOC

**Investigations**
- CBC (leukocytosis with left shift, and anemia from bloody diarrhea), electrolytes, elevated CRP, and ESR
- metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease

**Treatment**
- NPO, NGT, stop constipating agents, correct fluid and electrolyte abnormalities, and transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis, and anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD, and metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management)
  - worsening or persisting toxicity or dilation after 48-72 h
  - severe hemorrhage, perforation
  - high lactate and WBC, especially for *C. difficile*
- procedure: subtotal colectomy + end ileostomy (may be temporary, with second operation for re-anastomosis later)

**Prognosis**
- average 25-30% mortality

---

**Fistula**

**Definition**
- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, and entero-enteric)

**Etiology**
- foreign object erosion (e.g. gallstone, graft)
- inflammatory states (e.g. infection, IBD [Crohn's > UC], and diverticular disease)
- iatrogenic/surgery (e.g. post-operative anastomotic leak, and radiation)
- congenital, trauma
- neoplastic

**Investigations**
- U/S, CT scan, fistulogram
- measure amount of drainage from fistula

**Treatment**
- decrease secretion: octreotide/somatostatin/omeprazole
- surgical intervention: dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis
Stomas

Definition
- an opening of the GI tract onto the surface of the abdomen wall
- stomas can be constructed as either end stomas: the proximal end of the GI tract forms the stoma and the distal end of the GI tract is not part of the stoma, or loop stomas: a loop of the GI tract is brought up to the skin and the anti-mesenteric surface of the bowel is matured as a stoma. The proximal and distal GI tract remain in continuity

Ileostomy
- usually positioned in RLQ; ileum is brought through rectus abdominus muscles
- indications: after proctocolectomy for ulcerative colitis, in some cases of Crohn’s disease or familial polyposis
- conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
- continent ileostomy: reservoir is constructed from distal ileum, emptied by inserting catheter into stoma several times a day; rarely used, has mostly been replaced by ileal pouch anal anastomosis

Colostomy
- indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
- colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
- most common permanent colostomy is a sigmoid colostomy – expels stool once per day, no appliance required
- chronic paracolostomy hernia is a common complication

Complications (10%)
- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output), which may lead to fluid, electrolyte and nutritional imbalances

Anorectum

Hemorrhoids

Etiology
- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
- internal: superior hemorrhoidal veins, above dentate line, portal circulation
- external: inferior hemorrhoidal veins, below dentate line, systemic circulation

Risk Factors
- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal HTN, heavy lifting
Clinical Features and Treatment

- **internal hemorrhoids**
  - engorged vascular cushions usually at 3, 7, 11 o’clock positions (patient in lithotomy position)
  - PAINLESS rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, and rectal fullness
    - **1st degree**: bleed but do not prolapse through the anus
      - treatment: high fibre/bulk diet, sitz baths, steroid cream, paromoxine (Anusol®), rubber band ligation, sclerotherapy, and photocoagulation
    - **2nd degree**: bleed, prolapse with straining, and spontaneous reduction
      - treatment: rubber band ligation, and photocoagulation
    - **3rd degree**: bleed, prolapse, and requires manual reduction
      - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
    - **4th degree**: bleed, permanently prolapsed, and cannot be manually reduced
      - treatment: closed hemorrhoidectomy

- **external hemorrhoids**
  - dilated venules usually mildly symptomatic
    - PAIN after bowel movement, associated with poor hygiene
    - medical treatment: dietary fibre, stool softeners, steroid cream (short course), paromoxine (Anusol®), and avoid prolonged straining
  - thrombosed hemorrhoids are very painful
    - resolve within 2 wk, may leave excess skin = perianal skin tag
    - treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment

Table 17. Signs and Symptoms of Internal vs. External Hemorrhoids

<table>
<thead>
<tr>
<th>Internal Hemorrhoids</th>
<th>External Hemorrhoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless BRBPR</td>
<td>Sudden severe perianal pain</td>
</tr>
<tr>
<td>Rectal fullness or discomfort</td>
<td>Perianal mass</td>
</tr>
<tr>
<td>Mucus discharge</td>
<td></td>
</tr>
</tbody>
</table>

Anal Fissures

**Definition**

- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline, 10% anterior midline
- if off midline: consider other possible causes such as IBD, STIs, TB, leukemia, or anal carcinoma
- repetitive injury cycle after first tear
  - sphincter spasm occurs preventing edges from healing and leads to further tearing
  - ischemia may ensue and contribute to chronicity

**Etiology**

- forceful dilation of anal canal: large, hard stools and irritant diarrheal stools
- tightening of anal canal secondary to nervousness/pain leads to further tearing
- others: habitual use of stool bulking agents, and childbirth

**Clinical Features**

- acute fissure
  - very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - treatment is conservative: stool softeners, bulking agents, and sitz baths (heals 90%)
- chronic fissure (anal ulcer)
  - triad: fissure, sentinel skin tags, and hypertrophied papillae
  - treatment
    - stool softeners, increased fibre intake, and sitz baths
    - topical nitroglycerin or calcium channel blocker (nifedipine): increases local blood flow, promotes healing, and relieves sphincter spasm
    - lateral internal anal sphincterotomy (most effective): objective is to relieve sphincter spasm → increases blood flow and promotes healing; but 5% chance of fecal incontinence therefore not commonly done
    - alternative treatment: botulinum toxin: inhibits release of acetylcholine (ACh), reducing sphincter spasm
Anorectal Abscess

Definition
- infection typically originating within an obstructed anal crypt which forms an abscess
- common bacterial: *E. coli*, *Proteus*, *Streptococci*, *Staphylococci*, *Bacteroides*, and anaerobes

Clinical Features
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator), or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

Treatment
- I&D
  - curative in 50% of cases
  - 50% develop anorectal fistulas
  - may require antibiotics if diabetic, heart murmur, or cellulitis

Fistula-In-Ano

Definition
- fistula from anal canal to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

Etiology
- see Fistula, GS37
- same processes that lead to the formation of an anal abscess
- other causes: post-operative, trauma, anal fissure, malignancy, and radiation proctitis

Clinical Features
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract

Treatment
- identification
  - internal opening
    - Goodsall's rule
      - fistulas originating anterior to a transverse line through the anus will have a straight course and exit anteriorly, whereas those originating posterior to the transverse line will begin in the midline and have a curved tract
  - fistulous tract
    - probing or fistulography under anesthesia
• surgery
  • fistulotomy: unroof tract from external to internal opening, allow drainage, heals by secondary intention
  • low lying fistula (does not involve external sphincter) → primary fistulotomy
  • high lying fistula (involves external sphincter) → staged fistulotomy with Seton suture placed through tract
    • promotes drainage
    • promotes fibrosis and decreases incidence of incontinence
    • delineates anatomy
    • usually done to spare muscle
  • alternative for high lying fistula → LIFT (ligation of Intersphincteric fistula tract) procedure
    • access fistula between sphincter muscles, sparing them

Post-Operative
• sitz baths, irrigation, and packing to ensure healing proceeds from inside to outside

Complications
• recurrence
• rarely fecal incontinence

## Pilonidal Disease

### Definition
• pilo = hair, nidal = nest; cyst or abscess near or on the intergluteal cleft of the sacrococcygeal area containing hair and skin debris

### Epidemiology
• occurs most frequently in young men age 15-35 yr; rare in >50 yr

### Etiology
• obstruction of the hair follicles in this area → formation of cysts, sinuses, or abscesses
• associated with occupations that require prolonged sitting, obesity, and high amounts of body hair

### Clinical Features
• asymptomatic or chronically itchy until acutely infected, then pain/tenderness, purulent discharge, and increased moisture near the tailbone

### Treatment
• acute abscess
  • I&D (often performed by primary care doctors)
  • wound packed open
  • 40% develop chronic pilonidal sinuses
• surgery
  • indication: failure of healing after I&D, recurrent disease, or complex disease
  • pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention, primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

## Rectal Prolapse

### Definition
• protrusion of some or all of rectal mucosa through external anal sphincter

### Epidemiology
• extremes of ages: <5 yr old and >5th decade
• 85% women

### Etiology
• lengthened attachment of rectum secondary to constant straining
• 2 types
  1. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  2. true/complete (most common): full thickness extrusion of rectal wall, concentric folds in:
    • first degree: prolapse includes mucocutaneous junction
    • second degree: without involvement of mucocutaneous junction
    • third degree (internal intussusception): prolapse is internal, concealed, or occult

### Risk Factors
• gynecological surgery
• chronic neurologic/psychiatric disorders affecting motility
Clinical Features
- extrusion of mass with increased intra-abdominal pressure
- difficulty in bowel regulation
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration, and constant soiling
- may be associated with urinary incontinence or uterine prolapse

Treatment
- Type I
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- Type II
  - conservative: reduce if possible
  - surgery: abdominal, perineal, and transsacral approaches

Anal Neoplasms

ANAL CANAL

Squamous Cell Carcinoma of Anal Canal (Above Dentate Line)
- most common tumour of anal canal (75%)
- anus prone to human papillomavirus (HPV) infection, therefore at risk for anal squamous intra-epithelial lesions (ASIL)
  - high grade squamous intra-epithelial lesion (HSIL) and low grade squamous intra-epithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, and pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5-yr survival

Malignant Melanoma of Anal Canal
- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- treatment: wide excision or APR ± chemoradiation
- prognosis: <5% 5-yr survival

ANAL MARGIN
- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen’s disease (SCC in situ), and Paget’s disease

Liver

Figure 24. Anatomy of liver
Liver Cysts

Table 18. Characteristics of Liver Cysts

<table>
<thead>
<tr>
<th>Description</th>
<th>Simple Cysts</th>
<th>Polycystic Liver Disease</th>
<th>Choledochal Cysts</th>
<th>Hydatid (Cystic Echinococcosis)</th>
<th>Cystadenoma (Premalignant)/Cystadenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Contain clear fluid that do not communicate with the intrahepatic biliary tree</strong></td>
<td><strong>Several cysts that replace much of the liver</strong></td>
<td><strong>Congenital malformations of pancreaticobiliary tree high risk of malignancy majority present before age 10</strong></td>
<td><strong>Infection with parasite Echinococcus granulosus associated with exposure to dogs, sheep, and cattle in Southern Europe, Middle East, Australia, South America</strong></td>
<td><strong>Rare cystic tumours that occur in the liver parenchyma or the extrahepatic bile ducts Cystadenocarcinoma is an invasive carcinoma</strong></td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Usually asymptomatic may have multiple simple cysts</td>
<td>Progressive 50% associated with polycystic kidney disease</td>
<td>Recurrent abdominal pain Intermittent jaundice RUQ mass Cholangitis Pancreatitis</td>
<td>Asymptomatic mass chronic pain Hepatomegaly</td>
<td>Upper abdominal mass Abdominal pain Anorexia</td>
</tr>
<tr>
<td>Investigations</td>
<td>U/S: Used for diagnosis and follow-up CT: well demarcated lesion that does not enhance with contrast</td>
<td>U/S CT Transhepatic cholangiography L Ts</td>
<td>Anti-Echinococcus Ab (IgG) U/S CT: calcified mass Needle biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Not required unless very large Monitor if &gt;4 cm Only if asymptomatic partial liver resection drainage</td>
<td>Complete excision of cysts liver transplant if cyst involves intrahepatic bile ducts (Carol’s disease)</td>
<td>Albendazole (anti-helminthic) cure up to 30% Surgical (risk of spillage into abdomen): Conservative: open endohepatectomy or PNR (Percutaneous Aspiration, Injection of protoscolicidal agent, Re-aspiration) Radical: partial hepaatectomy or total pericystectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>Intracystic hemorrhage</td>
<td>Biliary cirrhosis, portal HTN, rupture, cholangiocarcinoma Abnormal pancreaticobiliary junction is associated with increased risk of malignancy</td>
<td>Inferior vena cava compression rupture can cause biliary colic, jaundice, cholangitis, pancreatitis, or anaphylactic reaction</td>
<td>Cystadenocarcinoma can invade adjacent tissues and metastasize</td>
<td></td>
</tr>
</tbody>
</table>

Liver Abscesses

Etiology
- types
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *E. coli, Klebsiella, Proteus, Strep. milleri*
  - parasitic (amoebic): *Entamoeba histolytica, Echinococcal cyst*
  - fungal: *Candida*
  - sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features
- fever, malaise, chills, anorexia weight loss, abdominal pain, and nausea
- RUQ tenderness, hepatomegaly, and jaundice

Investigations
- leukocytosis anemia, elevated liver enzymes, and echinococcal serology
- U/S, CXR (right basilar atelectasis/effusion), CT, cyst aspiration with C&S, and MRI

Treatment
- treat underlying cause
- bacterial abscesses generally will treat initially with antibiotics, and add surgical or percutaneous drainage and IV antibiotics for larger abscesses (initially ceftriaxone + metronidazole or piperacillin/tazobactam)
- consider potential source of sepsis (e.g. biliary source, infected tumour)

Prognosis
- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, and malnutrition
Neoplasms

BENIGN LIVER NEOPLASMS

Hemangioma (cavernous)

- pathogenesis: most common benign hepatic tumour; results from malformation of angioblastic fetal tissue
  - risk factors: F:M = 3:1
  - clinical features
    - usually small and asymptomatic
    - consumptive coagulopathy if giant (in children)
  - investigations
    - contrast CT (well-demarcated hypodense mass with peripheral enhancement on arterial phase with centripetal filling on delayed phases), U/S (homogenous hyperechoic mass), MRI
  - treatment
    - usually none

Focal Nodular Hyperplasia

- pathogenesis: unclear, may be regenerative response to hyperperfusion from anomalous arteries at centre of nodule
- risk factors: female, age 20-50
- clinical features: asymptomatic, rarely grows or bleeds, and no malignant potential
- investigations: central stellate scar on CT scan; MRL biopsy may be required
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential)
  - if confirmed to be FNH → no treatment required

Adenoma

- definition: benign glandular epithelial tumour
- risk factors: female, age 20-50, estrogen (OCP, pregnancy), and obesity
- clinical features: asymptomatic, rarely grows or bleeds, and no malignant potential
- investigations: CT (well-demarcated masses, often heterogeneous enhancement on arterial phase, isodense on venous phase without washout of contrast), U/S, MRI, biopsy often needed
- treatment
  - stop anabolic steroids or OCP
  - excise especially if large (>5 cm), due to risk of transformation to hepatocellular carcinoma and spontaneous rupture/hemorrhage

MALIGNANT LIVER NEOPLASMS

Primary

- most commonly hepatocellular carcinoma (HCC) and cholangiocarinomas
- others include angiosarcoma, hepatoblastoma, and hemangioendothelioma
- epidemiology: 3rd leading cause of cancer death worldwide, 9th in United States; highest in Africa, China, Taiwan
- risk factors
  - chronic liver inflammation: cirrhosis from any cause, chronic hepatitis B (inherently oncogenic) and hepatitis C, hemochromatosis, α1-antitrypsin deficiency, and non-alcoholic steatohepatitis
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, Betel nuts
  - chemical carcinogens ( aflatoxin, microcystin, and vinyl chloride – associated with angiosarcoma)
- clinical features
  - RUQ discomfort, and right shoulder pain
  - jaundice, weakness, weight loss, and fever (if central tumour necrosis)
  - hepatomegaly, bruise, and hepatic friction rub
  - ascites with blood (sudden intra-abdominal hemorrhage)
  - paraneoplastic syndromes – hypoglycemia, hypercalcemia, erythrocytosis, and watery diarrhea
  - metastasis: lung, bone, brain, and peritoneal seeding
- investigations
  - elevated ALP, bilirubin, and α-fetoprotein (80% of patients)
  - U/S (poorly-defined margins with internal echos), triphasic CT (enhancement on arterial phase and washout on portal venous phase), and MRI
  - liver enzyme and liver function tests: AST, ALT, ALP, bilirubin, albumin and INR
- treatment
  - cirrhosis is a relative contraindication to tumour resection due to decreased hepatic reserve
  - surgical: resection (10% of patients have resectable tumours)
  - liver transplant: may use bridging therapy while awaiting transplant
  - absolute contraindications: extrahepatic disease, and vascular invasion
  - relative contraindications: dependent on liver transplant protocol based on staging criteria followed by transplant centre

Differential Diagnosis of Metastatic Liver Mass

<table>
<thead>
<tr>
<th>Some GU Cancers Produce Bumpy Lumps</th>
<th>Stomach</th>
<th>Genitourinary cancers (kidney, ovary, uterus)</th>
<th>Colon</th>
<th>Pancreas</th>
<th>Breast</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder</td>
<td>Bladder</td>
<td>Prostate</td>
<td>Ovary</td>
<td>Uterus</td>
<td>Small Intestine</td>
<td></td>
</tr>
</tbody>
</table>

Staging Criteria for Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Milan Criteria*</th>
<th>UCSF Criteria*</th>
<th>Toronto Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tumour ≤5 cm</td>
<td>Up to 3 tumours each ≤3 cm</td>
<td>No tumour size of number restrictions</td>
</tr>
<tr>
<td>1 tumour &gt;5 cm</td>
<td>&gt;3 cm</td>
<td>Not poorly differentiated</td>
</tr>
</tbody>
</table>

*Each criteria assumes no extrahepatic and no macrovascular invasion

Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, Including Post-Operatively)

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>One Yr Survival</th>
<th>Two Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>7-8</td>
<td>B</td>
<td>87%</td>
<td>57%</td>
</tr>
<tr>
<td>9-10</td>
<td>C</td>
<td>49%</td>
<td>35%</td>
</tr>
<tr>
<td>11-15</td>
<td>D</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>16-20</td>
<td>E</td>
<td>10%</td>
<td>0%</td>
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</tbody>
</table>

Points

<table>
<thead>
<tr>
<th>Child-Turcotte-Pugh Score</th>
<th>Prognosis of Chronic Liver Disease/Cirrhosis, Including Post-Operatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>2</td>
<td>Early controlled</td>
</tr>
<tr>
<td>3</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>4</td>
<td>Controlled</td>
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<tr>
<td>5</td>
<td>Controlled</td>
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<tr>
<td>6</td>
<td>Advanced</td>
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<td>7</td>
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<td>19</td>
<td>Advanced</td>
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<tr>
<td>20</td>
<td>Advanced</td>
</tr>
</tbody>
</table>
Liver

- non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheater arterial chemoemobilization (TACE), chemotherapy (consider sorafenib for HCC; pre-operative chemotherapy for hepatoblastoma is standard of care), and radiotherapy
- prognosis
  - median survival: 6-20 mo
  - 5 yr survival: all patients – 5%; patients undergoing complete resection – 11-40%

Secondary
- metastases to the liver are the most common malignant tumours found in the liver
- etiology
  - GI (colorectal most common), lung, breast, pancreas, ovary, uterus, kidney, gallbladder, and prostate
treatment
- depends on the primary cancer site and prognosis. Often liver metastases are a manifestation of Stage IV disease, and chemotherapy is indicated
- metastasectomy may be appropriate for some cancers
  - hepatic resection of metastatic colorectal liver metastases is standard of care as part of multi-modality treatment that includes chemotherapy if complete resection of the primary cancer and metastases is possible
  - prognosis following liver resection for colorectal metastases is an overall survival of 30-60% at 5 yr

Liver Transplantation

<table>
<thead>
<tr>
<th>Parenchymal Disease</th>
<th>Cholestatic Disease</th>
<th>Inborn Errors</th>
<th>Tumours</th>
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<tr>
<td>Chronic hepatitis B or C</td>
<td>Biliary atresia**</td>
<td>α1-antitrypsin deficiency</td>
<td>Hepatocellular carcinoma</td>
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<td>Alcoholic cirrhosis</td>
<td>Primary biliary cirrhosis</td>
<td>Wilson’s disease</td>
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<td>Acute liver failure</td>
<td>Sclerosing cholangitis</td>
<td>Hemochromatosis</td>
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<td>Congenital hepatic fibrosis</td>
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<td>Autoimmune hepatitis</td>
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<td>Cryptogenic cirrhosis</td>
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<td>Drug induced hepatotoxicity</td>
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<td>Non-alcoholic steatohepatitis</td>
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*Leading cause in adults; **leading cause in children

Clinical Indications
- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially:
  - decompensated cirrhosis (ascites, esophageal variceal hemorrhage, spontaneous hepatic encephalopathy, coagulopathy, progressive jaundice, severe fatigue)
  - unresectable primary liver cancers
  - fulminating hepatic failure
  - end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate
  - suitable HCC not amenable to liver resection

Criteria for Transplantation
- Model for End-Stage Liver Disease (MELD): prognostic model to estimate 3 mo survival and disease severity if patient does not receive transplant; based on creatinine, bilirubin, INR; MELD scores from 6-40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: classification system to assess the prognosis and mortality of liver disease; patient must have ≥7 points (Class B)

Contraindications
- active alcohol/substance abuse
- extrahepatic malignancy within 5 yr advanced cardiopulmonary disease
- active uncontrolled infection

Post-Operative Complications
- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: HTN, renal disease, DM, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

Prognosis
- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrathoracic cancers. They commonly arise from breast, lung, and colorectal cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure

| Table 19. Conditions Leading to Transplantation |

Living Liver Donors vs. Deceased Liver Donors
The right lobe of a living donor liver is transplanted into the recipient, whereas whole livers from deceased donors are transplanted orthotopically into the recipient.

Which Matters Most: Number of Tumours, Size of the Largest Tumour, or Total Tumour Volume?
Liver Transplant 2011;17:S58-66
Purpose: To determine if the size and/or number of hepatocellular carcinoma (HCC) nodules predict disease recurrence and survival after liver transplantation.
Methods: Systematic review and meta-analysis.
Results: 74 studies were included for analysis. Patients beyond the Milan criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the UCSF criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the Milan criteria but within the UCSF criteria had reduced overall and disease-free survivals. Overall and disease-free survivals were reduced for patients with larger tumour diameter, a 10 cm vs. <10 cm and a 8 cm vs. <8 cm, respectively. Similarly, patients with higher diameter of largest tumour nodule (≥3 cm vs. <3 cm) had reduced overall survival and higher recurrence. Overall and disease-free survivals were reduced and recurrence higher for patients with tumour size ≤5 cm vs. >5 cm. Mixed results were found regarding number of tumour nodules.
Conclusion: Tumour size and volume are important actors in survival after liver transplantation.

Living Donor Liver Transplantation vs. Deceased Donor Liver Transplantation for Hepatocellular Carcinoma: Comparable Survival and Recurrence
Liver Transplant 2012;18:315-322
Purpose: To compare the overall survival and hepatocellular carcinoma (HCC) recurrence rates after living donor liver transplantation (LDLT) versus deceased donor liver transplantation (DDLT) in a series of patients with HCC.
Methods: Study conducted between 1996 and 2009 at a single centre 345 patients with HCC undergoing liver transplantation.
Results: The overall survival rates at 1, 3, and 5 yr did not significantly differ between the LDLT and DDLT groups (p=0.62). Disease-free survival at 1, 3, and 5 yr did not differ between the groups (p=0.62). The recurrence rates at 1, 3, and 5 yr also did not differ between the two groups (p=0.56).
Conclusion: LDLT and DDLT lead to similar survival and recurrence rates.
Biliary Tract

Cholelithiasis

Definition
• the presence of gallstones

Pathogenesis
• imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
• excess hepatic cholesterol secretion relative to bile salts and lecithin → supersaturated cholesterol which precipitates as gallstones
• North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors
• cholesterol stone
  ▪ obesity, age <50
  ▪ estrogens: female, multiparity, OCPs
  ▪ ethnicity: First Nations heritage (especially Pima Indians) > Caucasian > Black
  ▪ terminal ileal resection or disease (e.g. Crohn’s disease)
  ▪ impaired gallbladder emptying: starvation, TPN, DM
  ▪ rapid weight loss: rapid cholesterol mobilization and biliary stasis
• pigment stones (contain calcium bilirubinate)
  ▪ cirrhosis
  ▪ chronic hemolysis
  ▪ biliary stasis ( strictures, dilation, biliary infection)
  ▪ protective factors: statins, vitamin C, coffee, exercise

Clinical Presentation
• asymptomatic (80%)
  ▪ most do NOT require treatment
  ▪ consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli’s disease, porcelain or calcified gallbladder), sickle cell disease, pediatric patient, bariatric surgery, and immunosuppression
• biliary colic (10-25%)
• cholecystitis
• choledocholithiasis (8-15%)
• cholangitis
• gallstone pancreatitis (see Acute Pancreatitis, GS51)
• gallstone ileus (0.3-0.5%)
• other: empyema of the gallbladder, liver abscess, and gallbladder perforation with bile peritonitis

Risk Factors for Cholesterol Stones
4Fs
Fat
Female
Fertile
Forties
Investigations
- Labs
  - CBC, LFTs, amylase, and lipase
- U/S: diagnostic procedure of choice
  - image for signs of inflammation, obstruction, and localization of stones
  - 95% specific for detecting stones
- HIDA scan (cholescintigraphy)
  - used less commonly
- IV technetium-99 radioisotope is excreted into bile, allowing visualization of the biliary tree
- does not visualize stones; diagnosis based on occluded cystic duct or CBD

Biliary Colic

Pathogenesis
- gallstone transiently impacted in cystic duct, no infection

Clinical Features
- an episode of steady, severe dull pain in the epigastrium or RUQ lasting minutes to hours (<6 h), crescendo-decrescendo pattern
- can present with chest pain, right shoulder tip pain, scapular pain
- N/V
- frequently occurs at night or after fatty meal, not after fasting
- no peritoneal findings, no systemic signs

Investigations
- normal blood work: CBC, electrolytes, LFTs, bilirubin, amylase
- U/S shows cholelithiasis, may show stone in cystic duct

Treatment
- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success)
  - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, and vessel injury
  - laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery
  - risk of open cholecystectomy higher in emergency situations

Acute Cholecystitis

Pathogenesis
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see Acalculous Cholecystitis, GS48)

Clinical Features
- often have history of biliary colic
- severe constant (>6hr) epigastric or RUQ pain, anorexia, N/V, and low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable, and tender gallbladder (in 3%)
- Boas' sign: right subcapsular pain

Investigations
- blood work: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT, and ALP
- U/S: 98% sensitive, consider HIDA scan if U/S negative
  - signs: gallbladder wall thickening >4 mm, edema (double-wall sign), gallbladder sludge, pericholecystic fluid, and sonographic Murphy's sign

Complications
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct
- empyema of gallbladder: supplicative cholecystitis, pus in gallbladder, and sick patient
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall, or pericholecystic space (risk in diabetic patient); organisms involved in secondary infection: E. coli, Klebsiella, Enterococcus
- gangrenous gallbladder (20%), perforation (2%): result in abscess formation or peritonitis
- cholecystoenteric fistula, from repeated attacks of cholecystitis, can lead to gallstone ileus

Treatment
- admit, hydrate, NPO, NGT (if persistent vomiting from associated ileus), analgesics once diagnosis is made
- antibiotics
  - cefazolin if uncomplicated cholecystitis
  - ERCP prior to surgery if US if CBD stones are present
  - MRCP ± ERCP if CBD is markedly dilated or CBD stones suspected

Early vs. Delayed Laparoscopic Cholecystectomy for Uncomplicated Biliary Colic
Cochrane DB Syst Rev 2013;6:CD007196
Study: To assess the benefits and harms of early vs. delayed laparoscopic cholecystectomy for patients with uncomplicated biliary colic due to gallstones.
Results: One trial with 75 participants, average age 43 yr. Early laparoscopic cholecystectomy (<24 h) vs. delayed (mean wait period 4.2 mo). The proportion of serious adverse events was lower in the early vs. delayed group (0% vs. 22.5%, respectively). There was a shorter hospital stay in the early group (MD -1.25 d, 95% CI -2.05 to -0.45) and a shorter operating time in the early group (MD -14.80 min, 95% CI -18.02 to -11.58). There was no difference in the proportion of patients requiring conversion to open cholecystectomy in the two groups.
Conclusion: Early laparoscopic cholecystectomy (<24 h) decreased morbidity during the waiting period for elective laparoscopic cholecystectomy, hospital stay and operating time.
• cholecystectomy
  • early (within 72 h) vs. delayed (after 6 wk)
  • equal morbidity and mortality
  • early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
  • emergent OR indicated if high risk, e.g., emphysematous
• laparoscopic is standard of care (convert to open for complications or difficult case)
• laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-operative pain, and increased risk of bile duct injury
• intra-operative cholangiography (IOC)
• indications: clarify bile duct anatomy, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), and jaundice
• percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated

### Acute Cholecystitis

**Definition**
- acute or chronic cholecystitis in the absence of stones

**Pathogenesis**
- typically due to gallbladder ischemia, and stasis

**Risk Factors**
- DM, immunosuppression, ICU admission, trauma patient, TPN, and sepsis

**Clinical Features**
- see *Acute Cholecystitis, GS47*
  - occurs in 20% of cases of acute cholecystitis

**Investigations**
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis*)
- CT or HIDA scan

**Treatment**
- broad-spectrum antibiotics, cholecystectomy
- if patient unstable → cholecystostomy

### Choledocholithiasis

**Definition**
- stones in CBD

**Clinical Features**
- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, and fluctuating jaundice
- primary vs. secondary stones
  - primary: formed in bile duct, indicates bile duct pathology (e.g., benign biliary stricture, sclerosing cholangitis, choledochal cyst, and CF)
  - secondary: formed in gallbladder (85% of cases in U.S.)

**Investigations**
- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GGT later
- amylase/lipase: to rule out gallstone pancreatitis
- U/S: intra-/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
- MRCP (90% sensitive)
  - visualization of ampullary region, biliary and pancreatic anatomy
  - non-invasive diagnostic test of choice
- ERCP
  - CBD stones in periampullary region
  - diagnostic and therapeutic; removal of stones and sphincterotomy possible
- complications: retained stones, ERCP pancreatitis (1-2%), pancreatic or biliary sepsis

### Percutaneous Transhepatic Cholangiography
- percutaneous approach to the proximal biliary tree (i.e., intra-hepatic biliary system) via the hepatic parenchyma
- useful for proximal bile duct obstruction or when ERCP fails or not available
- requires prophylactic antibiotics

### Acalculous Cholecystitis

**Definition**
- acute or chronic cholecystitis in the absence of stones

**Pathogenesis**
- typically due to gallbladder ischemia, and stasis

**Risk Factors**
- DM, immunosuppression, ICU admission, trauma patient, TPN, and sepsis

**Clinical Features**
- see *Acute Cholecystitis, GS47*
  - occurs in 20% of cases of acute cholecystitis

**Investigations**
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis*)
- CT or HIDA scan

**Treatment**
- broad-spectrum antibiotics, cholecystectomy
- if patient unstable → cholecystostomy tube: critically ill or if general anesthetic contraindicated
Biliary Tract

- contraindications: coagulopathy, ascites, peri/intrahepatic sepsis, and disease of right lower lung or pleura
- complications: bile peritonitis, chylothorax, pneumothorax, biliary sepsis, and hemobilia

Complications
- cholangitis, pancreatitis, biliary stricture, and biliary cirrhosis

Treatment
- treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients

Acute Cholangitis

Pathogenesis
- obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration and biliary sepsis – may be life-threatening, especially in elderly

Etiology
- choledocholithiasis (60%), stricture, neoplasms (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), and biliary stent
- organisms: *E. coli*, *Klebsiella*, *Pseudomonas*, *Enterococcus* *B. fragilis*, and Proteus

Clinical Features
- Charcot's triad: fever, RUQ pain, and jaundice
- Reynold's pentad: fever, RUQ pain, jaundice, shock, and confusion
- may have N/V, abdominal distention, ileus, acholic stools, and tea-coloured urine (elevated direct bilirubin)

Investigations
- CBC: elevated WBC + left shift
- may have positive blood cultures
- LFTs: obstructive picture (elevated ALP, GGT, and conjugated bilirubin, mild increase in AST, ALT)
- amylase/lipase: rule out pancreatitis
- U/S: intra-/extra-hepatic duct dilatation

Treatment
- initial NPO, fluid and electrolyte resuscitation, ± NGT, IV antibiotics (treats 80%)
- biliary decompression
  - ERCP + sphincterotomy: diagnostic and therapeutic
  - PTC with catheter drainage: if ERCP not available or unsuccessful
  - laparotomy with CBD exploration and T tube placement if above fails
- all patients should also have a cholecystectomy, unless contraindicated

Prognosis
- suppurative cholangitis mortality rate: 50%

Gallstone Ileus

Pathogenesis
- repeated inflammation causes a cholecystoenteric fistula (usually duodenal) → large gallstone enters the GI track, impacting the ileocecal valve, causing a mechanical bowel obstruction (note: ileus is a misnomer in this context)

Clinical Features
- crampy abdominal pain, N/V, constipation/obstipation (see Large Bowel Obstruction, GS29)

Investigations
- AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, and air in biliary tree (pneumobilia) (40%)
- CT: biliary tract air, obstruction, and gallstone in intestine
- Rigler’s triad: pneumobilia, small bowel obstruction (partial or complete), and gallstone (usually in right iliac fossa)

Treatment
- fluid resuscitation, NGT decompression
- surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- may close fistula surgically or manage expectantly (can resolve spontaneously)
- cholecystectomy is generally not performed
Carcinoma of the Gallbladder

Risk Factors
- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (Salmonella, Helicobacter), and abnormal pancreaticobiliary duct junction

Clinical Features
- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of open cholecystectomies 0 1% in laparoscopic cholecystectomies)
- many patients are asymptomatic until late
- local: non-specific RUQ pain, ± palpable RUQ mass
- Courvoisier’s gallbladder: an enlarged, often palpable gallbladder in a patient with carcinoma of the head of the pancreas; associated with jaundice due to obstruction of the CBD
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- early local extension to liver, may extend to stomach, duodenum
- early metastasis common to liver, lung, bone

Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, and fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, good for staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, and distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

Treatment
- if carcinoma of the gallbladder is suspected pre-operatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy
- early metastasis: common to liver, lung, bone

Prognosis
- poor 5 yr survival (10%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

Cholangiocarcinoma

Definition
- malignancy of extra- or intrahepatic bile ducts

Risk Factors
- age 50-70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, Clonorchis sinensis infection (liver fluke), chronic intrahepatic stones (hepatolithiasis)

Clinical Features
- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, and pale stools
- anorexia, weight loss, RUQ pain, Courvoisier’s sign (if CBD obstructed), hepatomegaly
- early ascites are uncommon, but commonly tumour grows into portal vein or hepatic artery
- Klatskin tumour: cholangiocarcinoma located at bifurcation of common hepatic duct

Investigations
- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

Treatment
- if resectable: biliary drainage and wide excision margin
- intra-hepatic lesions: liver resection
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)
- chemotherapy ± radiotherapy
- role for transplantation in selected patients with Klatskins tumours

Prognosis
- overall 5 yr survival: 15%

Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centres

Purpose: To determine the effectiveness of neoadjuvant chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma and to determine the appropriateness of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) criteria for model of end-stage liver disease (MELD) exception for patients with this disease.

Methods: Study conducted from 1993-2010 in 12 transplant centres. 287 patients included.

Results: Median follow-up was 2.5 yr. 43% of patients (n=122) died after a median of 1.2 yr from presentation, and of these, 60 died posttransplant. Post-transplant, 43 patients had recurrences and 62 died. Recurrence-free survival at 2, 5, and 10 yr were 78%, 68%, and 58%, respectively. Intention-to-treat survival rates at 2 and 5 yr were 68% and 50%, respectively. 25% of patients left the waiting list after a median of 48 mo. The waiting list drop-out rate increased by an average of 11.5% every 3 yr. Patients who received transplantation outside of the criteria for MELD exception or who had a malignancy within 5 yr had significantly worse recurrence-free survival compared to those who met the criteria (HR=2.98, 95% CI 1.79, 4.95). Recurrence-free survival at 5 yr was shorter for patients with tumours >/=3 cm vs. <3 cm (p<0.001).

Conclusions: Neoadjuvant chemoradiation and liver transplantation are effective treatments for unresectable perihilar cholangiocarcinoma. Furthermore, the UNOS/OPTN criteria for MELD exception appear to be appropriate.

Ranson’s Criteria

A. At admission
1. Age >55 yr
2. WBC >16 x 10^9/L
3. Glucose >11 mmol/L
4. LDH >350 IU/L
5. AST >250 IU/L

B. During initial 48 h
1. Hct drop >10%
2. BUN rise >1.8 mmol/L
3. Arterial PO2 <60 mmHg
4. Base deficit >4 mmol/L
5. Calcium <2 mmol/L
6. Fluid sequestration >1 L

C. Interpretation
  a2 = difficult course
  a3 = high mortality (>15%)
Pancreas

Acute Pancreatitis

- see Gastroenterology, G44

GALLSTONE PANCREATITIS (45% of Acute Pancreatitis)

Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (Pancreatitis of Any Etiology)
- pain (epigastric pain radiating to back), N/V, ileus, peritoneal signs, jaundice, and fever
- Inglefinger's sign: pain worse when supine, and better when sitting forward
- may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)
- physical exam may show: tachypnea, tachycardia, hypotension, abdominal distention and tenderness, Cullen's sign, and Grey Turner's sign

Investigations
- lipase (most Sn and Sp), elevated amylase (higher than alcoholic pancreatitis), and leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), and edematous pancreas
- CXR, AXR, and CT (if severe to evaluate for complications)

Treatment
- supportive: e.g. NPO, hydration, analgesia, and early enteric nutrition
- antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if CBD stone impacted or cholangitis
- surgical indications in acute pancreatitis (rare):
  - drain placement and debridement for necrotizing pancreatitis if refractory to medical management, if septic or in ICU without other sources of sepsis

Complications
- Local complications
  - acute fluid collections
  - walled-off pancreatic fluid collection/pseudocyst (>4 wk old)
  - abscess/infection, necrosis
- Systemic complications
  - splenic/mesenteric/portal vessel thrombosis
  - pancreatic ascites/pancreatic pleural effusion
  - DM (b/c pancreatic & insulin insufficiency)
  - ARDS/sepsis/multiorgan failure
  - coagulopathy/DIC
  - severe hypocalcemia

Chronic Pancreatitis

- see Gastroenterology, G45

Surgical Treatment
- treatment is generally medical
- indications for surgery
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, and rupture
  - CBD obstruction (e.g. stricures), and duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- pre-operative CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery

The hallmark of chronic pancreatitis is epigastric pain radiating to the back

The hallmark of chronic pancreatitis is epigastric pain radiating to the back
surgical options
- drainage procedures: only effective if ductal system is dilated
  - Pancreaticoduodenectomy (Whipple procedure) for cure <5% mortality
  - Total pancreatectomy: best option in absence of dilated duct

proximal disease: Whipple procedure (pancreaticoduodenectomy) – pain relief in 80%
distal disease: distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy
total pancreatectomy: refractory disease
- islet cells autotransplantation can be used to control insulin-related morbidity
denervation of celiac ganglia and splanchnic nerves

WALLED-OFF PANCREATIC FLUID COLLECTIONS (PSEUDOCYST)
- localized fluid collections rich in pancreatic enzymes, with a non-epithelialized wall consisting of fibrous and granulation tissue
- complication of chronic and/or acute pancreatitis
- up to 40% resolve spontaneously
- cyst wall must be mature prior to drainage (4-6 wk)
- pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first

Treatment
- if asymptomatic: expectant management
- if symptomatic: choice of drainage procedure depends on location of fluid collection
  - surgical drainage: cystgastrostomy vs. cystoduodenostomy
  - percutaneous catheter drainage
  - surgical drainage: cystgastrostomy vs. cystenterostomy
  - resection
- consider biopsy of cyst wall to rule out cystadenocarcinoma

Pancreatic Cancer

Epidemiology
- fourth most common cause of cancer-related mortality in both men and women in Canada
  - M:F = 1.3:1, average age: 50-70

Risk Factors
- increased age
- smoking: 2.5x increased risk, most clearly established risk factor
- high fat/low fibre diets, heavy alcohol use
- obesity
- DM, chronic pancreatitis
- partial gastrectomy, cholecystectomy
- chemicals: betanaphthylamine, benzidine
- African descent

Clinical Features
- head of the pancreas (70%)
  - weight loss, obstructive jaundice, steatorrhea, and vague constant mid-epigastric pain (often worse at night, may radiate to back)
  - painless jaundice, pruritus, dark urine, pale stools, and Courvoisier’s sign
- body or tail of pancreas (30%)
  - tends to present later and usually inoperable (80% are unresectable at diagnosis)
  - weight loss, vague mid-epigastric pain
  - <10% jaundiced
  - sudden onset DM

Investigations
- serum chemistry is non-specific, can have elevated ALP and high bilirubin
- CA 19-9 (most useful serum marker of pancreatic cancer)
- U/S, CT (also evaluates metastasis and resectability) ± ERCP, MRI, EUS

Pathology
- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: pancreatic neuroendocrine tumours (non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma), mucinous cystic neoplasm (MCN), acinar carcinoma
- see Surgical Endocrinology, GS60 for functional pancreatic neuroendocrine tumours

Treatment
- resectable (10-20% of pancreatic cancer)
  - no involvement of liver, peritoneum, or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure <5% mortality
Pancreas

- distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
- adjuvant chemotherapy recommended (gemcitabine ± capecitabine, 5-FU/Leucovorin)
- locally advanced, borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
  - locally advanced, non-resectable (palliative → relieve pain, obstruction)
  - encasement of major vascular structures including arteries
  - most body/tail tumours are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochocoduodenostomy + gastroenterostomy)
  - palliative chemotherapy (gemcitabine + nab-paclitaxel, FOLFIRINOX) ± radiotherapy

**Prognosis**

- most important prognostic indicators are lymph node status, margin status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5 yr survival for all patients with pancreas cancer is 1%; following surgical resection 5 yr survival is 20%
- median survival for unresectable disease: 3-6 mo if metastatic, 8-12 mo if locally advanced at presentation

**Table 20. TNM Classification System for Exocrine and Endocrine Tumours of the Pancreas**

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX</td>
<td>M0</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tis</td>
<td>N1</td>
<td>M1</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour limited to pancreas, &lt;2 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour limited to pancreas, &gt;2 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends beyond pancreas, no involvement of celiac axis or SMA</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour involves celiac axis or SMA (unresectable)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 21. Staging and Treatment of Pancreatic Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>5 Yr Survival</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
<td>14%</td>
<td>Surgical resection ± chemotherapy</td>
</tr>
<tr>
<td>IA</td>
<td>T1, N0, M0</td>
<td>12%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IB</td>
<td>T2, N0, M0</td>
<td>7%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIA</td>
<td>T3, N0, M0</td>
<td>5%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-3, N1, M0</td>
<td>3%</td>
<td>Borderline resectable, trial of chemotherapy and radiation</td>
</tr>
<tr>
<td>III</td>
<td>T4, any N, M0</td>
<td>1%</td>
<td>Non-resectable, palliative treatments</td>
</tr>
<tr>
<td>IV</td>
<td>any T, any N, M1</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

**Steps of a Whipple Resection (Pancreaticoduodenectomy)**

1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the duodenum and head of the pancreas
3. Identification of the superior mesenteric vein and mobilization of the pancreatic neck
4. Mobilization of the stomach; dissection of the hepatoduodenal ligament and choledochectomy
5. Division of the stomach: proximal jejenum, and CBD
6. Transection of the pancreatic neck and dissection of the uncinate process from the retroperitoneum
7. Restoration of gastrointestinal continuity: construction of a pancreaticojejunostomy, hepaticojejunostomy, gastrojejunostomy using a neo-duodenum

**Diagnostic Value of Serum Carbohydrate Antigen 19-9 in Pancreatic Cancer: A Meta-Analysis**

Tumour Biol 2014 [Epub ahead of print]

Summary: 11 studies with 2,316 patients were included in the analysis. The sensitivity of CA19-9 in the diagnosis of pancreatic cancer was found to be 0.8 (95% CI 0.77-0.82) and the specificity also 80% (95% CI 0.77-0.82) with a diagnostic odds ratio of 14.79 (95% CI 8.50-25.58). Overall, CA19-9 plays an important role in the diagnosis of pancreatic cancer.

Figure 26. Schematic of Whipple resection, showing the resected components
Spleen

Splenic Trauma

- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr’s sign

Treatment

- non-operative
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemothorax
- operative
  - Hemodynamically unstable patients with positive FAST will undergo operative surgical exploration
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
  - partial splenectomy, rarely performed due to risk of recurrent hemorrhage
  - total splenectomy if patient unstable or high grade injury

Splenectomy

Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenic purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenic purpura (TTP), and sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIg

Complications

- short-term
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas)
  - post-operative thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk in those <16 yr old)
    - 50% mortality
    - prophylaxis with vaccinations, ideally 2 wk pre- or post-operative (pneumococcal, H. influenzae, and meningococcus)
    - liberal use of penicillin especially in children <6 yr old
  - splenosis: intra-abdominal "seeding" of splenic tissue during removal

Splenic Infarct

Pathophysiology

- splenic artery occlusion or oxygen-delivery insufficiency leading to parenchymal ischemia and necrosis
- can occur in sickle cell disease, thromboembolism, myelofibrosis, CML, hypercoagulable states
- patient can be asymptomatic or can have left-upper-quadrant pain (70%), N/V, fever, chills, and Kehr sign

Treatment

- non-operative: close follow-up, analgesia
- indications for splenectomy: complications such as rupture, abscess, persistent pseudocyst, bleeding, sepsis
### Benign Breast Lesions

**Three Categories**
1. nonproliferative
2. proliferative without atypia
3. atypical hyperplasia

**NONPROLIFERATIVE LESIONS**
- benign breast condition characterized by fibrous and cystic changes in the breast (fibrocystic changes/disease)
- most common: breast cysts
- other lesions include papillary apocrine change, epithelial-related calcifications and mild hyperplasia of the usual type
- no increased risk of breast cancer
- age 30 to menopause (and after if HRT used)
- clinical features
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, and nipple discharge (straw-like, brown, or green)
- treatment
  - evaluation of breast mass (U/S, mammography as indicated) and reassurance
  - analgesia (ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

**PROLIFERATIVE LESIONS – WITHOUT ATYPIA**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Clinical Features</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Risk of Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroadenoma</td>
<td>Most common breast tumour in women &lt;30 yr</td>
<td>Nodules: firm, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone-dependent (unlike cysts); needle aspiration yields no fluid</td>
<td>Core or excisional biopsy; some times required if concerned about malignancy; U/S and FNA alone cannot differentiate fibroadenoma from Phyllodes tumour; Consider excision if size ≥3 cm and growing on serial U/S (≥6 mm x 2 yr is usual follow-up); if symptomatic, formed after age 35, or patient preference or features on core biopsy suggestive of a Phyllodes tumour</td>
<td>Increased if complex, adjacent atypia or strong family history of breast cancer</td>
</tr>
<tr>
<td>Intraductal Papilloma</td>
<td>Solitary intraductal benign polyp</td>
<td>Can present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge = pathologic nipple discharge); breast mass, nodule on U/S</td>
<td>Surgical excision of involved duct to ensure no atypia</td>
<td>Can harbour areas of atypia or DDS</td>
</tr>
<tr>
<td>Usual Ductal Hyperplasia</td>
<td>Increased number of cells within the ductal space</td>
<td>Incidental finding on biopsy of mammographic abnormalities or breast masses</td>
<td>None required</td>
<td>Generally low risk, slightly increased if moderate or florid hyperplasia</td>
</tr>
<tr>
<td>Sclerosing Adenosis</td>
<td>Lobular lesion with increased fibrous tissue and glandular cells</td>
<td>Mass or mammographic abnormality</td>
<td>None required</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**Figure 27. Anatomy of the breast**

**Levels of Axillary Lymph Nodes**

- **Level I:** lateral to pectoralis minor
- **Level II:** deep to pectoralis minor
- **Level III:** medial to pectoralis minor

(higher level of nodal involvement = worse prognosis)

**DDx for Breast Mass**

- **Benign**
  - Fibrocystic changes
  - Fibroepithelial lesions (fibroadenoma most common; benign phyllodes also)
  - Fat necrosis
  - Papilloma/papillomatosis
  - Galactocele
  - Duct ectasia
  - Ductal/lobular hyperplasia
  - Sclerosing adenosis
  - Lipoma
  - Neurofibroma
  - Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
  - Abscess
  - Silicone implant

- **Malignant**
  - Breast cancer (likely invasive, DCIS rarely forms a breast mass)
  - Malignant phyllodes
  - Angiosarcoma (rare)
**ATYPICAL HYPERPLASIA**

- can involve ducts (atypical ductal hyperplasia) or lobules (atypical lobular hyperplasia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

**OTHER LESIONS**

**Fat Necrosis**
- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness
- regresses spontaneously, but complete imaging ± biopsy to rule out carcinoma

**Mammary Duct Ectasia**
- obstruction of a subareolar duct (see Obstetrics, OB45)

**Abscess**
- lactational vs. non-lactational (periductal/subareolar) (see Obstetrics, OB45)

**Breast Cancer**

**Epidemiology**
- leading cancer diagnosis in women in North America, 2nd leading cause of cancer mortality in women
- 1 in 8 (12.9% lifetime risk) women in Canada will be diagnosed with breast cancer in their lifetime
- 1 in 30 women in Canada will die from breast cancer
- all age relative survival is 88%

**Risk Factors**
- gender (99% female)
- age (80% >40 yr old)
- personal history of breast cancer and/or prior breast biopsy (regardless of pathology)
- family history of breast cancer (greater risk if relative was first degree and premenopausal)
- high breast density, nulliparity, first pregnancy >30 yr, menarche <12 yr, or menopause >55 yr
- decreased risk with lactation, early menopause, and early childbirth
- radiation exposure (e.g. mantle radiation for Hodgkin's disease)
- >5 yr HRT use, >10 yr OCP use
- BRCA1 and BRCA2 gene mutations
- alcohol use, obesity, and sedentary lifestyle

**Male breast cancer (<1%)**
- most commonly invasive ductal carcinoma
- often diagnosed at later stages
- stage-for-stage similar prognosis to breast cancer in females
- consider genetic testing; most often hormone receptor positive

**Investigations**
- mammography
  - indications: screening guidelines (see Family Medicine, FM4)
  - findings indicative of higher risk of malignancy
    - mass that is poorly defined, spiculated border
    - microcalcifications
    - architectural distortion
    - interval mammographic changes
  - normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity. Use Annual MRI + Mammography for patients with 25% lifetime risk of breast cancer
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
- metastatic workup indicated in Stage II-IV disease: bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), CT head (if specific neurological symptoms)
Diagnostic Procedures
- ‘triple test’ for diagnosis of breast cancer: clinical breast exam, imaging (U/S for <30 yr, mammography + U/S for > 30 yr), pathology (biopsy)
- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

Genetic Screening
- consider testing for BRCA1/2 if:
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer
  - young patient (<35 yr)
  - bilateral breast cancer in patients <50 yr

Staging
- patients are assigned a clinical stage pre-operatively (cTNM); following surgery the pathologic stage is determined (pTNM)
- clinical
  - tumour size by palpation, mammogram, U/S and/or MRI
  - nodal involvement by palpation, imaging
  - metastasis by physical exam, CXR, and abdominal U/S (or CT chest/abdomen/pelvis), bone scan (usually done post-operative if node-positive disease)
- pathological
  - tumour size and type (see Pathology)
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear, and mitotic grade
  - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, and sentinel lymph node biopsy (SLNB) positive/negative
  - tumour biology: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu oncogene status
  - margins: for invasive breast cancer negative margin is sufficient, for DCIS prefer 2 mm margin
  - lymphovascular invasion (LVI)
  - extensive in situ component (EIC): DCIS in surrounding tissue
  - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour</th>
<th>Nodes (regional) (clinical)</th>
<th>Metastasis</th>
<th>Survival (5 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>in situ</td>
<td>None</td>
<td>None</td>
<td>99%</td>
</tr>
<tr>
<td>I</td>
<td>&lt;2 cm</td>
<td>None</td>
<td>None</td>
<td>94%</td>
</tr>
<tr>
<td>II A</td>
<td>&lt;2 cm</td>
<td>Mobile ipsilateral</td>
<td>None</td>
<td>85%</td>
</tr>
<tr>
<td>II B</td>
<td>2-5 cm</td>
<td>None or mobile ipsilateral</td>
<td>None</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>or &gt;5 cm</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>III A</td>
<td>Any size</td>
<td>Fixed ipsilateral or internal mammary</td>
<td>None</td>
<td>52%</td>
</tr>
<tr>
<td>III B</td>
<td>Skin/chest wall invasion</td>
<td>Any</td>
<td>None</td>
<td>48%</td>
</tr>
<tr>
<td>III C</td>
<td>Any size</td>
<td>Ipsilateral infraclavicular/internal mammary y plus axillary nodes; ipsilateral supraclavicular node(s) ± axillary nodes</td>
<td>None</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>Distant</td>
<td>18%</td>
</tr>
</tbody>
</table>

Pathology

NON-INVASIVE

Ductal Carcinoma in situ (DCIS)
- proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
- 80% non-palpable, detected by screening mammogram
- risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
- treatment
  - lumpectomy with wide excision margins + radiation (5-10% risk of invasive cancer)
  - mastectomy if large area of disease, high grade, or multifocal (risk of invasive cancer reduced to 1%)
  - possibly tamoxifen as an adjuvant treatment
  - 99% 5 yr survival
Lobular Carcinoma in situ (LCIS)
- neoplastic cells completely contained within breast lobule
- no palpable mass, and no mammographic findings; usually incidental finding on breast biopsy for another indication
- LCIS is a risk factor for invasive carcinoma (approximately 1%/yr)
- treatment
  - if diagnosed on core biopsy, excisional biopsy necessary to rule out malignancy
  - if diagnosed on excisional biopsy, wide excision not needed since LCIS if often multicentric and not managed as precursor lesion
  - clinical follow-up and surveillance
  - consider chemoprevention (e.g. tamoxifen)

INVASIVE
Invasive Ductal Carcinoma (most common 80%)
- originates from ductal epithelium and infiltrates supporting stroma
- characteristics: hard, scirrhous, infiltrating tentacles, and gritty on cross-section

Invasive Lobular Carcinoma (8-15%)
- originates from lobular epithelium
- 20% bilateral (i.e. more often than infiltrating ductal carcinoma)
- does not form microcalcifications, harder to detect mammographically (may benefit from MRI)

Paget’s Disease (1-3%)
- ductal carcinoma that invades nipple with scaling, and eczematoid lesion

Inflammatory Carcinoma (1-4%)
- ductal carcinoma that invades dermal lymphatics
- most aggressive form of breast cancer
- clinical features: erythema skin edema, warm, swollen, and tender breast ± lump
- peau d’orange indicates advanced disease (IIIb-IV)

Sarcomas: rare
- most commonly Phyllodes tumour, a variant of fibroadenoma with potential for malignancy
- can also be angiosarcomas – after previous radiation

Lymphoma: rare

Other
- papillary, medullary, mucinous, and tubular cancers
- generally better prognosis

Treatment

Table 24. Breast Cancer Treatment by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Treatment Options</th>
<th>Adjuvant Systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (in situ)</td>
<td>BCS + radiotherapy</td>
<td>Consider post-operative tamoxifen for ER+, trastuzumab for HER2+</td>
</tr>
<tr>
<td></td>
<td>BCS alone if margins &gt;1 cm and low nuclear grade</td>
<td>Mastectomy* ± SLNB</td>
</tr>
<tr>
<td>I</td>
<td>BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB</td>
<td>May not be needed; discuss risks/benefits of chemotherapy and tamoxifen</td>
</tr>
<tr>
<td>II</td>
<td>BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB</td>
<td>Chemotherapy for premenopausal women or postmenopausal and ER negative, followed by tamoxifen if ER+</td>
</tr>
<tr>
<td>III</td>
<td>Likely mastectomy + axillary node dissection + radiotherapy after chemotherapy (neo)adjuvant</td>
<td>Neoadjuvant therapy should be considered i.e. pre-operative especially if not resectable chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-operative)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Mastectomy + axillary node dissection + radiotherapy</td>
<td>Neoadjuvant therapy</td>
</tr>
<tr>
<td>IV</td>
<td>Surgery as appropriate for local control</td>
<td>Primary treatment is systemic therapy i.e. chemotherapy and/or hormone therapy</td>
</tr>
</tbody>
</table>

* BC = breast conserving surgery; SLNB = sentinel lymph node biopsy
* If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient’s preference since choice of local treatment does not significantly affect survival if local control is achieved.
PRIMARY SURGICAL TREATMENT

Breast Conservation Surgery (BCS)
- lumpectomy must be combined with radiation for survival equivalent to mastectomy
- contraindications include
  - high risk of local recurrence e.g. extensive malignant-type calcifications on mammogram, and multifocal primary tumours
  - failure to obtain tumour-free margins after re-excision
  - not suitable for radiation therapy (pregnancy, previous radiation, and collagen vascular disease)
  - large tumour size relative to breast

Mastectomy
- radical mastectomy (rarely): removes all breast tissue, skin, pectoralis muscle, and axillary nodes
- modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
- simple mastectomy: removes all breast tissue and skin
- see Plastic Surgery, PL37 for breast reconstruction

Sentinel Lymph Node Biopsy (SLNB)
- perform in women with clinically node-negative invasive breast cancer and those with extensive DCIS who are undergoing mastectomy
- patients with clinically suspicious nodes should get U/S + FNA prior to decision to proceed with SLNB
technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
- intra-operative frozen section evaluated can be considered
- proceed with ALND if >3 positive nodes, with 1-3 nodes whole breast radiation therapy may be alternative
- 5% false negative rate

Axillary Lymph Node Dissection (ALND)
- perform in all patients with pathologic confirmation of nodal involvement (including positive SLNB as above)
- risk of arm lymphedema (10-15%) especially if getting radiation therapy, decreased arm sensation, and shoulder pain

ADJUVANT/NEOADJUVANT

Radiation
- indications
  - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy
  - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement

Hormonal
- indications
  - ER positive plus node-positive or high-risk node-negative
  - SERM if premenopausal (e.g. tamoxifen) or aromatase inhibitors if postmenopausal (e.g. anastrozole); optimal duration 5-10 yr
  - ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), and androgens (e.g. fluoxymesterone) are other options
  - palliation for metastatic disease

Chemotherapy
- indications
  - ER negative plus node-positive or high-risk node-negative
  - ER positive and young age
  - stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
  - palliation for metastatic disease
  - for HER2 positive breast cancer, add trastuzumab ± pertuzumab to the chemotherapy regimen

FOLLOW-UP

Post-Treatment Follow-Up
- assessment and physical exam q3-6mo x 3 yr, q6-12mo x 2 yr, and annually thereafter
- following BCS mammography q6-12mo; can reduce to annual once stable, no other routine imaging
- women who receive tamoxifen should have regular gynecologic follow-up (increased risk of endometrial cancer)
Local/Regional Recurrence
- recurrence in treated breast or ipsilateral axilla
- 1% per yr up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis
- bone > lungs > pleura > liver > brain
treatment is palliative: hormone therapy, chemotherapy, radiation
- overall survival of metastatic breast cancer is 36-60 mo

Surgical Endocrinology

Thyroid and Parathyroid

- see Endocrinology, E20 and Otolaryngology, OT33

Thyroidectomy
- indications: thyroid cancer, symptomatic thyroid mass or goitre, and medically refractory Graves' or hyperthyroidism
- contraindications: uncontrolled severe hyperthyroidism (i.e. Graves') due to risk of intra-operative or post-operative thyroid storm
- pre-operative workup: thyroid U/S for thyroid nodules, FNA for large nodules, U/S of the neck for lesions suspicious for papillary or medullary thyroid cancer, CT neck useful to rule out extension, and vocal cord function
- complications: hypocalcemia secondary to hypoparathyroidism, recurrent/superior laryngeal nerve injury, neck hematoma, infection, and thyrotoxic storm

Parathyroidectomy
- indications: symptomatic primary hyperparathyroidism due to effects of PTH on bone or kidneys, asymptomatic primary hyperparathyroidism with specific laboratory criteria (elevated serum Ca++, marked hypercalciuria, Cr clearance <30% normal, bone density reduction with T score <2.5, <50 yr)
- contraindications: familial hypocalciuric hypercalcemia
- pre-operative workup: 99mTc sestamibi scanning, ± SPECT or CT, U/S
- complications: recurrent/superior laryngeal nerve injury, post-operative hypocalcemia, infection, and bleeding

Adrenal Gland

- see Endocrinology, E29
- functional anatomy
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), and reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine, normetanephrine)
- types of adrenal tumours: functional (e.g. Cushing's syndrome, Conn's syndrome) or non-functional

INCIDENTALOMA
- adrenal mass discovered by investigation of unrelated symptoms

Epidemiology
- benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, and kidney
- peak incidence of carcinoma: females age 50-60, risk decreases with increasing age and male gender

Investigations
MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
- functional studies
  - pheochromocytoma: 24 h urine epinephrine, norepinephrine, metanephrine, normetanephrine, VMA (vanillylmandelic acid)
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, aldosterone:renin level, saline suppression test if appropriate
  - adrenal androgens: 17-OH progesterone, and DHEAS
- FNA biopsy: if suspect metastasis to adrenal (must exclude pheochromocytoma first to prevent a hypertensive crisis)
- indicated if history of cancer or patient is smoker
- iodocholesterol scintigraphy: may distinguish benign vs. malignant disease
Treatment
• functional tumour: resect
• non-functional tumour
  ■ >4 cm: resect
  ■ <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement

## Pancreas

### INSULINOMA
- tumour that secretes insulin
- most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

#### Clinical Features
- Whipple's triad
  - palpitations, trembling, diaphoresis, confusion, seizure, and personality changes
- blood work: decreased serum glucose and increased serum insulin and C-peptide
- U/S, CT: insulinomas evenly distributed throughout head, body, tail of pancreas

#### Treatment
- only 10% are malignant
- enucleation of solitary insulinomas may be done endoscopically
  - tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

### GASTRINOMA
- tumour secreting gastrin; cause of Zollinger-Ellison syndrome

#### Clinical Features
- abdominal pain, PUD, severe esophagitis
- multiple ulcers in atypical locations refractory of antacid therapy

#### Investigations
- blood work: serum gastrin levels (usually >1,000 pg/mL), secretin stimulation test
- U/S, CT: 70-90% found in Passaro's triangle (head of pancreas medially, 2nd portion of duodenum inferiorly, and the confluence of the cystic and CBD superiorly)
- octreotide scintigraphy scan

#### Treatment
- 50% are malignant
- surgical resection of tumour dependent on location
- non-surgical treatment: chemotherapy, somatostatin analogues, interferon, and chemoembolization
- if inoperable, vagotomy can be performed for symptomatic control

### VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR
- tumour secreting VIP; commonly located in the distal pancreas and most are malignant when diagnosed

#### Clinical Features
- severe watery diarrhea causing dehydration, weakness, and electrolyte imbalance

#### Investigations
- blood work: serum VIP levels
- U/S, CT

#### Treatment
- somatostatin analogues
- surgical resection/palliative debulking
### Pediatric Surgery

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology and Risk Factors</th>
<th>Pathophysiology</th>
<th>Clinical Features and History</th>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocele (see Umbilical US)</strong></td>
<td>1%-2% of live births Present at birth, majority close spontaneously by 1 yr M:F = 6:1 Prematurity</td>
<td>Communicating hydrocele: processus vaginalis fails to close with small opening for fluid to move freely between peritoneal cavity through patent processus (if opening progresses to allow passage of intestine, it is a hernia) Noncommunicating hydrocele: fluid trapped in tunica vaginalis; in older children, may be secondary to testicular pathology (reactive hydrocele)</td>
<td>Painless scrotal mass Communicating hydroceles increase in size with standing or valsalva, may be absent in the morning and large in the evening Transillumination suggests hydrocele Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk</td>
<td>US if suspect pathology</td>
<td>Most resolve spontaneously by 1 yr Surgical repair if: Persistence &gt;2 yr Pain Fluctuating in size which suggests communication Cosmetic reasons Infection</td>
<td>&lt;2% recurrence</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertrophic Pyloric Stenosis</strong></td>
<td>0.03-1.0% of live births Can present at 1-20 wk, most commonly at 6-8 wk M:F = 4:1 Early erythromycin exposure (&lt;13 d old)</td>
<td>Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction</td>
<td>Hypovolemia caused by emesis of gastric contents causes hypochloremic, hypokalemic metabolic alkalosis Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria</td>
<td>Electrolytes (assess hypokalemia, dehydration) U/S shows pyloric length &gt;14 mm, muscle thickness &gt;4 mm Upper GI series necessary only when U/S unavailable or non-diagnostic will show “string sign”</td>
<td>Fluid resuscitate with normal saline, correct electrolytes and acid/base abnormalities with DL, 1/2NS + 20 mEq/L KCl at maintenance rate NGT decompression unnecessary Pyelotomyomy open (Ranestadt vs. transumbilical or laparoscopic approach) Alternative therapies such as 1P/N/acet an impractical due to long time course of effect</td>
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<td><strong>Congenital Diaphragmatic Hernia</strong></td>
<td>1 in 2,000 to 5,000 live births Present within hours of life although some cases of delayed presentation N=1 F &gt;10% are associated with other congenital anomalies Prenatal diagnosis common</td>
<td>Left-sided: small bowel, large bowel stomach, and solid viscera (spine, left lobe of liver) herniate into thorax Right-sided: liver, large bowel herniating into thorax Pulmonary hypoplasia Pulmonary HTN</td>
<td>Early respiratory distress Cyanosis Scaphoid abdomen Prenatal diagnosis</td>
<td>Decreased air entry ± bowel sounds in the chest Displaced heart sounds Prenatal US/MRI ABG CXR (bowel loops in hemithorax, shifted heart) Echocardiography Genetic consultation if warranted</td>
<td>Intubate</td>
<td>Better outcomes in later presentations Haring defect (40%) Associated GERD MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy Long-term surveillance for potential recurrence Failure to thrive Chronic lung disease if severe hypoplasia</td>
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<tr>
<td><strong>Meckel’s Diverticulum</strong></td>
<td>1% of population M:F = 3:1 Present most frequently during first 5 yr of life Symptomatic in 2% of cases</td>
<td>Failure of vitreous duct to regress 5-7 wk i utero; 50% can an heterotopic tissue (e.g. gastric mucosa, ectopic pancreas) other associated anomalies include omphalocelemenent fistula, umbilical sinus, umbilical cyst, fibrous band</td>
<td>BRRPR (heterotopic gastric mucosa in Meckel’s causing mucosal ulceration and bleeding in adjacent small bowel mucosa) Abdominal sepsis (Meckel’s diverticulitis + perforation) Small bowel volvulus around fibrous band</td>
<td>AXR Meckel scan: scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 65%, specificity 90%)</td>
<td>Stabilize, ressect by laparotomy or laparoscopy ± incidental appendectomy</td>
<td>Resection curative</td>
<td>Stabilize, ressect by laparotomy or laparoscopy ± incidental appendectomy</td>
</tr>
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<tr>
<td><strong>Intestinal Atresia</strong></td>
<td>Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or &quot;double-bubble&quot; sign on x-ray for duodenal atresia Decreased with increasing age</td>
<td>Failure of gut to normally rotate around SMA with associated abnormal intestinal attachments and anatomic positions Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high risk for volvulus)</td>
<td>Bilious emesis = THE cardinal sign, especially if abdomen non-distended If bilious enteritis in ill child with distended abdomen, consider surgical exploration to rule out volvulus Rectal bleed (late/onset signs)</td>
<td>AXR: obstruction of proximal SBO, double-bubble sign, intestinal wall thickened Immediate UGI: duodenal/dysmotional segment (Lipament of Treitz) right of midline and not fixed posteriorly over spinal column, &quot;corkscrew&quot; sign indicating volvulus US: &quot;whirlpool&quot; sign, abnormal SMA-SVV relationship indicates UGI to rule out rotational anomalies</td>
<td>IV antibiotics Fluid resuscitation ENERGENT LAPAROTOMY Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd's bands, division of parietal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide concomitant adhesions), ± appendectomy Positioning the bowel into non-rotation (SBO in right abdomen, LBO in left abdomen)</td>
<td>Mortality related to length of bowel loss: 10% necrosis – 100% survival rate, 75% necrosis – 90% survival rate Recurrence 2-6%</td>
<td></td>
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<tr>
<td><strong>Gastric d stension and vomiting (usually bilious)</strong></td>
<td>Duodenal – may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal, and vertebral anomalies), 24-28% have Down syndrome Jejunal/ileal – within 2 d of birth, may be associated with CF Colonc – within 3 d of birth</td>
<td>Complete physical examination. Special attention to abdominal examination. Peristalsis and anus include evaluation of respiratory distress and signs of volume depletion Congenital anomalies Jaundice</td>
<td>Contrast enema ± USI with small bowel lube through (SBFT) Group and screen INR and PTT if for surgery</td>
<td>NPO NGT decompression Flud resuscitate TPN Broad spectrum antibiotics Duodenal – duodenodudenoenterostomy or duodenojejunostomy Jejunal/ileal – primary anastomosis, if atresia associated with short bowel then may create and stoma or defer surgery for bowel lengthening procedures Colonc – primary anastomosis</td>
<td>Long-term survival Duodenal – 86% Jejunal/ileal – 64% Colonc – 100%</td>
<td></td>
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</tr>
<tr>
<td><strong>Umbilical Hernia</strong></td>
<td>Incidence 2-14% Increases with premenatal Decreases with increasing age</td>
<td>Incomplete closure of peritoneal and fascial layers within umbilicus by 4 yr Hernia is peritoneum-lined and skin-covered Size of fascial defect determines chances of spontaneous closure</td>
<td>Majority asymptomatic Majority (95%) spontaneously resolve by age 4 Incarceration prior to age 5 very rare Most symptoms occur in late adequence or adulthood</td>
<td>None if uncomplicated Repair if not spontaneously closed by age 5 Earlier repair of large &quot;proboscoid&quot; hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect</td>
<td>Repair if not spontaneously closed by age 5 Earlier repair of large &quot;proboscoid&quot; hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect</td>
<td>Almost never become incarcerated Low risk of recurrence</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrochisis</strong></td>
<td>1:2,000 live births Antenatal diagnosis common Increases with younger maternal age and associated with IUGR MF = 1:1</td>
<td>Defect of abdominal wall, with free extrusion of intestine into amniotic cavity No specific environmental factor identified Defect in embryogenesis unclear</td>
<td>Associated with genetic syndromes 10% with intestinal atresia Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel</td>
<td>Prenatal US Elevated MS-AFP</td>
<td>NGT decompression IV fluids IV antibiotics Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with abs May have bowel dysfunction requiring motility medications</td>
<td>&gt;80% survival rate</td>
<td></td>
</tr>
<tr>
<td><strong>Omphalocele</strong></td>
<td>1:5,000 live births Antenatal diagnosis common Lower gestational age Increased maternal age MF = 1:5:1</td>
<td>Defect of abdominal wall and umbilical ring, with extrusion of sac-covered viscera (amnion, Wharton's jelly, peritoneum) Balbim's theory – failure of body wall morphogenesis Commonly associated with rotational abnormalities of the intestine</td>
<td>Associated with genetic syndromes 30-70% (e.g. Pentalogy of Cantrell congential heart disease, BeckwithWiedemann syndrome, Trisomy 18) Associated pulmonary hypoplasia a</td>
<td>Prenatal US Elevated MS-AFP</td>
<td>NGT decompression IV fluids, IV antibiotics Small defect (&lt;2 cm): Primary closure Medium (2-4 cm) and large (&gt;4 cm) defects: silver sulfadiazine coupled with compression dressing (to allow epithelialization and gradual reduction) or Sit-On Sim Pouch, followed by future repair ± mesh</td>
<td>40-10% survival rate Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles</td>
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<td><strong>Hirschsprung’s Disease</strong></td>
<td>1:50,000 births M:F = 3:1 to 4:1, approaches 1:1 when male tocol corresponds, has have some genes of small bowel as well Familial Hirschsprung’s in &lt; 5% of cases</td>
<td>Defect in migration of neurocrest cells to interstitio resulting in aganglionic bowel that fails to relax and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively; always starts in the rectum and variable involvement proximally; RET mutation</td>
<td>Failure to pass meconium spontaneously within 48 h of life is the classic history (95% pass meconium within 24h, 5% within 48h) Symptoms of bowel obstruction: abdominal distension, constipation, bulitus emesis Enterocolitis/sepsis Failure to thrive</td>
<td>Rectal biopsy (gold standard) – look for aganglionosis and neural hypertrophy</td>
<td>AXR</td>
<td>Duhamel pull-through procedure: surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis</td>
<td>Most have normal/ near-normal anorectal function Complications: Fecal incontinence and constipation, post operative enterocolitis (medical emergency if progresses to sepsis)</td>
</tr>
<tr>
<td><strong>Cryptorchidism</strong></td>
<td>2-5% of term males – most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend Suspect in prematurity</td>
<td>Idiopathic Descent is mediated by desman which is created in response to testosteron. Descent usually begins at 28 wk</td>
<td>Palpable testicle within inguinal canal or testicle which can be milled down into scrotum (called retrac testis) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities</td>
<td>Scoliosis asymmetry Bi-annual testicular exam with palpation Distinction truly undescended testes from retractile testis (which is &quot;high&quot; testis due to hyperactive cremasteric muscles)</td>
<td>Depends on age of presentation Older child LH, FSH, MIS, hCG stimulation test for gonadotropin production Infant: US FSH, LH, karyotype, MIS, 17 hydroxy-progesterone If non-palpable: Exam under anesthesia, exploratory laparoscopy</td>
<td>hCG to stimulate testosterone production and descent Orchidopexy – especially if undescended by age 6 mo-2 yr</td>
<td>Orchidopexy Decreased risk of torsion and blunt trauma to testicle No effect on malignant potential of testis Descant can preserve spermatogenesis if performed by 1 yr of age</td>
</tr>
<tr>
<td><strong>Intussusception</strong></td>
<td>Most common cause of bowel obstruction between 6-36 mo 26:100,000 newborns M:F = 3:2 Pathologic lead points: e.g. Meckel’s diverticulum CF, lymphoma, BDI may increase risk</td>
<td>Idiopathic is most common Usually starts at ileocecal junction Telescoping of bowel itself causing an obstruction and vascular compromise</td>
<td>Acute onset of abdominal pain which is classic episodic &quot;colicky&quot; pain Vomiting = bilious Abdominal pain Current-jelly stool suggests mucosal necrosis and straining</td>
<td>Abdominal exam Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness Signs of bowel obstruction: distended abdomen Look for localized peritonitis which suggests transmural ischemia</td>
<td>AXR for signs of bowel obstruction or perforation US if suspect pathology</td>
<td>If perforation, then consider operative management Non-operative management involves reduct or via air contrast enema Operative reduction can be done open or laparoscopically Resection of involved colon if failure to reduce or bowel appears compromised</td>
<td>If recurrent = more likely non-idiopathic If successfully reduced by enema in older age allow 2wk resolution of edema then perform SBFT to rule out pathologic lead points</td>
</tr>
<tr>
<td><strong>Tracheoesophageal Fistula (TEF)</strong></td>
<td>1:3,000-1,500 newborns Associated anomalies in 50%: VACTERL association</td>
<td>Fistulae vary with type of fistulae May have history of maternal polyhydramnios May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds, respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth and nose that return after suctioning</td>
<td>X-ray: anatomic abnormalities, NGT curled in pouch</td>
<td>X-ray: anatomic abnormalities, NGT curled in pouch</td>
<td>Investigate for other congenital anomalies, early repair by surgical ligation to prevent lung damage and maintain nutrition and growth</td>
<td>Complications: pneumonia, sepsis, reactive airways disease Following repair: esophageal stenosis and stricture at repair site, GERD and poor swallowing (i.e. dysphagia, reguritation)</td>
<td></td>
</tr>
<tr>
<td><strong>Inguinal Hernias</strong></td>
<td>5% of all term newborns 2x risk and more likely bilateral if pre-term M:F = 4:1 Low birth weight increases risk 1/5 inguinal hernias will become incarcerated if patient is &lt; 1yr old Incarceration is more common in females Associated with other conditions: androgen insensitivity, connective tissue diseases</td>
<td>All infant hernias are indirect: descent of intra-abdominal contents through the internal inguinal ring through a patent tuberculum Morgue LInguinal hernia can be reducible, incarcerated (irreducible) or strangulated</td>
<td>Most common presentation: painless intermittent mass in groin may also note extension into scrotum (scrotum mass in absence of inguinal mass is a hydrocele) If incarcerated: tender, vomiting, firm mass, erythema then cyanosis of mass may be noted</td>
<td>Palpate for “bag of worms” suggests possible texticular varicocele Biannual testicular exam + palpation along inguinal canal to evaluate for any masses &quot;Silk sign&quot; – palpable thickening of cord Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen Must always try reduction to confirm that hernia is not incarcerated</td>
<td>Physical exam is gold standard US only if physical exam uncertain (e.g. in small infants where exam can be difficult)</td>
<td>Manual reduction – (in the DR) to relieve acute symptoms (then repair) For reducible hernia repair within a few weeks (if &lt; 1 yr vs. elective repair if &gt; 1 yr) For incarcerated hernia: repair immediately (emergency) Hemorrhage – definitive treatment by reduction of herniated contents and high ligation of ssc for indirect hernias Laparoscopic or open techniques</td>
<td>Risk of recurrence after surgical reduction &lt; 3% but higher if repair done in premature infants or if hernia was incarcerated/ strangulated at repair</td>
</tr>
</tbody>
</table>
Skin Lesions

• see Dermatology, D5; Emergency Medicine, ER43; Plastic Surgery, PL5

Common Medications

Antiemetics
• dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6h
• prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM bid-tid
• metoclopramide (Maxeran®) 10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs)
• ondansetron (Zofran®) 4-8 mg PO qid
• granisetron (Kytril®) 1 mg PO bid (for nausea from chemotherapy/radiation)

Analgesics
• acetaminophen ± codeine (Tylenol® #3/plain) 1-2 tabs q4-6h PO/PR pm
• hydromorphone i-i tabs PO q4-6h pm, 0.5-2 mg IV q4-6h pm
• ibuprofen 200-400 mg PO q4-6h pm
• morphine 2.5-10 mg IM/SC q4-6h pm + 1-2 mg IV q1h pm for breakthrough
• ketorolac (Toradol®) 30-60 mg IM/IV q6h pm
• Percocet® (acetaminophen/oxycodeone, 325/5 mg) 1-2 tabs PO q4-6h pm

DVT Prophylaxis
• heparin 5,000 units SC bid, if cancer patient then heparin 5,000 units SC tid
• dalteparin (Fragmin®) 5,000 units SC daily
• enoxaparin (Lovenox®) 40 mg SC daily

Antidiarrheals
• loperamide (Imodium®) 4 mg PO bid after each loose stool up to 16 mg/d
• diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PD qid

Laxatives
• sennosides (Senokot®) 1-2 tabs qhs
• docusate sodium (Colace®) 100 mg PO bid
• glycerine suppository 1 tab PR pm
• lactulose 15-30 mL PO qid
• milk of magnesia (MOM) 30-60 mL PO qid
• bisacodyl (Dulcolax®) 10-15 mg PO qd

Sedatives
• zopiclone (Imovane®) 5-7.5 mg PO qhs
• lorazepam (Ativan®) 0.5-2 mg PO/SI q3q4h

Antibiotics
• cefazolin (Ancef®) 1 g/IM on call to OR or q8h – GP except Enterococcus, GN only E. coli, Klebsiella, and Proteus
• cefalexin (Keflex®) 250-500 mg PO qid – Listeria, GP except Enterococcus and E. coli, Klebsiella, and Proteus
• ceftaxone 1-2 g IM/IV q24h – broad coverage including Pseudomonas
• ampicillin 1-2 g IV q4-6h – Listeria, GP (Enterococcus except Strep, stachylococcus and E. coli, oral anaerobes except Bacteroides
• gentamicin 3.5 mg/kg/d IM/IV divided q8h; monitor creatinine, gentamicin levels – GN including Pseudomonas
• ciprofloxacin 400 mg IV q12h, 500 mg PO bid – GN including Pseudomonas
• metronidazole (Flagyl®) 500 mg PO bid (500 mg PO tid for C. difficile) – anaerobes
• clindamycin 600-900 mg IV q8h, 150-400 mg PO qd – GP except Enterococcus, anaerobes
• piperacillin/tazobactam 4.5 mg q6h – GP, GN, and anaerobes
• vancomycin 1g IV q12h – GP and MRSA
• sulfamethoxazole/trimethoprim DS (Septra®) PO bid – GP, GN including Nocardia

Over-the-Counter Medications
• Pepto-Bismol® (bismuth subsalicylate) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d
• Alka-Seltzer® (ASA + citrate + bicarbonate) 2 tabs or 4 oz water PO q4h pm, max 8 tabs
• Maalox® (aluminum hydroxide + magnesium hydroxide) 10-20 mL or 1-4 tabs PO pm
• Tums® (calcium carbonate) 1-3 g PO q4h
• Rolaids® (calcium carbonate and magnesium hydroxide) 2-4 tabs PO q1h pm, max 12 tabs/d

References

References


Acronyms ................................................. 2

Physiology and Pathology of Aging ................. 2

Differential Diagnoses of
Common Presentations ................................. 2
Frailty (Functional Decline/Failure to Thrive)
Delirium, Dementia and Depression
Falls
Osteoporosis
Gait Disorders
Hypertension
Malnutrition
Constipation
Incontinence
Immobility
Pressure Ulcers
Hazes of Hospitalization
Elder Abuse
Immunizations
Presbyacusis

Driving Competency .............................. 11
Reporting Requirements
Conditions that may Impair Driving

Health Care Institutions .......................... 13

Palliative and End-of-Life Care ............... 13
Principles and Quality of Life
End-of-Life Care Discussions
Power of Attorney
Instructional Advance Directives
Symptom Management

Geriatric Pharmacology ........................... 15
Pharmacokinetics
Pharmacodynamics
Polypharmacy
Inappropriate Prescribing in the Elderly

Common Medications ............................ 16

Landmark Geriatric Trials ....................... 17

References .......................................... 17
Acronyms

Definition

- Major categories of impairment that appear with old age and affect the physical, mental, and social domains of the elderly, usually due to many predisposing and precipitating factors, rather than a single cause.

Table 1. Changes Occurring Frequently with Aging

<table>
<thead>
<tr>
<th>System</th>
<th>Physiological Changes</th>
<th>Pathological Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Decreased wakefulness, brain mass, cerebral flow, increased white matter changes</td>
<td>Increased insomnia, neurodegenerative disease, stroke, decreased reflex response</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Decreased lacrimal gland secretion, lens transparency, dark adaptation, decreased sense of smell and taste</td>
<td>Increased glaucoma, cataracts, macular degeneration, presbycusis, presbyopia, tinnitus, vertigo, oral dryness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased sBP, dBP, decreased HR, CO</td>
<td>Increased atherosclerosis, CAD, MI, CHF, hypertension, arrhythmias, orthostatic hypotension</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased tracheal cartilage calcification, mucous gland hypertrophy</td>
<td>Increased COPD, pneumonia, pulmonary embolism</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Increased intestinal villous atrophy</td>
<td>Increased cancer diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction, malnutrition, weight loss</td>
</tr>
<tr>
<td>Renal and Urologic</td>
<td>Increased proteinuria, urinary frequency</td>
<td>Increased urinary incontinence, nocturia, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Decreased androgen, estrogen, sperm count, vaginal secretion</td>
<td>Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Increased NE, PTH, insulin, vasopressin</td>
<td>Increased DM, hypothyroidism, stress response</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Increased calcium loss from bone</td>
<td>Increased arthritis, bursitis, osteoporosis, muscle weakness with gait abnormalities, polymyalgia rheumatica</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Atrophy of sebaceous and sweat glands</td>
<td>Increased lentigo, cherry hemangiomas, pruritus, seboreic keratosis, herpes zoster, decubitus ulcers, skin cancer, easy bruising</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Increased bilateral brain activity for memory tasks and loss of synaptic plasticity</td>
<td>Increased depression, dementia, delirium, suicidality, anxiety, sleep disruption</td>
</tr>
</tbody>
</table>

Differential Diagnoses of Common Presentations

Frailty (Function Decline/Failure to Thrive)

Definition

- Frailty: clinical state of older adults with increased vulnerability to acute stressors resulting from functional decline.
- Functional decline: progressive limitation in the ability to carry out basic functional activities.
- Failure to thrive: a state of decline that may be characterized by weight loss, decreased appetite, poor nutrition, and inactivity.

Four Syndromes in Failure to Thrive

- My Pa Can’t Drive
- Malnutrition
- Physical impairment
- Cognitive impairment
- Depression
**Etiology**
- multifactorial - malnutrition, functional impairment, cognitive impairment, and depression

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Cause of Failure to Thrive</th>
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<tbody>
<tr>
<td>Cancer</td>
<td>Metastases, malnutrition, cachexia</td>
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<tr>
<td>Chronic lung disease</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>Steroid myopathy, diabetes, osteoporosis, vision loss</td>
</tr>
<tr>
<td>Cirrhosis, hepatitis</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Depression, other psychiatric disorders</td>
<td>Major depression, psychosis, poor functional status, cognitive loss</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Malabsorption, poor glucose homeostasis, end-organ damage</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Hip, long bone fracture</td>
<td>Functional impairment</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Myocardial infarction, congestive heart failure</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Recurrent UTI, pneumonia</td>
<td>Chronic infection, functional impairment</td>
</tr>
<tr>
<td>Rheumatologic disease (GCA, RA, SLE)</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Stroke</td>
<td>Dysphagia, depression, cognitive loss, functional impairment</td>
</tr>
<tr>
<td>Tuberculosis, other systemic infections</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>

Adapted from: *Clin Geriatr Med* 1997;13:769-778

**Indicators**
- Depression
- Malnutrition
- Cognitive impairment
- Functional impairment (decreased mobility)

**Investigations**
- Limited laboratory tests and radiologic survey
- MMSE, ADL, and IADL scales
- “Up and Go Test”
- Geriatric Depression Scale
- Nutritional assessment
- Medication review
- Chronic disease evaluation
- Environmental assessment

**Failure to Thrive**

**Depression**
- Psychotherapy
- Antidepressants
- Modify environment

**Malnutrition**
- Speech therapy evaluation
- Treat oral pathology
- Increase frequency of feedings
- Nutritional supplements

**Cognitive Impairment**
- Optimize living conditions
- Treat depression
- Treat malnutrition
- Treat infection
- Administer dementia-delaying medications

**Functional Impairment**
- Physical therapy
- Occupational therapy
- Modify environment

**If response is positive, continue to treat**

**If no or minimal response, conduct conference with patient, patient’s family, and caregivers**

**Repeat evaluations, if appropriate**

**Consider discussion of end-of-life and hospice options**

*A positive response is defined as achievement of ≤t pretreatment goals, as determined by the patient, the patient’s family, and participating caregivers.*

**Figure 1. Failure to thrive in elderly patients**
Adapted from: *American Family Physician* 2004;70: 343-350
**Delirium, Dementia, and Depression**

- see Psychiatry, PS19, PS20, PS10 and Neurology, N20

**Definition**
all of the above may present with pathologic decrease in memory, language, or executive function

**Differential Diagnosis**
- delirium, dementia, or pseudodementia of depression (see Psychiatry)

**Delirium Prevention in Elderly**
- ensure optimal vision and hearing to support orientation (e.g. appropriate eye wear and hearing aids)
- provide adequate nutrition and hydration (up in chair to eat and drink whenever feasible)
- encourage regular mobilization to build and maintain strength, balance, and endurance
- avoid unnecessary medications and monitor for drug interactions
- avoid bladder catheterization if possible
- ensure adequate sleep

**Table 3. Differentiating the Three Ds of Cognitive Impairment**

<table>
<thead>
<tr>
<th></th>
<th>Dementia</th>
<th>Delirium</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Gradual or step-wise decline</td>
<td>Acute (hours to days)</td>
<td>Subacute</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Months to years</td>
<td>Days to weeks</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Natural History</strong></td>
<td>Progressive, usually irreversible</td>
<td>Fluctuating, reversible</td>
<td>Recurrent</td>
</tr>
<tr>
<td><strong>Level of Consciousness</strong></td>
<td>Normal</td>
<td>Fluctuating</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>Intact initially</td>
<td>Decreased, wandering</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Intact in tially</td>
<td>Impaired, fluctuates</td>
<td>Intact</td>
</tr>
<tr>
<td><strong>Behaviour</strong></td>
<td>Disinhibition, loss of ADL/ IADLs, personality change</td>
<td>Severe agitation/retardation</td>
<td>Importuning, self-harm/suicide</td>
</tr>
<tr>
<td><strong>Psychomotor</strong></td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
<td>Slowing</td>
</tr>
<tr>
<td><strong>Sleep-Wake Cycle</strong></td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep-wake cycle</td>
<td>Early morning awakening</td>
</tr>
<tr>
<td><strong>Mood and Affect</strong></td>
<td>Labile but not usually anxious</td>
<td>Anxious, irritable, fluctuating</td>
<td>Depressed, stable</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>Decreased executive function, paucity of thought</td>
<td>Fluctuation preceded by mood changes</td>
<td>Concentration impaired</td>
</tr>
<tr>
<td><strong>Memory Loss</strong></td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
<td>Recent</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>Agnosia, aphasia, decreased comprehension, repetition</td>
<td>Dysnomia, dysgraphia, speech rambling, subject changes, incoherence</td>
<td>Not affected</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
<td>Compensatory</td>
<td>Nightmarish, poorly formed</td>
<td>Nihilistic, somatic</td>
</tr>
<tr>
<td><strong>Hallucinations</strong></td>
<td>Variable, vacuous, bland</td>
<td>Visual common, frightening/bizarre</td>
<td>Self-deprecatory</td>
</tr>
</tbody>
</table>

**Falls**

**Definition**
an event which results in a person coming to rest inadvertently on the ground or floor or other lower level

**Epidemiology**
- 30–40% of people >65 yr old and ~50% of people >80 yr old fall each year
- equally common between men and women, but more likely to result in injury in women and death in men
- falls are the leading cause of death from injury in persons ≥65 yr
- 25% associated with serious injuries (e.g. hip fracture, head injury, bruises, laceration)
- between 25-75% do not recover to previous level of ADL function

**Etiology**
intrinsic factors
- age-related changes and diseases associated with aging: musculoskeletal (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), metabolic (glucose, electrolytes)
- orthostatic/syncopal
- side effects of medications and substance abuse  e.g alcohol
- acute illness, exacerbation of chronic illness

**Antipsychotics for Delirium**
**Cochrane DB Syst Rev 2009;CD005594**

**Objectives:** To compare the efficacy and incidence of adverse effects of haloperidol with risperidone, olanzapine, and placebo in the management of delirium and in the incidence of adverse drug reactions. Decreases in delirium scores were not significantly different when comparing the effect of low dose haloperidol (<3.0 mg/d) with olanzapine and risperidone (odds ratio 0.63; 95% CI 10.29-1.38; p=0.23). High dose haloperidol (>4.5 mg/d) was associated with an increased incidence of extrapyramidal adverse effects compared with olanzapine. Low dose haloperidol decreased the severity and duration of delirium in post-op native patients, although not the incidence of delirium compared to placebo.

**Selection Criteria:** Types of studies included, unconfounded, randomized trials with concealed allocation of subjects.

**Results:** Three studies were included, comparing haloperidol with risperidone, olanzapine, and placebo in the management of delirium. A meta-analysis of the studies showed that haloperidol decreased the severity and duration of delirium in post-operative patients, although not the incidence of delirium compared to placebo.

**Conclusions:** There is no evidence that haloperidol in low dosage has different efficacy in comparison with the atypical antipsychotics olanzapine and risperidone in the management of delirium or has a greater frequency of adverse drug effects than these drugs. High dose haloperidol was associated with a greater incidence of side effects. Low dose haloperidol may be effective in decreasing the degree and duration of delirium in post-operative patients, compared with placebo. However, all studies were small and should be repeated.

**Key Physical Findings in the Elderly Patient**
**Who Falls or Nearly Falls**

**I HATE FALLING**
Inflammation of joints
Hypotension (orthostatic changes)
Auditory and visual abnormalities
Tremor
Equilibrium (balance) problem
Foot Problems
Arrhythmia, heart block or valvular disease
Leg-length discrepancy
Lack of conditioning (generalized weakness)
Illness
Nutrition
Gait disturbance
Am Fam Phys 2001;61:2159-2172
extrinsic factors
- environmental (e.g. home layout, slippery surfaces, overcrowding, new environments)
- situational factors
  - activities (e.g. rushing to the toilet, walking while distracted)

**History and Physical Exam**
- history: previous falls and/or gait inability, inquire about intrinsic, extrinsic and situational factors, associated symptoms, loss of consciousness, medication and alcohol use
- have a witness present if possible for interview
- physical exam: Orthostatic blood pressure, visual acuity, examination of feet and footwear, Performance-Oriented Assessment of Mobility, Timed Up-And-Go Test

**Investigations**
- comprehensive geriatric assessment to identify all potential causes
- CBC, electrolytes, BUN, creatinine, glucose, Ca++, TSH, B12, urinalysis, cardiac enzymes, ECG, CT head (as directed by history and physical)

**Prevention**
- multidisciplinary, multifactorial, health, and environmental risk factor assessment and intervention programs in the community
- muscle strengthening, balance retraining, and group exercise programs (e.g. Tai Chi)
- home hazard assessment and modification (e.g. remove loose rugs and tripping hazards, add shower bars and stair railing, improve lighting)
- prescription of vitamin D 1000 IU daily
- tapering or gradually discontinuation of psychotropic medication
- postural hypotension, heart rate, and rhythm abnormalities management
- eyesight and footwear optimization
- support hose for varicose veins and ankle swelling
- connect patient to lifeline button signaling system

**Figure 2. Approach to falls in the elderly**

Adapted from: Davidson S, Dhammar jan TS. Clinical Geriatrics 2013;21(10)
Osteoporosis
- see Endocrinology, E40

Gait Disorders
- see Neurology, N10

Hypertension
- see Family Medicine, FM34

Definition
- blood pressure at which an otherwise healthy person would have increased risk of cardiovascular disease
- definition of high blood pressure has changed over time and differs between guidelines proposed by expert bodies

Epidemiology
- 60-80% of elderly (>65 yr) have HTN
- 60% of these have isolated systolic HTN
- the benefit of treating HTN in the elderly is 2-4 times greater than that achieved in the treatment of younger patients with primary HTN
- sBP and pulse pressure are major predictors of outcome in the elderly patient
- in older adults, base treatment on sBP

Management
- targets
  - <140/90 mmHg for adults ≤80 yr
  - <130/80 mmHg for individuals with DM or CKD
  - <150 sBP for adults aged 80 or older
- for patients ≥60 yr, initiate pharmacological therapy when BP ≥150/90mmHg
- if there is comorbid DM, initiate pharmacological therapy when BP ≥140/90mmHg
- 1. non-pharmacologic treatments; 2. thiazide or thiazide-like diuretic monotherapy are first line pharmacological treatments in patients without comorbidities; 3. second line treatments depend on comorbidities
- add ACEI/ARB if also atherosclerosis, DM, CHF or CKD
- add β-blockers if also angina or CHF

Malnutrition

Definition
- involuntary weight loss (community: ≥2% over 1 mo, >10 lbs over 6 mo or ≥4% over 1 yr; nursing home: ≥5% over 1 mo, ≥10% over 180 d)
- hypoalbuminemia, hypocholesterolemia
- other features include: insufficient energy intake, loss of muscle mass, fluid accumulation (e.g. edema), loss of subcutaneous fat, decreased hand-grip function

Etiology
- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals or feeding oneself due to functional impairment)
  - stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
  - mechanical: dental problems, dysphagia
  - age-related changes: appetite dysregulation, decreased thirst
  - mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

Clinical Features
- history
  - recent or chronic illness
  - depression, GI symptoms
  - functional disability: impaired ADLs and IADLs
  - social factors: economic barriers, dental problems and living situation (e.g. living alone)
  - constitutional symptoms (e.g. recent weight loss)
• physical exam
  - BMI <23.5 in males, <22 in females should raise concern
  - temporal wasting, muscle wasting, presence of triceps skin fold
  - assess cognition

Investigations
- CBC, electrolytes, Ca\(^{2+}\), Mg\(^{2+}\), PO\(_4^{3-}\), creatinine, LFTs (albumin, INR, bilirubin), B12, folate, TSH, transferrin, lipid profile, urinalysis, ESR, CXR

Treatment
- direct treatment at underlying causes
- dietary modification: high calorie foods, oral nutritional supplementation; patient specific meal replacement products (e.g. Ensure\(^{TM}\), Glucerna\(^{TM}\), Nepro\(^{TM}\)), food/drink thickeners (e.g. Thicken-Up\(^{TM}\)), vitamins/minerals (e.g. B12, calcium, vitamin D)
- referral: speech language pathologist, nutritionist

Constipation
- see Gastroenterology, G24

Definition
- <3 bowel movements in one wk and/or hard stools, straining, sense of blockade, needing manual maneuvers or incomplete evacuation on more than 25% of occasions for at least 12 wk (does not need to be consecutive). Symptoms must have occurred in the last 3 mo, with symptom onset ≥6 mo before diagnosis can be made

Epidemiology
- chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation and 1/2 of patients >80 yr)
- in the elderly, chronic constipation may present as fecal impaction

Pathophysiology
- impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
- colorectal dysmotility

Figure 3. Treatment algorithm for the management of chronic constipation in the elderly
Adapted from: Clin Interv Aging 20 0;5: 63-171

Calculating Basic Caloric and Fluid Requirements
WHO daily energy estimates for adults
- Male: 13.5 x (weight in kg) + 487
- Female: 10.5 x (weight in kg) + 596

Maintenance fluid requirements for the elderly without cardiac or renal disease: 1500-2500 cc/24 h

Common Causes of Constipation in the Geriatric Population include:
- GI (colon cancer, diverticulosis)
- Neurologic (stroke dementia, Parkinson’s)
- Psychiatric (depression, anxiety)
- Drugs (see below)
- Diet (dehydration, “tea and toast” diet)

Drugs Associated with Constipation include:
- OTC (antihistamines, NSAIDs)
- Opioids
- Psychotropic (antipsychotics, TCAs)
- Anticholinergics
- Calcium channel blockers
- Diuretics
- Supplements (iron or calcium)

Treatment of Constipation in Older Adults CMAJ 2013;185(8):663-70
Objectives: To discuss management of constipation in older adults.
Results/Conclusions: In older adults, the predominant symptom of constipation is more frequently straining than decreased stool frequency. MCTs support the use of osmotic agents to treat symptoms of constipation in older adults. In contrast evidence supporting the use of bulk agents, stool softeners stimulants and prokinetic agents is lacking, limited and inconsistent.

Figure 3. Treatment algorithm for the management of chronic constipation in the elderly
Adapted from: Clin Interv Aging 20 0;5: 63-171
Treatment
- non-pharmacological
  - increase fibre intake
  - ensure adequate fluid intake
- pharmacological
  - discourage chronic laxative use
  - review medication regime, reduce dosages or substitute

see Common Medications, GM11

Incontinence

Fecal Incontinence

Definition
- involuntary passage or the inability to control the discharge of fecal matter through the rectum
- severity can range from unintentional flatus to the complete evacuation of bowel contents
- there are three subtypes:
  1. passive incontinence: involuntary discharge of stool or gas without awareness
  2. urge incontinence: discharge of fecal matter in spite of active attempts to retain bowel contents
  3. fecal: leakage of stool following otherwise normal evacuation

Epidemiology
- age is independently associated with fecal incontinence
- the incidence of fecal incontinence differs by setting: community (17-36%), hospital (16%) and nursing home (33-65%)

Etiology
- physiological changes with age >80 yr (e.g. decreased external sphincter strength, decreased resting tone of internal sphincter, weakened anal squeeze, increased rectal compliance, and impaired anal sensation)
- trauma (e.g. vaginal delivery, pudendal nerve damage, cauda equina)
- iatrogenic
  - surgical (e.g. anal resection, hemorrhoidectomy, colorectal resection)
  - radiation (e.g. pelvic radiation)
- neurogenic (e.g. neuropathy, stroke, MS, diabetic neuropathy)
- anorectal/colorectal diseases (e.g. rectal prolapse, hemorrhoids, IBD, rectocele, cancer)
- medication (e.g. laxative, anticholinergics, antidepressants, caffeine, muscle relaxants)
- cognitive (e.g. dementia, willful soiling with psychosis)
- constipation/fecal impaction

Investigations (if cause not apparent from history and physical)
- differentiate true incontinence from frequency and urgency (e.g. IBS, IBD)
- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

Management
- physiological changes with age: medication management (anti-motility agents (e.g. loperamide), diet/bulking agents for loose stool) increase fluid intake, biofeedback, retraining of pelvic floor muscles, surgery
- trauma: direct surgical repair or augmentation of the sphincters
- iatrogenic: surgical repair, artificial sphincters
- neurogenic: medication management, abdominal massage, digital stimulation for dysfunction, biofeedback and behavioural training, prevent autonomic dysreflexia in spinal injury
- anorectal/colorectal diseases: treat underlying cause (optimize IBD medications), surgical (e.g. mass removal, prolapse repair, hemorrhoid removal, colostomy)
- medication-related causes: stop laxatives, lower dose or discontinue any other offending agents
- cognitive: regular defecation program in patients with dementia, psychiatric consult (optimize medications and cognitive function)
- constipation/fecal impaction: disimpaction, prevent impaction, enema or rectal irrigation

Urinary Incontinence
- see Urology, U5

Definition
- complaint of any involuntary loss of urine
- can be further classified according to patients symptoms as urgency urinary incontinence, stress urinary incontinence, mixed urinary incontinence, nocturnal enuresis, post-micturition dribble, and continuous urinary leakage
**Epidemiology**
- 15-30% prevalence dwelling in community and at least 50% of institutionalized seniors
- morbidly: cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality

**Pathophysiology**
- not a normal part of aging, urinary incontinence is a loss of control due to a combination of:
  - genitourinary pathology: increased post void residual volume, increased involuntary bladder contractions (urge incontinence)
  - age-related changes: decreased bladder capacity
  - comorbid conditions and medications
  - functional impairment
  - in elderly women: decline n bladder outlet and urethral resistance pressure promoting stress incontinence
  - in elderly men: prostatic enlargement can cause overflow and urge incontinence

**Immobility**
- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- musculoskeletal: atrophy, contractures, bone loss
- skin: pressure ulcers
- psychological: sensory deprivation, delirium, depression

**Pressure Ulcers**
- see Plastic Surgery, PL17

**Risk Factors**
- extrinsic factors: friction, pressure, shear force
- intrinsic factors: immobility, malnutrition, moisture, sensory loss
- geriatric specific factors: age related skin changes, bed-bound, cognitive impairment, chronic illness, use of antihypertensive medications

**Table 4. Classification of Pressure Ulcers**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Changes include skin temperature, tissue consistency or sensation. An area of persistent erythema in lightly pigmented, intact skin; in darker skin, it may appear red, blue or purple.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Partial thickness skin loss involving the epidermis, dermis or both. The ulcer is superficial and presents as an abrasion, blister or shallow crater.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Full thickness skin loss involving damage or necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia. Presents as a deep crater with or without undermining of adjacent tissue.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures. May have associated undermining and/or sinus tracts.</td>
</tr>
</tbody>
</table>

**Prevention**
- pressure reduction
- frequent repositioning
- pressure-reducing devices (static, dynamic)
- maintaining nutrition, encouraging mobility and managing incontinence

**Treatment**
- optimize nutritional status
- minimize pressure on wound
- analgesia
- all ulcers with necrosis warrant debridement (mechanical, enzymatic and autolytic are non-urgent forms of debridement whereas, sharp debridement is performed urgently due to risk for sepsis or cellulitis)
- dressing application (exudate absorbing, barrier products to reduce friction)
- diabetic foot ulcers: offloading with removable cast walker (e.g. aircast boot), orthopedic shoes and orthotics
- maintain moist wound environment to enable re-epithelialization
• treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
• swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
• referral to Wound Care
• consider other treatment options
  ▪ negative pressure wound therapy/vacuum-assisted closure
  ▪ biological agents: application of fibroblast growth factor, platelet-derived growth factor to wound
  ▪ non-contact normothermic wound therapy
  ▪ electrotherapy

### Hazards of Hospitalization

| Table 5. Recommendations for Sequelae of Hospitalization in Older Patients |
|-----------------------------|----------------------------------------------------------------------------------------------------------|
| **Sequelae**                | **Recommendations**                                                                                     |
| Malnutrition                | No dietary restrictions (except diabetes), assistance, dentures if necessary, sitting in a chair to eat   |
| Urinary Incontinence        | Medication review, remove environmental barriers, discontinue use of catheter                           |
| Depression                  | Routine screening                                                                                        |
| Adverse Drug Event          | Medication review                                                                                        |
| Confusion/Delirium          | Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints |
| Pressure Ulcers             | Low-resistance mattress, daily inspection, repositioning every 2 h                                       |
| Infection                   | Early mobilization, remove unnecessary IV lines, catheters, NG tubes                                     |
| Falls                       | Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review          |
| Hypotension/Dehydration      | Early recognition and repletion (ideally oral rehydration, if possible)                                   |
| Diminished Aerobic Capacity/Loss of Muscle Strength/Contractures | Early mobilization                                                                                     |
| Decreased respiratory function | Incentive spirometry, physiotherapy                                                                     |
| Functional decline          | Structured exercise, progressive resistance training, walking programs                                   |


### Elder Abuse

**Definition**
• includes physical abuse, sexual abuse, emotional/psychological abuse, financial abuse, abandonment, institutional abuse and neglect
• elder abuse is a criminal offence under the Criminal Code of Canada
• in the U.S., most states have criminal penalties for elder abuse

**Epidemiology**
• in Canada in 2013, almost 3000 seniors were victims of family violence. The perpetrators of family violence against seniors were identified to be their grown child (43% of cases) and their spouses (28% of the cases)
• in the U.S., estimates of the frequency of elder abuse range from 3-8%
• insufficient evidence to include/exclude screening in the Periodic Health Exam

**Risk Factors**

<table>
<thead>
<tr>
<th>Table 6. Risk Factors for Elder Abuse</th>
</tr>
</thead>
</table>
| **Situational Factors**                | Isolation
|                                       | Unstable or unsafe living arrangements
|                                       | Lack of family, community or living facility resources for additional care
| **Victim Characteristics**             | Physical or emotional dependence on caregiver
|                                       | Lack of close family ties
|                                       | History of family violence
|                                       | Dementia or recent deterioration in health
| **Perpetrator Characteristics**        | Related to victim
|                                       | Living with victim
|                                       | Long duration of care for victim (mean 9.5 yr)
|                                       | Financial, marital, occupational or other stressors
|                                       | Has mental disorder or alcohol/substance abuse

**Red Flags for Elder Abuse**
• Delay in seeking medical attention
• Disparity in histories
• Implausible or vague explanations
• Frequent emergency room visits for exacerbations of chronic disease despite plan for medical care and adequate resources
• Presentation of functionally impaired patient without designated caregiver
• Lab findings inconsistent with history
• Physical signs: bruising, broken bones, injuries
• Suspicious changes in accounts: POA, wills
• Deserted in public place
Caregiver Abuse Screen (CASE)

- **instructions**
  - to be answered by caregivers, if answer "yes" to a question, further explore issue
  - the more "yes" responses, the more likely the presence of abuse

- **screening tool**
  - please answer the following questions as a helper/caregiver:
    1. Do you sometimes have trouble making _____ control his/her temper or aggression?
    2. Do you often feel you are being forced to act out of character/do things you feel badly about?
    3. Do you find it difficult to manage _____’s behaviour?
    4. Do you sometimes feel that you are forced to be rough with _____?
    5. Do you sometimes feel that you can’t do what is really necessary or what should be done for _____?
    6. Do you often feel you have to reject/ignore ______?
    7. Do you often feel so tired and exhausted that you cannot meet _____’s needs?
    8. Do you often feel you have to yell at ____?

From: NICE. Case: Caregiver Abuse Screen. 2010. Reproduced with permission from NICE.

**Management**

- interview patient alone
- assess safety and determine capacity to make decisions about living arrangements
- establish need for hospitalization or alternate accommodation (e.g. immediate risk of physical harm by self or caregiver)
- involve multidisciplinary team (e.g. nurse, social worker, family members, and physicians including geriatrician, psychiatrist or family physician)
- educate and assist caregiver, contact local resources (e.g. legal aid, crisis support, PSW, caregiver support groups)
- interpret critical and lab findings that are key in exclusion, differentiation and diagnosis

**Immunizations**

- the following immunizations are recommended for people ≥65 yr
  - tetanus and diptheria: Td every 10 yr
  - pneumococcus
    - if no previous vaccinations, PCV13 followed by PPSV23 in the following yr
    - if previously received PCV13, a second dose is not required
  - influenza every autumn
  - herpes zoster: one time dose

**Presbycusis**

- see Otolaryngology, OT19

**Driving Competency**

**Reporting Requirements**

- physician-reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia, and Alberta, where it is discretionary
- British Columbia, Ontario: must refer for re-test at ≥ 80 yr
- not an issue unique to geriatrics – any patient may suffer from a medical condition that impairs their ability to drive should be reported
- in the U.S., varies by state
### Conditions that may Impair Driving

<table>
<thead>
<tr>
<th>Condition</th>
<th>Impairment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohol</strong></td>
<td>Patients with history of impaired driving and those with high probability of future impaired driving should not drive until further assessed. Alcohol dependence or abuse: if suspected, should be advised not to drive. Alcohol withdrawal seizure: must complete a rehabilitation program and remain abstinent and seizure-free for 6 mo before driving.</td>
</tr>
<tr>
<td><strong>Blood Pressure Abnormalities</strong></td>
<td>Hypertension: sustained BP &gt;170/110 should be evaluated carefully. Hypotension: sustained BP &lt;90/60; if syncopal, discontinue until attacks are treated and preventable.</td>
</tr>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td>Suspected asymptomatic CAD or stable angina: no restrictions. STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for one mo following hospital discharge. NSTEMI with minor LV damage, unstable angina: no driving for 48 h if PCI or 7 d if no PCI performed.</td>
</tr>
<tr>
<td><strong>Cerebrovascular Conditions</strong></td>
<td>TIA: should not be allowed to drive until a medical assessment is completed. Stroke: should not drive for at least one mo; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure.</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>Mild/moderate impairment: no restrictions. Moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen.</td>
</tr>
<tr>
<td><strong>Cognitive Impairment/Dementia</strong></td>
<td>Moderate to severe dementia is a contraindication to driving; defined as the “inability to independently perform 2 or more IADLs or any basic ADL”. Patients with mild dementia should be assessed; if indicated refer to specialized driving testing centre; if deemed fit to drive, re-evaluate patient every 6-12 mo. Poor performance on MMSE, clock drawing or Trails B suggests a need to investigate driving ability further. MMSE score alone (whether normal or low) is insufficient to determine fitness to drive.</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>Diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular or cerebrovascular disease). Insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 mo.</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants. Degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving.</td>
</tr>
<tr>
<td><strong>Hearing Loss</strong></td>
<td>Effect of impaired hearing on ability to drive safely is controversial. Acute labyrinthitis, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves.</td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td>Physician’s role is to report etiology, prognosis and extent of disability (pain, range of motion, coordination, muscle strength).</td>
</tr>
<tr>
<td><strong>Post-Operative</strong></td>
<td>Outpatient, conscious sedation: no driving for 24 h. Outpatient, general anesthesia: no driving for ≥24 h.</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head. Epilepsy: can drive if seizure-free on medication and physician has insight into patient compliance.</td>
</tr>
<tr>
<td><strong>Sleep Disorders</strong></td>
<td>If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive.</td>
</tr>
<tr>
<td><strong>Visual Impairment</strong></td>
<td>Visual acuity: contraindicated to drive if &lt;20/50 with both eyes examined simultaneously. Visual field: contraindicated to drive if &lt;120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously.</td>
</tr>
</tbody>
</table>

N.B. guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving.
Health Care Institutions

Table 8. Classification of Health Care Services and Institutions

<table>
<thead>
<tr>
<th>Institution/Service</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Support Services</td>
<td>Health care services offered at home for those who can live independently at home or under the care of family members including professional health care services, personal care and support (ADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks, etc.)</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>Health care services offered in an institution to optimize patients’ function, independence and quality of life</td>
</tr>
<tr>
<td>Residential</td>
<td>Divided into short (&lt;60-90 d/yr) and long (indefinite) stay</td>
</tr>
<tr>
<td>a) Seniors Affordable Housing</td>
<td>Seniors who live independently and manage their own care but prefer to live near other seniors; usually has accessibility features and rent is adjusted based on income</td>
</tr>
<tr>
<td>b) Retirement Home</td>
<td>Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned</td>
</tr>
<tr>
<td>c) Supportive Housing</td>
<td>Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment and may offer some phys therapy and rehabilitation services</td>
</tr>
<tr>
<td>d) Long-term Care/Skilled Nursing Facility</td>
<td>Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy, and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital</td>
</tr>
<tr>
<td>e) Hospice</td>
<td>Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤ 3 mo</td>
</tr>
</tbody>
</table>

- names of community health care institutions, types of facilities, and services offered vary between geographical locations
- factors to consider when seeking services/institutions include level of care required, support networks, duration of stay, and cost

Palliative and End-of-Life Care

Principles and Quality of Life

- support, educate, and treat both patient and family
- address physical, psychological, social and spiritual needs
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

End-of-Life Care Discussions

When to initiate End-of-Life Care Discussions
- recent hospitalization for serious illness
- severe progressive medical condition(s)
- death expected within 6-12 mo
- patient inquires about end-of-life care

Suggested Topics for Discussion
- goals of care (disease vs. symptom management)
- advance directives, power of attorney, public guardian and trustee
- location (e.g. hospice, home, palliative care facility etc.)
- patient wishes (medical assistance/feasibility to fulfill)
- physician assisted death (patient initiated discussion)
- treatment options and likelihood of success
- common medical interventions
  - mechanical ventilation
  - antibiotic therapy
  - feeding tubes
- resuscitation options and likelihood of success (Full Code vs. DNR status including preferences for CPR intubation, ICU admission, artificial hydration)

Guidance on the Management of Pain in Older People

*Age and Aging* 2013; 42:1-57
The three most common sites of pain in older adults are the back, leg/knee and hip. Acetaminophen should be considered first line treatment for the management of both acute and persistent pain, particularly that which is of musculoskeletal origin. NSAIDs should be prescribed with caution and co-prescribed with a PPI.
Power of Attorney

- see Ethical, Legal, and Organizational Medicine, ELOM10

Instructional Advance Directives

- see Ethical, Legal, and Organizational Medicine, ELOM10

Symptom Management

Assessment Tools

- Edmonton Symptom Assessment System (ESAS): a tool that asks patients to rate the intensity of symptoms from 0 to 10 and allows for tracking of the efficacy of interventions. Assesses: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and “other problems”
- Palliative Performance Scale (PPS): a tool that uses functional status to predict survival in terminally ill patients. Assesses 5 components: ambulation, activity and evidence of disease, self-care, intake and conscious level

Source: J Palliat Care 1991;7:6-9 and Victoria Hospice Society 2006;120-121

Table 9. Management of Common End-of-Life Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Non-Pharmacologic Management</th>
<th>Pharmacologic Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Rule out obstruction, impaction, anorectal disease; hydration and high fibre intake; increase mobility</td>
<td>Stop unnecessary opioids and medications with anticholinergic side effects; increase peristalsis (e.g. sempra), alter water and electrolyte secretion (e.g. magnesium hydroxide, lactulose, peg3350)</td>
</tr>
<tr>
<td>Terminal Pulmonary Secretions (“Death Rattle”)</td>
<td>Oral suctioning Discontinue unnecessary IV solutions Oral hygiene Re-positioning (on side, elevated)</td>
<td>Scopolamine SC or transdermal Hydrocortisone, Glycopyronium, Atropine</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Oral hygiene q2h, ice cubes, sugarless gum</td>
<td>Artificial saliva substitutes, Biotene TM products, Baking Soda mouth rinse, bethanechol, plopcarbine 1% solution as no thrice</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Frequent small feeds, ideally seated, keep head of bed elevated for 30 min after eating, suction as necessary</td>
<td>Treat painful mucositis (diphenhydramine; lidocaine: Maalox® in a 1:2:8 mixture), candidiasis (fluconazole)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Elevate head of bed, eliminate allergens, open window/ use fan</td>
<td>Oxygen, bronchodilators, opioids (e.g. morphine, hydromorphone)</td>
</tr>
<tr>
<td>Hiccups</td>
<td>Dry sugar, breathing in paper bag</td>
<td>Chlorpromazine, haloperidol, metoclopramide, baclofen, marijuana</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Frequent and small meals, avoid offensive strong colours, treat constipation if present</td>
<td>Raised ICP: dexamethasone Anticipatory nausea, anxiety: lorazepam Vestibular disease, vertigo: dimenhydrate Drug induced, hepatic or renal failure: prochlorperazine, haloperidol GERD: PPI or H2 antagonist Gastric stasis: metoclopramide Bowel obstruction: metoclopramide, dexamethasone, octreotide</td>
</tr>
<tr>
<td>Pain</td>
<td>Hot and cold compresses, music therapy, relaxation techniques, individualized program of physical activity designed to improve flexibility, strength and endurance and CBT</td>
<td>Nonopiceptive pain: NSAIDs, acetaminophen, weak opioids (codeine, hydrocodone, oxycodone), strong opioids (morphine, hydromorphone, oxycodone, fentanyl) Neuropathic pain: antidepressants (TCAs, SSRIs), steroids (dexamethasone) Bony pain: non-opioids, weak opioids, bisphosphonates, radiation therapy</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Bathing with tepid water, avoid soap, bath oils; sodium bicarbonate for jaundice</td>
<td>Antihistamines, phenothiazines, topical corticosteroids, calamine lotion</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Modify environment and activities to decrease energy expenditure</td>
<td>Treat insomnia, anemia, depression; consider psychostimulants (e.g. Dexmethylasone, Dextroamphetamine, Methylenphedate)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Spiritual counselling CBT Support groups Art/Music Therapy</td>
<td>Anxiety: benzodiazepines Agitation: antipsychotics Confusion/Delirium: treat underlying etiology Depression: Standard SSRIs, SNRIs may be too slow depending on patient prognosis, consider psychostimulants (e.g. methylphenidate, ketamine)</td>
</tr>
</tbody>
</table>


WHO’s Pain Relief Ladder

Freedom from Cancer Pain

<table>
<thead>
<tr>
<th>Non-opioid ± Adjuvant</th>
<th>Pain persisting or increasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from Cancer Pain</td>
<td>Pain persisting or increasing</td>
</tr>
</tbody>
</table>

Terminal Respiratory Secretions (“Death Rattle”)

Noise caused by the oscillatory movement of mucous secretions in the upper airway with inspiration and expiration

Opioid Equivalent Doses (to 10 mg of IV morphine)

<table>
<thead>
<tr>
<th>Opioid SC/IV dose (mg)</th>
<th>Opioid SC/IV dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine 10 mg</td>
<td>20-30 mg</td>
</tr>
<tr>
<td>Codeine Not recommended</td>
<td>180-240 mg</td>
</tr>
<tr>
<td>Oxycodone Not recommended</td>
<td>10-15 mg</td>
</tr>
<tr>
<td>Hydromorphone 2 mg</td>
<td>4-6 mg</td>
</tr>
</tbody>
</table>

Fentanyl transdermal 25 µg/h = morphine 90 mg q4h or OD, however fentanyl takes 12-16 h to reach steady state N.B. Dosing may need to be adjusted in the elderly adult population

Necrotic Pain

Somatic: localized to bone/skin/joint/muscle; graving, dull pain Visceral: not well localized; crampy pain, pressure

Neuropathic Pain

Burning, shooting, radiating pain; localized to dermatomal regions

Serum creatinine does not reflect creatinine clearance in the elderly

Instead, use: CrCI = (weight in kg x 140 – age) x 1.23 (mL/min) (serum creatinine in µmol/L)

Multiply by 0.85 for females
Geriatric Pharmacology

Pharmacokinetics

Table 10. Age-Associated Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age Effect</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Increased gastric pH</td>
<td>Drug-drug and drug-food interactions are more likely to affect absorption</td>
</tr>
<tr>
<td>(less significant)</td>
<td>Decreased splanchnic blood flow, GI absorptive surface and dermal vascularity; delayed gastric emptying</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Increased total body fat and α1-glycoprotein</td>
<td>Lipophilic drugs have a larger volume of distribution</td>
</tr>
<tr>
<td></td>
<td>Decreased lean body mass, total body water, and albumin</td>
<td>Decreased binding of acidic drugs, increased binding of basic drugs</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)</td>
<td>Lower doses may be therapeutic</td>
</tr>
<tr>
<td>(less significant)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacodynamics

Drug Sensitivity
- changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives, antipsychotics, digoxin and narcotics
- decreased sensitivity to β-blockers in majority of elderly patients, though some may have increased sensitivity

Decreased Homeostasis
- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

Polypharmacy

Definition
- prescription, administration or use of five or more medications at the same time

Epidemiology
- in Canada, >60% of elderly individuals reported using ≥5 medications
- hospitalized elderly are given an average of 10 medications during admission

Risk Factors for Non-Compliance
- risk of non-compliance correlates with medication factors, not age
  - number of medications: compliance with 1 medication is 80%, but drops to 25% with ≥6 medications
  - increased dosing frequency, complicated container design, financial constraints, and cognitive impairment

Adverse Drug Reactions (ADRs)
- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in the elderly
  - intrinsic: comorbidities, age-related changes in pharmacokinetics and pharmacodynamics
  - extrinsic: number of medications, multiple prescribers, unreliable drug history
- 90% of ADRs are from: ASA, analgesics, anticoagulants, antimicrobials, antineoplastics, digoxin, diuretics, hypoglycemics, and steroids

Preventing Polypharmacy
- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical comorbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an ADR with another medication
Inappropriate Prescribing in the Elderly

Epidemiology
- the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

Beers Criteria
- a list of medications to avoid in adults ≥65 yo due to safety concerns
- examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives
- the elderly are also often under-treated (ACEI, ASA, β-blockers, thrombolytics, warfarin)

Beers Criteria
For full list of medications, consult the following reference:
The American Geriatrics Society 2012 Beers Criteria Update Expert Panel
J Am Geriatr Soc 2012;60(4):616-31
http://www.americangeriatrics.org

Table 11. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>donepezil</td>
<td>Aricept®</td>
<td>5-10 mg PO daily</td>
<td>Moderate to severe dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, caution in pulmonary disease, sick sinus syndrome, seizure disorder</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increased need for pacemaker insertion</td>
<td>Reversible inhibition of acetylcholinesterase</td>
</tr>
<tr>
<td>galantamine</td>
<td>Remini®</td>
<td>8-12 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, caution in sick sinus syndrome, seizure disorder, pulmonary disease, low body weight</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increased need for pacemaker insertion</td>
<td>Reversible inhibition of acetylcholinesterase</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>Exelon®</td>
<td>1-5 mg PO daily (starting) up to 6 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, severe hepatic disease, caution in sick sinus syndrome, pulmonary disease, seizure disorder</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increased need for pacemaker insertion</td>
<td>Acetylcholinesterase inhibition (reversible but very slow)</td>
</tr>
<tr>
<td>memantine</td>
<td>Ebixa®/Namenda® (Can)/Namenda® (U.S.)</td>
<td>5 mg PO daily (starting) up to 10 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, conditions that alkalinize urine, caution in cardiovascular conditions</td>
<td>Agitation, fatigue, dizziness, headache, hypertension, constipation</td>
<td>NMDA-receptor antagonist</td>
</tr>
</tbody>
</table>

Laxatives

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>bran</td>
<td>All-Bran®</td>
<td>1 cup OD</td>
<td>Constipation</td>
<td></td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
</tr>
<tr>
<td>psyllium</td>
<td>Metamucil®/Probiem Plain®</td>
<td>1 tsp PO tid</td>
<td>Constipation, hypercholesterolemia</td>
<td>N/V, abdominal pain, obstruction</td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
</tr>
<tr>
<td>lactulose</td>
<td>Chronulac®/Cephulac®/Kristulose® (U.S.)/Aclac/Apo-Lactulose®/Laxilose/PMS Lactulose (Can)</td>
<td>15-30 cc PO OD/bid</td>
<td>Constipation, hepatic encephalopathy, bowel evacuation following barium exam</td>
<td>Patients on low galactose diets</td>
<td>Abdominal pain, N/V</td>
<td>Hyperosmolar agent, lowers pH of colon to decrease blood ammonia levels</td>
</tr>
<tr>
<td>senna</td>
<td>Senokot®/Ex-lax®/Glyssenn®</td>
<td>1-2 tabs PO daily or 10-15 cc syrup PO daily</td>
<td>Constipation</td>
<td>Abdominal pain, N/V</td>
<td>Cramps, N/V, diarrhea</td>
<td>Stimulant laxative</td>
</tr>
<tr>
<td>PEG 3350 (polyethylene glycol)</td>
<td>Lax-A-Day®, RestoraLAX®, Pegalax® (Can)</td>
<td>17 g (~1 heaping tablespoon) dissolved in 120 to 240 mL (4 to 8 ounces) of beverage, OD</td>
<td>Constipation bowel prep (different dosing schedule)</td>
<td>Known/suspected bowel obstruction, known hypersensitivity, renal impairment</td>
<td>Abdominal cramps, bloating of the stomach, diarrhea, flatulence, nausea</td>
<td>Osmotic laxative</td>
</tr>
<tr>
<td>bisacodyl</td>
<td>Dulcolax®</td>
<td>5-15 mg PO (10 mg PR)</td>
<td>Constipation</td>
<td>Ileus, obstruction, abdominal pain, N/V, severe dehydration</td>
<td>Cramps, pain, diarrhea</td>
<td>Stimulant laxative</td>
</tr>
</tbody>
</table>
## Table 11. Common Medications (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>zopiclone</td>
<td>Imovane®</td>
<td>3.75 mg PO qhs (initially)</td>
<td>Insomnia</td>
<td>Known hypersensitivity, caution in myasthenia gravis, severe hepatic disease</td>
<td>Bitter taste, palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor, sweating, cognitive impairment, falls</td>
<td>Short-acting hypnotic (no tolerance effects)</td>
</tr>
<tr>
<td>temazepam</td>
<td>Restoril®</td>
<td>15 mg PO qhs</td>
<td>Short-term management of insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, sleep apnea</td>
<td>Drowsiness, dizziness, impaired coordination, hangover, lethargy, dependence, cognitive impairment, falls</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
<tr>
<td>lorazepam</td>
<td>Ativan®</td>
<td>0.5 mg PO qhs (initially)</td>
<td>Anxiety, insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, narrow-angle glaucoma</td>
<td>Dizziness, drowsiness, lethargy, dependence, cognitive impairment falls</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
<tr>
<td>melatonin</td>
<td>Several brands OTC</td>
<td>Immediate release 5 mg PO qhs (initially), or extended release 2 mg PO qhs</td>
<td>Insomnia</td>
<td>Known hypersensitivity, concurrent immunosuppressive treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in the elderly

## Landmark Geriatric Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal management of urinary tract infections in older people</td>
<td>Clin Interv Aging 2011;6:173-180</td>
<td>UTIs are over diagnosed and over treated in older people. Asymptomatic bacteriuria is very common in later life and should not be screened for or treated</td>
</tr>
<tr>
<td>Delirium is a strong risk factor for dementia in the oldest-old: a population based cohort study</td>
<td>Brain 2012;135(9): 2809-16</td>
<td>First population study to show that delirium is a strong risk factor for dementia and cognitive decline in elderly patients</td>
</tr>
<tr>
<td>Donepezil and Memantine for Moderate-to-Severe Alzheimer’s Disease</td>
<td>NEJM 2012;366:893-903</td>
<td>Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer’s disease</td>
</tr>
<tr>
<td>Early palliative care for metastatic lung cancer</td>
<td>NEJM 2010;363:733-742</td>
<td>Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end-of-life but longer survival</td>
</tr>
<tr>
<td>Hip protectors for fracture prevention</td>
<td>NEJM 2000;343:1506-1513</td>
<td>The risk of hip fracture can be reduced in frail elderly adults by the use of an anatomically designed external hip protector</td>
</tr>
<tr>
<td>HYVET</td>
<td>NEJM 2008;358:1887-1898</td>
<td>Antihypertensive treatment withdipropamil (sustained release), with or without perindopril, in adults 80 yr or older is beneficial</td>
</tr>
<tr>
<td>PROFET</td>
<td>Lancet 1999;353:93-97</td>
<td>Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment</td>
</tr>
<tr>
<td>Yale Delirium Prevention Trial</td>
<td>NEJM 1999;340:669-676</td>
<td>A risk-factor intervention strategy can result in significant reductions in the number and duration of episodes of delirium in hospitalized older patients</td>
</tr>
</tbody>
</table>

## References

### Constipation

### Delirium, Dementia, and Depression
Donepezil and Memantine for Moderate-to-Severe Alzheimer’s Disease | NEJM 2012;366:893-903 | Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer’s disease |
| Early palliative care for metastatic lung cancer | NEJM 2010;363:733-742 | Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end-of-life but longer survival |
| Hip protectors for fracture prevention | NEJM 2000;343:1506-1513 | The risk of hip fracture can be reduced in frail elderly adults by the use of an anatomically designed external hip protector |
| HYVET | NEJM 2008;358:1887-1898 | Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in adults 80 yr or older is beneficial |
| PROFET | Lancet 1999;353:93-97 | Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment |
| Yale Delirium Prevention Trial | NEJM 1999;340:669-676 | A risk-factor intervention strategy can result in significant reductions in the number and duration of episodes of delirium in hospitalized older patients |

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Gynecology

Maria Daniel, Tammy Ryan, Michal Sheinis, and Evelyn Waugh, chapter editors
Sangwoo Leem and Mark Shafarenko, associate editors
Jin Kyu Kim and Shubham Shan, EBM editors
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Acronyms ............................................. 2

Basic Anatomy Review .......................... 2

Menstruation ................................. 4
Menstrual Cycle
Stages of Puberty
Premenstrual Syndrome
Premenstrual Dysphoric Disorder

Differential Diagnoses of Common Presentations
Abnormal Uterine Bleeding
Dysmenorrhea
Pruritus
Pelvic Pain
Pelvic Mass
Dyspareunia
First and Second Trimester Bleeding

Common Investigations and Procedures ...... 8
Imaging
Endometrial Biopsy
Hysterectomy

Disorders of Menstruation ................. 10
Amenorrhea
Abnormal Uterine Bleeding
Dysmenorrhea

Endometriosis ............................... 13
Adenomyosis .................................. 15

Fibroids ........................................ 15

Contraception ............................. 17
Hormonal Methods
Intrauterine Device
Emergency Postcoital Contraception

Termination of Pregnancy ............. 20

Pregnancy-Related Complications .... 21
Spontaneous Abortions

Ectopic Pregnancy ........................ 21

Infertility .................................. 23
Female Factors
Male Factors

Polycystic Ovarian Syndrome ......... 24

Gynecological Infections .............. 26
Physiologic Discharge
Vulvovaginitis
Sexually Transmitted Infections
Bartholin Gland Abscess
Pelvic Inflammatory Disease
Toxic Shock Syndrome
Surgical Infections

Sexual Abuse ............................... 33

Sexuality and Sexual Dysfunction .... 33

Menopause ................................. 34
Hormone Replacement Therapy

Urogynecology ............................ 36
Prolapse
Urinary Incontinence

Gynecological Oncology ............... 38
Uterus
Ovary
Cervix
Vulva
Vagina
Fallopian Tube
Gestational Trophoblastic Disease/Neoplasia

Common Medications .................. 51

References ................................. 53
Figure 1. Vulva and perineum

A. EXTERNAL GENITALIA
- referred to collectively as the vulva
- blood supply: internal pudendal artery
- sensory innervation: pudendal nerve
- lymphatic drainage: inguinal nodes

B. VAGINA
- muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
- lined by rugated, stratified-squamous epithelium
- upper vagina separated by cervix into anterior, posterior, and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastomoses from uterine, inferior vesical, and middle rectal arteries

C. UTERUS
- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterus corpus
    - blood supply: uterine artery (branch of the internal iliac artery, anterior division)
  - cervix
    - blood supply: cervical branch of uterine artery
- supported by the pelvic diaphragm, the pelvic organs, and 4 paired sets of ligaments
- round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals then terminate in the labia majora
  - function: anteversion
- blood supply: Sampson's artery (branch of uterine artery running through round ligament)
- uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
  - function: mechanical support for uterus, prevent prolapse and contain autonomic nerve fibres
- cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
  - function: mechanical support, prevent prolapse
- broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics
• infundibulopelvic ligament: continuous tissue that connects ovary to pelvic wall
  - contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
• position of the uterus
  - anteverted (majority), retroverted, neutral

---

**D. FALLOPIAN TUBES**

- 8-14 cm muscular tubes extending laterally from the uterus to ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

**E. OVARIES**

- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

---

**Figure 2. Genital organs and positioning of the uterus**

**Figure 3. Vascular supply**
**Menstruation**

**GY4 Gynecology**

**Toronto Notes 2018**

**Menstruation**

**Menstrual Cycle**

**FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)**

<table>
<thead>
<tr>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiating Events</td>
<td>↓ E and ↓ P (from end of previous cycle)</td>
<td>↑ FSH acts on ovarian granulosa cells</td>
</tr>
<tr>
<td>HP0 Axis</td>
<td>↑ GnRH pulse frequency</td>
<td>↑ E from follicles (ovary)</td>
</tr>
<tr>
<td>Hormones</td>
<td>↑ FSH</td>
<td>↑ LH pulse frequency</td>
</tr>
<tr>
<td>Feedback on HP0 Axis</td>
<td>Negative feedback E → ↓ FSH, ↓ LH</td>
<td>↑ E from follicles, especially from dominant follicle</td>
</tr>
<tr>
<td>Ovaries</td>
<td>↑ FSH + follicular growth in 3-30 follicles</td>
<td>↑ follicular growth (by reducing atresia) → ↑ E</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Menses from P withdrawal (from end of previous cycle)</td>
<td>E builds up endometrium</td>
</tr>
<tr>
<td>Cervical Mucus</td>
<td></td>
<td>Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy</td>
</tr>
</tbody>
</table>

**LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)**

<table>
<thead>
<tr>
<th>Early-Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVULATION</td>
<td>Switch back to negative feedback</td>
</tr>
<tr>
<td>▲ LH pulse amplitude (LH surge)</td>
<td>↓ LH</td>
</tr>
<tr>
<td>E peaks → LH surge → ovulation</td>
<td>↑ P from corpus luteum</td>
</tr>
<tr>
<td>Positive feedback: E and P → ↑ FSH, ↑ LH</td>
<td>↓ P secondary to degeneration of corpus luteum</td>
</tr>
<tr>
<td>Negative feedback P → ↓ FSH, ↓ LH</td>
<td>Cessation of P from corpus luteum</td>
</tr>
<tr>
<td>P stabilizes endometrium</td>
<td>Withdrawal of P → menses</td>
</tr>
<tr>
<td></td>
<td>Opaque, scant amount, Spinnbarkeit 1-2 cm</td>
</tr>
</tbody>
</table>

**CHARACTERISTICS**

- Menarche 10-15 yr
- Average 12.2 yr
- Entire cycle 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

**ESTROGEN**

ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle.

Estrogen effects

- On the follicles in the ovaries
- Reduces atresia
- On the endometrium
- Proliferation of glandular and stromal tissue
- On all target tissues
- Decreases E receptors

**PROGESTERONE**

PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle).

Progesterone effects

- On the endometrium
  - Cessation of mitoses (stops building endometrium up)
  - "Organization" of glands (initiates secretions from glands)
  - Inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues
  - Decrease E receptors (the "anti-estrogen" effect)
  - Decrease P receptors
Stages of Puberty

- see Pediatrics, P30
- adrenarche: increase in secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8 yr
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding

Premenstrual Syndrome

- synonyms: "ovarian cycle syndrome," "menstrual molimina" (moodiness)

Etiology

- multifactorial: not completely understood; genetics likely play a role
- CNS-mediated neurotransmitter interactions with sex steroids (progesterone, estrogen, and testosterone)
- serotonergic dysregulation – currently most plausible theory

Diagnostic Criteria for Premenstrual Syndrome

- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness, abdominal bloating, headache, swelling of extremities
- symptoms relieved within 4 d of onset of menses
- symptoms present in the absence of any pharmacologic therapy, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or economic performance

Premenstrual Dysphoric Disorder

Clinical Presentation

- irritability, depressed mood
- breast pain and bloating

Diagnostic Criteria for Premenstrual Dysphoric Disorder

- at least 5 of the following 11 symptoms during most menstrual cycles of the last year (with at least 1 of the first 4)
  - depressed mood or hopelessness
  - anxiety or tension
  - affective symptoms
  - anger or irritability
  - decreased interest in activities
  - difficulty concentrating
  - lethargy
  - change in appetite
  - hypersomnia or insomnia
  - feeling overwhelmed
  - physical symptoms: breast tenderness/swelling, headaches, joint/muscle pain, bloating, or weight gain
- symptoms interfere with social or occupational functioning
- symptoms must be discreetly related to the menstrual cycle
- 1, 2 and 3 must be confirmed during at least 2 consecutive symptomatic menstrual cycles
Differential Diagnoses of Common Presentations

Abnormal Uterine Bleeding

Abnormal Uterine Bleeding (AUB)
- Heavy Menstrual Bleeding
- Intermenstrual Bleeding

Structural Causes (PALM)
- Polyp (AUB-P)
- Adenomyosis (AUB-A)
- Leiomyoma (AUB-L)
- Submucosal (AUB-L_{sm})
- Other (AUB-LO)
- Malignancy and hyperplasia (AUB-M)

Non-Structural Causes (COEIN)
- Coagulopathy (AUB-C)
- Ovulatory dysfunction (AUB-D)
- Endometrial (AUB-E)
- Iatrogenic (AUB-I)
- Not yet classified (AUB-N)

Figure 6. Differential diagnosis of abnormal uterine bleeding

- see Disorders of Menstruation, GY11
- menstrual bleeding should be evaluated by ascertaining: frequency/regularity of menses, duration, volume of flow, affects on quality of life and timing (inter or premenstrual or breakthrough)
- classified as:
  - regular: cycle to cycle variability of <20 d
  - irregular: cycle to cycle variability of ≥20 d
  - heavy menstrual bleeding: ≥80 cc of blood loss per cycle or ≥8 d of bleeding per cycle or bleeding that significantly affects quality of life
  - postmenopausal bleeding: any bleeding that presents >1 yr after menopause; must rule out endometrial cancer

Dysmenorrhea

- see Disorders of Menstruation, GY13
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease
  - IUD (copper)
  - foreign body

Pruritus

- see Gynecological Infections, GY26
- physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn’s disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)
Pelvic Pain

20% of chronic pelvic pain patients have a history of previous sexual abuse/assault; remember to ask about it.

Pelvic Mass

Figure 7. Approach to pelvic pain

Figure 8. Differential diagnosis of pelvic mass
Common Investigations and Procedures

Dyspareunia

Figure 9. Approach to dyspareunia

First and Second Trimester Bleeding

Approach to the Patient with Bleeding in T1/T2

History
- risk factors for ectopic pregnancy (see Ectopic Pregnancy, GY21)
- previous spontaneous abortion
- recent trauma
- characteristics of the bleeding (including any tissue passed)
- characteristics of the pain (cramping pain suggests spontaneous abortion)
- history of coagulopathy
- gynecological/obstetric history
- fatigue, dizziness, syncopal episodes due to hypovolemia, fever (may be associated with septic abortion)

Physical
- vitals (including orthostatic changes)
- abdomen (symphysis fundal height, tenderness, presence of contractions)
- perineum (signs of trauma, genital lesions)
- speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness, cervical motion tenderness)

Investigations
- β-hCG (may be lower than expected for GA in spontaneous abortion, can be used to diagnose viable pregnancy vs. ectopic pregnancy vs. abortion)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Common Investigations and Procedures

Imaging

Ultrasound (U/S)
- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
- detects early pregnancy if β-hCG ≥1,500 (β-hCG must be ≥6,500 for transabdominal U/S)
- may be used to identify pelvic pathology
- identify ectopic pregnancy, intrauterine pregnancy
- assess uterine, adnexal, cul-de-sac, ovarian masses (e.g. solid or cystic)
- determine endometrial thickness, locate/characterize fibroids
- monitor follicles during assisted reproduction
- assess endometrial lining in postmenopausal women

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured
Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cytotec) if nulliparous or postmenopausal
- more invasive procedure (D&C) may be done in the office or operating room ± hysteroscopy. This may be required if endometrial biopsy is not possible in the office setting or if there is suspicion for an endometrial polyp
- indications
  - AUB/PMB
  - age >40
  - risk factors for endometrial cancer
  - failure of medical treatment
  - significant intermenstrual bleeding
  - consider in women with infrequent menses suggesting anovulatory cycles

Hysterectomy

Indications
- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications
- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

Approaches
1. open (abdominal approach): uterus removed via transverse (pfannenstiel) or midline laparotomy
2. minimally invasive approaches
  - vaginal hysterectomy: entire procedure performed through the vagina. No abdominal incisions
  - laparoscopic assisted vaginal hysterectomy: vascular pedicles are divided by a combination of laparoscopic and vaginal approaches
  - total laparoscopic hysterectomy: all vascular pedicles including the colpotomy approached laparoscopically
  - robotic: a type of laparoscopic approach. May be advantageous in high BMI patients. More costly

Table 1. Classification of Hysterectomy

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tissues Removed</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal Hysterectomy</td>
<td>Uterus</td>
<td>Inaccessible cervix (e.g. adhesions) Patient choice/preference Severe endometriosis</td>
</tr>
<tr>
<td>Total Hysterectomy (extrafascial simple hysterectomy/type 1)</td>
<td>Uterus, cervix, uterine artery ligated at uterus</td>
<td>Uterine fibroids Endometriosis Adenomyosis Heavy menstrual bleeding DUB</td>
</tr>
<tr>
<td>Total Hysterectomy (extrafascial simple hysterectomy/type 1) + Bilateral Salpingo-Oophorectomy</td>
<td>Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries</td>
<td>Endometrial cancer Malignant adnexal masses Consider for endometriosis</td>
</tr>
<tr>
<td>Modified Radical Hysterectomy (type 2)</td>
<td>Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterosacral ligaments and upper 1-2 cm vagina</td>
<td>Cervical cancer (up to stage IBI)</td>
</tr>
<tr>
<td>Radical Hysterectomy (type 3)</td>
<td>Uterus, cervix, upper 1/3-1/2 vagina, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum)</td>
<td>Cervical cancer</td>
</tr>
</tbody>
</table>
Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

<table>
<thead>
<tr>
<th>With Secondary Sexual Development</th>
<th>Without Secondary Sexual Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal breast and pelvic development</td>
<td>Normal breast, abnormal uterine development</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>PCOS</td>
<td>Hypothalamic dysfunction</td>
</tr>
<tr>
<td>Androgen insensitivity</td>
<td>Müllerian agenesis, uterovaginal septum, imperforate hymen</td>
</tr>
<tr>
<td>Normal breast, abnormal uterine development</td>
<td></td>
</tr>
<tr>
<td>High FSH (hypergonadotropic hypogonadism)</td>
<td>Low FSH (hypogonadotropic hypogonadism)</td>
</tr>
<tr>
<td>Conception disorders (type 1 DM)</td>
<td>Pituitary tumours</td>
</tr>
<tr>
<td>Anatomic abnormalities</td>
<td>Müllerian agenesis</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>PCOS</td>
</tr>
<tr>
<td>Hypothalamic dysfunction</td>
<td>Functional hypothalamic amenorrhea</td>
</tr>
</tbody>
</table>

Table 3. Differential Diagnosis of Secondary Amenorrhea

<table>
<thead>
<tr>
<th>With Hyperandrogenism</th>
<th>Without Hyperandrogenism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>Hypergonadotropic hypogonadism (i.e. primary ovarian insufficiency: high FSH, low estradiol)</td>
</tr>
<tr>
<td>Autonomous hyperandrogenism (androgen secretion independent of the HPO axis)</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Ovarian: tumour, hyperthecosis</td>
<td>Autoimmune: type 1 DM, autoimmune thyroid disease, Addison’s disease</td>
</tr>
<tr>
<td>Adrenal androgen-secreting tumour</td>
<td>Late onset or mild congenital adrenal hyperplasia (rare)</td>
</tr>
<tr>
<td>Late onset or mild congenital adrenal hyperplasia (rare)</td>
<td>Hypergonadotropic hypogonadism (low FSH):</td>
</tr>
<tr>
<td></td>
<td>Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigations

Figure 10 Diagnostic approach to amenorrhea
• β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
• progesterone challenge to assess estrogen status
  ■ medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10-14 d
  ■ any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive test/
    withdrawal bleed
    • withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus
      withdrawal of progesterone results in bleeding
    • if no bleeding occurs, this may be secondary to inadequate estrogen (hypoestrogenism),
      excessive androgens, or progesterones (decidualization) or pregnancy
• karyotype: indicated if primary ovarian insufficiency or absent puberty
• U/S to confirm normal anatomy, identify PCOS

Treatment

Table 4. Management of Amenorrhea

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1º AMENORRHEA</td>
<td></td>
</tr>
<tr>
<td>Androgen insensitivity syndrome</td>
<td>Gonadal resection after puberty</td>
</tr>
<tr>
<td>psychological counselling</td>
<td></td>
</tr>
<tr>
<td>Creation of neo-vagina with dilation</td>
<td></td>
</tr>
<tr>
<td>Anatomical</td>
<td></td>
</tr>
<tr>
<td>Imperforate hymen</td>
<td>Surgical management</td>
</tr>
<tr>
<td>Transverse vaginal septum</td>
<td>Surgical management</td>
</tr>
<tr>
<td>Cervical agenesis</td>
<td>Suppression and ultimately hysterectomy</td>
</tr>
<tr>
<td>Müllerian dysgenesis (MRKH syndrome)</td>
<td>Psychological counselling</td>
</tr>
<tr>
<td></td>
<td>Creation of neo-vagina with dilation</td>
</tr>
<tr>
<td></td>
<td>Diagnostic study to confirm normal urinary system and spine</td>
</tr>
<tr>
<td>2º AMENORRHEA</td>
<td></td>
</tr>
<tr>
<td>Uterine defect</td>
<td>Evaluation with hysterosalpingography or sonohysterography</td>
</tr>
<tr>
<td>Asherman’s syndrome</td>
<td>Hysteroscopy: excision of synchiae</td>
</tr>
<tr>
<td>HP-axis dysfunction</td>
<td>Identify modifiable underlying cause</td>
</tr>
<tr>
<td></td>
<td>Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast</td>
</tr>
<tr>
<td></td>
<td>development (NOT proven to work)</td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td>Screen for DM, hypothyroidism, hypoparathyroidism, hypocorticulism</td>
</tr>
<tr>
<td></td>
<td>Hormonal therapy with estrogen + progestin to decrease risk of osteoporosis; can use</td>
</tr>
<tr>
<td></td>
<td>OCP after induction of puberty</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>MRI/CT head to rule out lesion</td>
</tr>
<tr>
<td></td>
<td>If no demonstrable lesions by MRI</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine, cabergoline if fertility desired</td>
</tr>
<tr>
<td></td>
<td>Combined OCPs if no fertility desired</td>
</tr>
<tr>
<td></td>
<td>Demonstrable lesions by MRI: surgical management</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>See Polycystic Ovarian Syndrome, GY24</td>
</tr>
</tbody>
</table>

Abnormal Uterine Bleeding

Figure 11. Diagnostic approach to abnormal uterine bleeding
**Disorders of Menstruation**

**Approach**
- **is it regular?**
  - regular: cycle to cycle variability of <20 d – “Can you predict your menses within 20 days?”
  - irregular: cycle to cycle variability of ≥20 d
- **is it heavy**
  - ≥80 cc of blood loss per cycle or
  - ≥8 d of bleeding per cycle or
  - bleeding that significantly affects quality of life
- **is it structural?**
  - PALM
- **is it non-structural?**
  - COEIN

**Table 5. AUB – Etiologies, Investigations, and Management**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRUCTURAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyps (AUB-P)</td>
<td>Transvaginal Sonography</td>
<td>Polypectomy (triage based on symptomatic polyp size, histopathology and patient age)</td>
</tr>
<tr>
<td>Adenomyosis (AUB-A)</td>
<td>Transvaginal Sonography MRI</td>
<td>See Adenomyosis, GY15</td>
</tr>
<tr>
<td>Leiomyoma (AUB-L)</td>
<td>Transvaginal Sonography</td>
<td>See Fibroids (Leiomyomata) GY15</td>
</tr>
<tr>
<td>Submucosal (AUB-Lsm)</td>
<td>Saline Infusion Sonohysterography</td>
<td></td>
</tr>
<tr>
<td>Other (AUB-Lo)</td>
<td>Diagnostic Hysteroscopy</td>
<td></td>
</tr>
<tr>
<td>Malignancy and Hyperplasia (AUB-M)</td>
<td>Transvaginal Sonography</td>
<td>Endometrial Biopsy - consider biopsy in women &gt;40 yr with AUB to exclude endometrial cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NON-STRUCTURAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulopathy (AUB-C)</td>
<td>CBC, coagulation profile (especially in adolescents), vWF, Ristocetin Cofactor, Factor VIII</td>
<td>Dependent on diagnosis (Hormonal modulation (e.g. OCP), Mirena IUD, endometrial ablation)</td>
</tr>
<tr>
<td>Ovulatory dysfunction (AUB-O)</td>
<td>Bloodwork: β-hCG, ferritin, prolactin, FSH, LH, serum androgens (free testosterone, DHEA), progesterone, 17-hydroxy progesterone, TSH, FT4 pelvic ultrasound</td>
<td>See Infertility, GY23</td>
</tr>
<tr>
<td>Endometrial (AUB-E)</td>
<td>Endometrial Biopsy</td>
<td>Transaxamic acid</td>
</tr>
<tr>
<td>Iatrogenic (AUB-I)</td>
<td>TransvaginalSonography (rule out forgotten IUD)</td>
<td>Remove offending agent</td>
</tr>
<tr>
<td>Not yet classified (AUB-N)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

*Ferrous gluconate 300 mg PO TID w ll raise Hb 10 points per wk

**Treatment**
- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider AUB
- medical
  - mild AUB
    - NSAIDs
    - anti-fibrinolytic (e.g. Cyklokapron*) at time of menses
    - combined OCP
    - progestins (Provera*) on first 10-14 d of each month or every 3 mo if AUB-O
    - Mirena* IUD
    - Danazol
    - Correct anemia - iron
  - acute, severe AUB
    - replace fluid losses, consider admission
    - estrogen (Premarin*) 25 mg IV q4h x 24 h with Gravol* 50 mg IV/PO q4h or anti-fibrinolytic (e.g. Cyklokapron*) 10 mg/kg IV q8h
    - tapering OCP regimen, 35µg pill TID x7d then taper to 1 pill/d for 3w with Gravol* 50 mg IV/PO q4h
    - or taper to 1 tab tid x 2 d → bid x 2 d → OD
  - after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
surgical
  - endometrial ablation
    - if finished childbearing
    - repeat procedure may be required if symptom recur especially if <40 yr
  - hysterectomy: definitive treatment

Dysmenorrhea

Etiology
  - see Differential Diagnoses of Common Presentations, GY6

Table 6. Comparison of Primary and Secondary Dysmenorrhea

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Dysmenorrhea</th>
<th>Secondary Dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent, crampy lower abdominal pain that occurs during menses in the absence of demonstrable disease</td>
<td>Similar features as primary dysmenorrhea but with an underlying disorder that can account for the symptoms, such as endometriosis, adenomyosis or uterine fibroids</td>
</tr>
<tr>
<td>Signs and Symptoms</td>
<td>Colicky pain in abdomen, migrating to the lower back and labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h)</td>
<td>Associated dyspareunia, abnormal bleeding, infertility</td>
</tr>
<tr>
<td></td>
<td>Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated)</td>
<td>Rule out underlying pelvic pathology and confirm cyclic nature of pain</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Associated dyspareunia, abnormal bleeding, infertility</td>
<td>Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women &lt;20 yr)</td>
</tr>
<tr>
<td></td>
<td>U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis Screening for infections (vaginal and cervical cultures) may be required</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>NSAIDs: should be started before onset of pain OCP: suppress ovulation/reduce menstrual flow</td>
<td>Treat underlying cause</td>
</tr>
</tbody>
</table>

Endometriosis

Etiology
  - not fully understood
  - proposed mechanisms (combination likely involved)
    - retrograde menstruation (Sampson's theory)
    - immunologic theory: altered immunity may limit clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
    - metaplasia of coelomic epithelium
    - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

Epidemiology
  - incidence: 15-30% of pre-menopausal women
  - mean age at presentation: 25-30 yr
  - regresses after menopause

Risk Factors
  - family history (7-10x increased risk if affected 1st degree relative)
  - obstructive anomalies of the genital tract (earlier onset) – resolve with treatment of anomaly
  - nulliparity
  - age >25 yr

Sites of Occurrence
  - ovaries: 60% patients have ovarian involvement
  - broad ligament, vesicouterine fold
  - peritoneal surface of the cul de sac, uterosacral ligaments
  - rectosigmoid colon, appendix
  - rarely may occur in sites outside abdomen/pelvis, including lungs
Clinical Features

- may be asymptomatic and can occur with one of 3 presentations
  
  1. pain
    - menstrual symptoms
      - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
      - secondary dysmenorrhea
      - sacral backache with menses
      - pain may eventually become chronic, worsening perimenstrually
      - deep dyspareunia
    - bowel and bladder symptoms
      - frequency, dysuria, hematuria
      - cyclic diarrhea/constipation, hematochezia, dyschezia (suggestive of deeply infiltrating disease)
  
  2. infertility
    - 30–40% of patients with endometriosis will be infertile
    - 15–30% of those who are infertile will have endometriosis
  
  3. mass (endometrioma)
    - ovarian mass can present with any of above symptoms or be asymptomatic
    - physical
      - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
      - fixed retroversion of uterus
      - firm, fixed adnexal mass (endometrioma)

Investigations

- definitive diagnosis can be made based on:
  - direct visualization of lesions typical of endometriosis at laparoscopy
  - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)

- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - "powder-burn" lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
  - CA-125
    - may be elevated in patients with endometriosis but should NOT be used as a diagnostic test

Figure 12. SOGC guidelines for treatment of endometriosis

Treatment

- surgical confirmation of disease is NOT required prior to starting medical management. Asymptomatic endometriosis does not require treatment. Management depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)
- medical
  - NSAIDs (e.g. naproxen sodium – Anaprox®)
  - 1st line
    - cyclic/continuous estrogen-progestin (OCP)
    - progestin (IM medroxyprogesterone (Depo-Provera®) or oral dienogest (Visanne®)
    - Mirena® IUS
  - 2nd line
    - GnRH agonist with addback
    - Progestin IUS
  - 3rd line
    - Reconsider diagnosis additional testing and/or non-gynecologic referrals
    - Chronic pain management and multidisciplinary support

Endometriosis – Take Home Points

- Suggestive history even with a negative exam should be considered adequate for a presumptive diagnosis
- Pelvic pain that is not primary dysmenorrhea should be considered endometriosis until proven otherwise
- Medical management is the mainstay of endometriosis
Adenomyosis

- synonym: “endometriosis interna” (uterine wall may be diffusely involved)

**Epidemiology**
- 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

**Clinical Features**
- often asymptomatic
- heavy menstrual bleeding, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm
- Halban sign: tender, softened uterus on premenstrual bimanual exam

**Investigations**
- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

**Treatment**
- iron supplements for anemia
- analgesics, NSAIDs
- OCP, medroxyprogesterone (Depo-Provera*)
- GnRH agonists (e.g. leuprolide)
- Mirena* IUS
- low dose danazol 100-200 mg PO OD (trial x 4 mo)
- definitive: hysterectomy

---

Fibroids

**Epidemiology**
- diagnosed in approximately 40-50% of pre-menopausal women >35 yr
- more common in African Americans, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential (1:1,000)
- typically regress after menopause; enlarging fibroids/uterus in a postmenopausal woman should prompt consideration of malignancy, specifically sarcoma

**Pathogenesis**
- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - fibroids can degenerate, become calcified, have sarcomatous component or obtain parasitic blood supply

**Clinical Features**
- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, heavy menstrual bleeding
- pressure/bulk symptoms (20-50%)
  - pelvic pressure/heaviness
  - increased abdominal girth
  - urinary frequency and urgency
  - acute urinary retention (extremely rare but surgical emergency!)
  - constipation, bloating (rare)
• acute pelvic pain
  • fibroid degeneration
  • fibroid torsion (if pedunculated subserosal)
• infertility, recurrent pregnancy loss
• pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)

**Investigations**
- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or if intracavitary growth
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 yr)
- occasionally MRI is used for pre-operative planning (e.g. before myomectomy)

**Treatment**
- only if symptomatic, rapidly enlarging, heavy menstrual bleeding, menometrorrhagia, or intracavitary
- treat anemia if present
- conservative approach (watch and wait) if:
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach to treat AUB-L
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - OCP/Depo-Provera*
  - GnRH agonist: leuprolide (Lupron®)
    - often used pre-myomectomy or pre-hysterectomy to reduce fibroid size
    - reduced bleeding and correct anemia
    - can be used long term to bridge to menopause in combination with add back progestin or estrogen
  - ulipristal acetate: a selective progesterone receptor agonist
    - 5 mg daily for 3 mo
    - courses can be repeated provided patients menstruate in between
    - shown to control menstrual bleeding symptoms and shrink fibroid
    - associated with benign, non-physiological endometrial changes (selective progesterone receptor
      modulator-associated endometrial changes PAEC) which are reversible with discontinuation of
      therapy
- interventional radiology approach
  - uterine artery embolization (occludes both uterine arteries) → shrinks fibroids by 50% at 6 mo;
    improves heavy bleeding in 90% of patients within 1-2 mo; not an option in women considering
    childbearing
- surgical approach
  - myomectomy (hysteroscopic, transabdominal, or laparoscopic): preserves fertility
  - hysteroscopic resection of fibroid and endometrial ablation for AUB-Lsm
  - hysterectomy (see Hysterectomy, GY9)
    - note: avoid operating on fibroids during pregnancy (due to → vascularity and potential pregnancy
      loss); expectant management usually best

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**Ulipristal Acetate vs. Leuprolide Acetate for Uterine Fibroids**
*NEJM* 2012;366:421-432

**Study:** Phase III, double-blind RCT of the efficacy and side-effect profile of ulipristal acetate versus those of leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery.

**Outcomes:** Control of uterine bleeding at week 13 was the primary outcome. Secondary outcomes included bleeding pattern, amenorrhea, changes in fibroid/uterine volume, and global pain score.

**Patients:** 307 premenopausal women with symptomatic fibroids and excessive uterine bleeding were randomly assigned to oral ulipristal acetate (5 mg or 10 mg) or intramuscular injections of leuprolide acetate.

**Results:** Control of bleeding at week 13 was not significantly different between the treatment groups. All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group (47% reduction) than in the ulipristal groups (20-22%). 40% of the leuprolide group reported moderate-to-severe hot flashes, but only 11% (5 mg) and 10% (10 mg) of the ulipristal groups did.

**Conclusions:** Oral ulipristal acetate (5 mg or 10 mg) is noninferior to intramuscular leuprolide acetate for control of uterine bleeding due to fibroids, and it had a better side-effect profile.
Contraception

• see Family Medicine, FM20

Table 7. Classification of Contraceptive Methods

<table>
<thead>
<tr>
<th>Type</th>
<th>Effectiveness (Perfect Use, Typical Use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td></td>
</tr>
<tr>
<td>Withdrawal/coitus interruptus</td>
<td>96%, 77%</td>
</tr>
<tr>
<td>Rhythm method/calendar/mucus/symptothermal</td>
<td>76%</td>
</tr>
<tr>
<td>Lactational amenorrhea</td>
<td>98% (first 6 mo postpartum)</td>
</tr>
<tr>
<td>Chance – no method used</td>
<td>15%</td>
</tr>
<tr>
<td>Abstinence of all sexual activity</td>
<td>100%</td>
</tr>
<tr>
<td>Barrier Methods</td>
<td></td>
</tr>
<tr>
<td>Condom alone</td>
<td>98%, 82%</td>
</tr>
<tr>
<td>Spermicide alone</td>
<td>82%, 72%</td>
</tr>
<tr>
<td>Sponge – Par us</td>
<td>80%, 76%</td>
</tr>
<tr>
<td>– Nulliparous</td>
<td>91%, 88%</td>
</tr>
<tr>
<td>Diaphragm with spermicide</td>
<td>94%, 88%</td>
</tr>
<tr>
<td>Female condom</td>
<td>95%, 79%</td>
</tr>
<tr>
<td>Cervical cap – Parous</td>
<td>74%, 68%</td>
</tr>
<tr>
<td>– Nul/parous</td>
<td>91%, 84%</td>
</tr>
<tr>
<td>Hormonal</td>
<td></td>
</tr>
<tr>
<td>OCP</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Nuva Ring®</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Transdermal (Ortho Evra®)</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Depo-Provera®</td>
<td>98.7%, 97%</td>
</tr>
<tr>
<td>Progestin-only pill (Micronor®)</td>
<td>90-99%</td>
</tr>
<tr>
<td>Mirena® IUS</td>
<td>99.9%</td>
</tr>
<tr>
<td>Jaydess® IUS</td>
<td>99.8%</td>
</tr>
<tr>
<td>Copper IUD</td>
<td>99.3%</td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>99.65%</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>99.9%</td>
</tr>
<tr>
<td>Emergency Postcoital Contraception (EPC)</td>
<td></td>
</tr>
<tr>
<td>Yuzpe® method</td>
<td>98% (within 24 h), decreases by 30% at 72 h</td>
</tr>
<tr>
<td>“Plan B” levonorgestrel only</td>
<td>98% (within 24 h), decreases by 70% at 72 h</td>
</tr>
<tr>
<td>Postcoital IUD</td>
<td>99.9%</td>
</tr>
<tr>
<td>Ba</td>
<td>98% (within 120 h)</td>
</tr>
</tbody>
</table>

Effectiveness: percentage of women reporting no pregnancy after 1 yr of use

Hormonal Methods

Combined Oral Contraceptive Pills
- most contain low dose ethinyl estradiol (20-35 µg) plus progestin (norethindrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

Transdermal (Ortho Evra®)
- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks NOT breast
- worn for 3 consecutive weeks (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

Contraceptive Ring (Nuva Ring®)
- thin flexible plastic ring; releases etonogestrel 120 µg/d and estradiol 15 µg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

Starting Hormonal Contraceptives
- thorough history and physical exam, including blood pressure and breast exam
- can start at any time during cycle but ideal if within 5 d of LMP
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam not required as STI screening can be done by urine and pap smear screening does not start until >21 yr
Table 8. Combined Estrogen and Progestin Contraceptive Methods

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Advantages</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulatory suppression through inhibition of LH and FSH/ Decidualization of endometrium/ Thickening of cervical mucus resulting in decreased sperm penetration</td>
<td>Highly effective/ Reversible/ Cycle regulation/ Decreased dysmenorrhea and heavy menstrual bleeding (less anemia)/ Decreased benign breast disease and ovarian cyst development/ Decreased risk of ovarian and endometrial cancer/ Increased cervical mucus which may lower risk of STIs/ Decreased PMS symptoms/ Improved acne/ Osteoporosis protection (possibly)</td>
<td>Estrogen-related/ Nausea/ Breast changes (tenderness, enlargement)/ Fluid retention/bloating/edema/ Weight gain (rare)/ Migraine, headaches/ Thromboembolic events/ Liver adenoma (rare)/ Breakthrough bleeding (low estradiol levels)/ Progestin-related/ Amenorrhea/break through bleeding/ Headaches/ Breast tenderness/ Increased appetite/ Dec eased libido/ Mood changes/ HTN/ Acne/oyl skin*/* Hirsutism*</td>
<td>Absolute/ Known/suspected pregnancy/ Undiagnosed abnormal vaginal bleeding/ Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis/ Cerebrovascular or coronary artery disease/ Estrogen-dependent tumours (breast, uterus)/ Impaired liver function associated with acute liver disease/ Congenital hypertriglyceridemia/ Smoker age &gt; 35 yr/ Migraines with focal neurological symptoms (excluding aura)/ Uncontrolled HTN/ Relative/ Migraines (non-focal with aura &lt; 1 h)/ CM complicated by vascular disease/ SLE/ Controlled HTN/ Hyperlipidemia/ Sickle cell anemia/ Gall bladder disease</td>
</tr>
</tbody>
</table>

Reference: World Health Organization Guidelines for Oral Contraceptive Pill Use

Table 9. Selected Examples of OCPs

<table>
<thead>
<tr>
<th>Type</th>
<th>Active Compounds (estriol and progestin derivative)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alesse®</td>
<td>20 µg ethinyl estradiol and 0.5 mg levonorgestrel</td>
<td>Low dose (20 µg) OCP Less estrogen side effects</td>
<td>Love-dose pills can often result in breakthrough bleeding If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content</td>
</tr>
<tr>
<td>Tri cyclen®</td>
<td>35 µg ethinyl estradiol and 0.160/0.215/0.250 mg norgestimate Triphasic oral contraceptive (graduated levels of progesterone)</td>
<td>Low androgenic activity can help with acne</td>
<td>Triphasic OCPs not ideal for continuous use &gt;3 weeks in a row (unlike monophasic formulation)</td>
</tr>
<tr>
<td>Yasmin® and Yaz®</td>
<td>Yasmin*: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin) / Yaz*: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4 d pill (d d pill free interval) Drospirenone has antimineralocorticoid activity and antiandrogenic effects</td>
<td>Decreased perception of cyclic weight gain/bloating Fewer PMS symptoms Improved acne</td>
<td>Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency) Check potassium if patient also on ACEI, ARB, K+-sparking diuretic, heparin Continue use of spironolactone</td>
</tr>
</tbody>
</table>

PROGESTIN-ONLY METHOD

Table 10. Progestin Only Contraceptive Methods

<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suitable for postpartum women (does not affect breast milk supply)/ Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease)/ Women intolerant of estrogenic side effects of combined OCPs</td>
<td>Progestin prevents LH surge/ Thickening of cervical mucus/ Decrease tubal mobility/ Endometrial decidualization/ Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs</td>
<td>Irregular menstrual bleeding/ Weight gain/ Headache/ Breast tenderness/ Mood changes/ Functional ovarian cysts/ Acne/oyl skin/ Hirsutism</td>
<td>Absolute/ None</td>
</tr>
</tbody>
</table>

SELECTED EXAMPLES OF PROGESTIN-ONLY METHODS

Progestin-Only Pill ("minipill")

- Micronor® 0.35 mg norethindrone
- taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1–13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited only in 60% of women; most have regular cycles (but may cause oligo/amenorrhea)
- highly effective if also post-partum breastfeeding, or if &gt;35 yr
- relies on the progestin effects on the cervical mucus and endometrial lining

Reference: World Health Organization Guidelines for Oral Contraceptive Pill Use

Depo-Provera®
- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wk (convenient dosing)
- initiate ideally within 5 d of beginning of normal menses, immediately postpartum in breastfeeding and non-breastfeeding women. Can consider quick start
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
- highly effective 99%; failure rate 0.3%
- suppresses ovulation very effectively
- side effect: decreased bone density (may be reversible) and weight gain
- disadvantage: restoration of fertility may take up to 9 mo

**Intrauterine Device**

### Table 11. IUS/IUD Contraceptive Methods

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| Copper-Containing IUD (Nova T®): mild foreign body reaction in endometrium toxic to sperm and alters sperm motility | Both Copper and Progesterone IUD
Breakthrough bleeding
Expulsion (5% in the 1st yr, greatest in 1st mo and in nulliparous women)
Uterine wall perforation (1/1,000) on insertion | Absolutes
Both Copper and Progesterone IUD
Known or suspected pregnancy
Undiagnosed genital tract bleeding
Acute or chronic PID
Lifestyle risk for STIs®
Copper IUD
Known allergy to copper
Wilson’s disease |
| Progestrone-Releasing IUS (Mirena®, Kyleena®, Jaydess®): decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation | Copper IUD: increased blood loss and duration of menses, dysmenorrhea | Relative
Both Copper and Progesterone IUD
Valvular heart disease
Past history of PID or ectopic pregnancy
Presence of prosthesis
Abnormalities of uterine cavity, intracavitary fibroids
Cervical stenosis
Immunsuppressed individuals (e.g. HIV) |
| | Progesterone IUD: bloating, headache | Both Copper and Progesterone IUD
Known or suspected pregnancy
Undiagnosed genital tract bleeding
Acute or chronic PID
Lifestyle risk for STIs® |

* Cervical swabs for gonorrhea and chlamydia should be done prior to insertion

### Emergency Postcoital Contraception

### Table 12. Emergency Contraceptive Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| *Yuzpe Method*
Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d
Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg/levonorgestrel 500 µg)
Can substitute with any OCP as long as same dose of estrogen used | Unknown; theories include: Suppresses ovulation or causes deficient luteal phase
Alters endometrium to prevent implantation
Affects sperm/ova transport | Nausea (due to estrogen; treat with Gravol®)
Irregular spotting
Pre-existing pregnancy (although not teratogenic)
Cautions in women with contraindications to OCP (although NO absolute contraindications) |
| *Plan B*
Consists of levonorgestrel 750 µg q12h for 2 doses (can also take 2 doses together); taken within 72 h of intercourse.
Can be taken up to 5 d
Greater efficacy (75-95%) if used within 24 h and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if >24 h
No estrogen thus very few contraindications/side effects (less nausea)
Less effective in overweight individuals (>75 kg less effective, >80 kg not recommended) | Same as above | Same as above but no caution in women with contraindications to OCP |
| *Uligilast*
30 mg PO within 5 d | Selective Progesterone Receptor Modulator (SPERM) with primarily antiprogestin activity; may delay ovulation by up to 5 d | Headache, hot flashes
Constipation, vertigo
Endometrial thickening | Same as above but no caution in women with contraindications to OCP |

**HORMONAL**

**NON-HORMONAL**

**Postcoital IUD (Copper)**
Insert up to 7 d postcoitus
Prevents implantation
1% failure rate
Can use for short duration in higher risk individuals
Minena® IUS cannot be used as EPC

---

Toronto Notes 2018
Follow-up
- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counselling

Termination of Pregnancy

Definition
- termination of pregnancy by medical or surgical means

Indications
- patient desires an end to pregnancy
- may be for medical reasons (mother or fetus unhealthy) or social reasons including patient request

Legal Issues
- no current law in Canada concerning abortion therefore considered legal at any gestational age
- CPSO: a physician must refer for abortion services regardless of personal beliefs but not compelled to perform procedure

Rates
- 24 induced abortions / 100 Live births in Canada (2010 data)
- worldwide: 42 million induced abortions per year; half are unsafe (WHO data)
  - maternal mortality almost zero where induced abortion is safe and legal; rises to 100 maternal deaths/100 000 live births in sub-Saharan Africa and other countries where abortion is illegal and unsafe
  - in Canada, 75% of induced abortions occur <16 weeks GA; very rare after 24 weeks (usually only for maternal/fetal reasons)

Methods of induced abortion
- medical
  - gold standard up to 9 weeks GA: mifepristone and misoprostol: 95-98% effective
  - Mifepristone blocks the progesterone receptor (progesterone required in early pregnancy)
  - Misoprostol induces uterine contractions
  - can also use misoprostol alone or methotrexate and misoprostol (with lower success rates of 90-95%)
  - side effects: bleeding (self-limited) and pain (while tissue passes) are expected side effects
- surgical
  - <14 wk:
    - manual vacuum aspiration – up to about 8-9 weeks with hand held aspiration device
    - suction dilatation + aspiration ± curettage may involve pre-surgical preparation of cervix with laminaria tents and/or misoprostol
  - 14-24 weeks: dilatation and evacuation; pre-surgical preparation of cervix required with laminaria tents
  - pain or discomfort during procedure mitigated by use of appropriate analgesia/sedation/anesthesia (including paracervical blocks)
  - rare complications (1-5%): laceration of cervix, infection/endometritis, retained products of conception, ongoing pregnancy
  - very rare complications: (0.1-2%): hemorrhage, perforation of uterus, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), future preterm birth (controversial and likely only with repeated abortion)
- counselling
  - options counselling always provided; always offer possibility of carrying pregnancy with/without adoption
  - offer future contraception and family planning services
  - ensure follow-up

There is no association between termination of pregnancy and either future breast cancer or future development of psychiatric disease.
Pregnancy-Related Complications

Spontaneous Abortions

- see Termination of Pregnancy for therapeutic abortions

Table 13. Classification of Spontaneous Abortions

<table>
<thead>
<tr>
<th>Type</th>
<th>History</th>
<th>Clinical</th>
<th>Management (± Rhogam®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened</td>
<td>Vaginal bleeding ± cramping</td>
<td>Cervix closed and soft</td>
<td>Watch and wait &lt;5% go on to abort</td>
</tr>
<tr>
<td>Inevitable</td>
<td>Increasing bleeding and cramps ± rupture of membranes</td>
<td>Cervix closed until products start to expel, then external os opens</td>
<td>a) Watch and wait b) Misoprostol 400-800 µg PO/PV c) D&amp;C</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Extremely heavy bleeding and cramps ± passage of tissue noticed</td>
<td>Cervix open</td>
<td>a) Watch and wait b) Misoprostol 400-800 µg PO/PV c) D&amp;C</td>
</tr>
<tr>
<td>Complete</td>
<td>Bleeding and complete passage of sac and placenta</td>
<td>Cervix closed bleeding stopped</td>
<td>No D&amp;C – expectant management</td>
</tr>
<tr>
<td>Missed</td>
<td>No bleeding (fetal death in uterus)</td>
<td>Cervix closed</td>
<td>a) Watch and wait b) Misoprostol 400-800 µg PO/PV c) D&amp;C</td>
</tr>
<tr>
<td>Recurrent</td>
<td>≥3 consecutive spontaneous abortions</td>
<td></td>
<td>Evaluate mechanical, genetic, environmental, and other risk factors</td>
</tr>
<tr>
<td>Septic</td>
<td>Contents of uterus infected – infrequent</td>
<td></td>
<td>IV broad spectrum antibiotics for 24 h followed by uterine evacuation</td>
</tr>
</tbody>
</table>

Ectopic Pregnancy

Definition
- embryo implants outside of the endometrial cavity

Figure 14. Sites of ectopic pregnancy implantation
ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

Epidemiology
- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)
Ectopic Pregnancy

Etiology
- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube

Risk Factors
- previous ectopic pregnancy
- gynecologic
  - current IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with C. trachomatis), salpingitis
  - infertility
  - infertility treatment (IVF pregnancies following ovulation induction [7% ectopic rate])
  - previous procedures
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
- smoking
- structural
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

Investigations
- serial β-hCG levels normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
  - rise of <20% of β-hCG is 100% predictive of a non-viable pregnancy
  - prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - specific finding on transvaginal U/S is a tubal ring
  - suspect ectopic in case of empty uterus by TVUS with β-hCG >2000-3000mIU/ml
- laparoscopy (sometimes used for definitive diagnosis)

Treatment
- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical = laparoscopy
  - linear salpingostomy an option if tube salvageable, however, patient must be reliable to follow-up with weekly β-hCG
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
  - 15% risk of persistent trophoblast if salpingectomy; must monitor β-hCG titles weekly until they reach non-detectable levels
  - consider Rhogam® if Rh negative
  - may require laparotomy if patient is unstable, extensive abdominal surgical history, etc.

DDx of Lower Abdominal Pain
- Urinary tract: UTI, kidney stones
- GI: diverticulitis, appendicitis
- Gyn: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

Any woman presenting with abdominal pain, vaginal bleeding and amenorrhea is an ectopic pregnancy until proven otherwise

Figure 15. Algorithm for suspected ectopic pregnancy
• medical = methotrexate (for indications see Figure 4)
  ■ use 50 mg/m2 body surface area; given in a single IM dose
  ■ this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)
  ■ follow β-hCG levels weekly until β-hCG is non-detectable
    • plateau or rising levels suggest persisting trophoblastic tissue (requires further treatment)
  ■ 82-95% success rate, but up to 25% will require a second dose
  ■ administer a second dose if β-hCG does not decrease by at least 15% between days 4 and 7
  ■ tubal patency following methotrexate treatment approaches 80%

**Prognosis**
• 9% of maternal deaths during pregnancy
• 40-60% of patients will become pregnant again after surgery
• 10-20% will have subsequent ectopic pregnancy

---

### Infertility

**Epidemiology**
• 10-15% of couples, must investigate both members of the couple

**Female Factors**

**Etiology**
• ovulatory dysfunction (15-20%)
  ■ hypothalamic (hypothalamic amenorrhea)
    • stress, poor nutrition, excessive exercise (even with presence of menstruation), history of eating disorders
  ■ pituitary (prolactinoma, hypopituitarism)
  ■ ovarian
    • PCOS
    • primary ovarian insufficiency
    • luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  ■ systemic diseases (thyroid, Cushing's syndrome, renal/hepatic failure), diabetes
  ■ congenital anomalies (Turner's syndrome, gonadal dysgenesis or gonadotropin deficiency)
• outflow tract abnormality (15-20%)
  ■ tubal factors (20-30%)
    • PID
    • adhesions (previous surgery, peritonitis, endometriosis)
    • ligation/occlusion (e.g. previous ectopic pregnancy)
  ■ uterine factors (<5%)
  ■ cervical factors (5%)
    ■ hostile or acidic cervical mucus, anti-sperm antibodies
    ■ structural defects (cone biopsies, laser or cryotherapy)
• endometriosis (15-30%)
• multiple factors (30%)
• unknown factors (10-15%)

**Investigations**
• ovulatory
  • day 3: FSH, LH, TSH, prolactin ± DHEA free testosterone (if hirsute) add estradiol for proper FSH interpretation
  • day 21-23: serum progesterone to confirm ovulation
  • initiate basal body temperature monitoring (biphasic pattern)
  • postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
• tubal factors
  ■ HSG (can be therapeutic – opens fallopian tube)
  ■ SHG (can be therapeutic; likely less – opens fallopian tube)
  ■ laparoscopy with dye insufflation (or tubal dye test) rarely done as diagnostic
  ■ peritoneal/uterine factors
  ■ HSG/SHG, hysteroscopy
• other
  ■ karyotype

---

### Contraindications to Methotrexate Therapy for Ectopic Pregnancy
• Abnormalities in hematologic, hepatic or renal function
• Immune deficiency
• Active pulmonary disease
• Peptic ulcer disease
• Hypersensitivity to methotrexate
• Heterotopic pregnancy with coexisting viable intrauterine pregnancy
• Breastfeeding
• Unwilling or unable to adhere to methotrexate protocol

### When Should Investigations Begin?
• <35 yr: after 1 yr of regular unprotected intercourse
• 35-40 yr: after >6 mo
• >40 yr: immediately
• Earlier if
  • History of PID
  • History of infertility in previous relationship
  • Prior pelvic surgery
  • Chemotherapy/rad ation in either partner
  • Recurrent pregnancy loss
  • Moderate severe endometriosis

### Controversial and Evolving Ethical Issues
• Infertility demands non-judgmental discussion
• Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial
• If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician
Polycystic Ovarian Syndrome

**Etiology**
- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptoorchidism (~8%)
- immunologic (~3%)

**Investigations**
- semen analysis and culture
- postcoital (Huhner) test: rarely done

**Male Factors**
- see Urology, U34

**Treatment**
- education: timing intercourse relative to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
- medical
  - ovulation induction
    - clomiphene citrate (Clomid®): estrogen antagonist causing a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; which increases FSH and LH and induces ovulation (better results if anovulatory)
  - followed by β-hCG for stimulation of ovum release
  - Letrozole: aromatase inhibitor. May be associated with a higher rate of live births in patients with PCOS
  - may add
    - bromocriptine (dopamine agonist) if elevated prolactin
    - dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
    - metformin (for PCOS)
  - luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
  - anticoagulation and ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
  - thyroid replacement to keep TSH <2.5
- surgical/procedural
  - tubuloplasty
  - lysis of adhesions
  - artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intratubal insemination (ITI)
  - sperm washing
  - IVP (in vitro fertilization)
  - IFT (intrafallopian transfer)
    - GIFT® (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
    - ZIFT® (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
    - TET* (tubal embryo transfer): transfer after >24 h culture
    - ICSI (intracytoplasmic sperm injection)
    - IVM (in vitro maturation)
    - ± oocyte or sperm donors
- ± pre-genetic screening for single gene defects in karyotype of zygote

*not performed in Canada

**Polycystic Ovarian Syndrome**
- also called chronic ovarian androgenism

**Etiology**
- polycystic ovarian syndrome – HAIR-AN
  - Hirsutism
  - Hyperandrogenism
  - Infertility
  - Insulin Resistance
  - Acanthosis Nigricans

**Insulin**
- ↑ estrogen
  - ↓ FSH secretion + ↑ LH secretion
  - ↓ Anovulation
  - ↑ peripheral conversion to estrogen
  - ↓ ovarian secretion of androgens
  - ↓ Oligomenorrhea
  - ↓ Hirsutism
  - ↓ Infertility

*Figure 16. Pathophysiology of polycystic ovarian syndrome*
Polycystic Ovarian Syndrome

Diagnosis
- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence - hirsutism or acne or
    - biochemical evidence - raised free testosterone
  - polycystic ovaries on U/S (not appropriate in adolescents)

Clinical Features
- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis as adolescence resembles PCOS
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- acanthosis nigricans: browning of skin folds in intertriginous zones (indicative of insulin resistance)
- insulin resistance occurs in both lean and obese patients
- family history of DM

Investigations
- goal: identify hyperandrogenism or chronic anovulation; and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, 17-hydroxyprogesterone, free testosterone, DHEA-S, TSH, free T4, androstenedione, SHBG
  - LH:FSH >2:1; LH is chronically high with FSH mid-range or low (low sensitivity and specificity)
  - increased DHEA-S, androstenedione and free testosterone (most sensitive), decreased SHBG
  - transvaginal or transabdominal U/S: polycystic-appearing ovaries ("string of pearls" – 12 or more small follicles 2-9 mm, or increased ovarian volume)
  - tests for insulin resistance or glucose tolerance
    - fasting glucose:insulin ratio <4.5 is consistent with insulin resistance (U.S. units)
    - 75 g OGTT yearly (particularly if obese)
- laparoscopy
  - not required for diagnosis
  - most common to see white, smooth, sclerotic ovaries with a thick capsule; multiple follicular cysts in various stages of atresia; hyperplastic theca and stroma
- rule out other causes of abnormal bleeding

Treatment
- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - OCP monthly or cyclic Provera* to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if type 2 diabetic or if trying to become pregnant
  - tranexamic acid (Cyklokapron*) for menorrhagia only
  - infertility
    - medical induction of ovulation: clomiphene citrate, letrozole, human menopausal gonadotropins (HMG [Pergonal®]), LHRH, recombinant FSH, and metformin
    - metformin may be used alone or in conjunction with clomiphene citrate for ovulation induction
    - ovarian drilling (perforate the stroma), wedge resection of the ovary
    - bromocriptine (if hyperprolactinemia)
  - hirsutism
    - any OCP can be used
      - Diane 35* (cyproterone acetate): antiandrogenic
      - Yasmin* (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
    - mechanical removal of hair
    - finasteride (5-a reductase inhibitor)
    - flutamide (androgen reuptake inhibitor)
    - spironolactone: androgen receptor inhibitor

Conclusions
- Metformin increases the likelihood of ovulation (OR 4.39, 95% CI 1.45-9.40). The effect of combination therapy was most prominent in clomiphene-resistant and obese women with PCOS. Furthermore, the combination therapy had a higher likelihood of having a live birth compared to clomiphene alone, but this did not reach significance (OR 1.74, 95% CI 0.79-3.86).

Results
- 1,639 patients with PCOS were followed up for up to 12 mo.
- Compared to placebo, metformin increased the odds of ovulation (OR 2.94, 95% CI 1.43-6.02). However, when used alone, metformin did not significantly increase the odds of achieving pregnancy (OR 1.36, 95% CI 0.74-2.33). When compared to clomiphene alone, the combination of metformin and clomiphene increased the likelihood of ovulation (OR 4.39, 95% CI 1.94-9.56) and pregnancy (OR 2.67, 95% CI 1.45-4.94). The effect of combination therapy was most prominent in clomiphene-resistant and obese women with PCOS.
- Metformin increases the likelihood of ovulation and pregnancy, especially in clomiphene-resistant and obese women.

Use of Metformin in Polycystic Ovary Syndrome: A Meta-Analysis
- Obstet Gynecol 2000;111(4):859-68
- Study: This meta-analysis of 17 RCTs assessed the efficacy of metformin or metformin in combination with clomiphene citrate in women with PCOS who were seeking pregnancy.
- Main Outcomes: Ovulation, pregnancy, and live birth. Patients: 1,639 patients with PCOS were followed up for up to 12 mo.
- Results: Compared to placebo, metformin increased the odds of ovulation (OR 2.94, 95% CI 1.43-6.02). However, when used alone, metformin did not significantly increase the odds of achieving pregnancy (OR 1.36, 95% CI 0.74-2.33). When compared to clomiphene alone, the combination of metformin and clomiphene increased the likelihood of ovulation (OR 4.39, 95% CI 1.94-9.56) and pregnancy (OR 2.67, 95% CI 1.45-4.94). The effect of combination therapy was most prominent in clomiphene-resistant and obese women with PCOS. Furthermore, the combination therapy had a higher likelihood of having a live birth compared to clomiphene alone, but this did not reach significance (OR 1.74, 95% CI 0.79-3.86).
- Conclusions: Metformin increases the likelihood of ovulation and pregnancy. When used together with clomiphene, metformin increases the likelihood of both ovulation and pregnancy, especially in clomiphene-resistant and obese women.
Gynecological Infections

Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 3.8–4.2
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features
  - irritation, pruritus
  - discharge
  - vulvar erythema
  - vaginal bleeding (specifically due to Group A Streptococci and Shigella)
- differential diagnosis
  - non-specific vulvovaginitis (25–75%)
  - infections (respiratory, enteric, systemic, sexually acquired)
  - foreign body (toilet paper most common)
  - Candida (if using diapers, chronic antibiotics or chronically immunosuppressed)
  - pinworms
  - polyps, tumour (ovarian malignancy)
  - vulvar skin disease (lichen sclerosis, condyloma acuminata)
  - trauma (accidental straddle injury, sexual abuse)
  - psychosomatic vaginal complaints (specific to vaginal discharge)
  - endocrine abnormalities (specific to vaginal bleeding)
  - blood dyscrasia (specific to vaginal bleeding)
- etiology
  - infectious:
    - poor hygiene, proximity of vagina to anus
    - recent infection (respiratory, enteric, systemic)
    - STI: investigate sexual abuse
  - non-specific:
    - lack of protective hair and labial fat pads
    - lack of estrogenization
    - susceptible to chemicals, soaps (bubble baths), medications, and clothing
    - enuresis
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
  - pH, wet-mount, and KOH smear in adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no
    tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate
    fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

<table>
<thead>
<tr>
<th>Table 14</th>
<th>Other Common Causes of Vulvovaginitis in Prepubertal Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Pinworms</td>
</tr>
<tr>
<td></td>
<td>Cellophane tape test</td>
</tr>
<tr>
<td>Treatment</td>
<td>Empirical treatment with mebendazole</td>
</tr>
</tbody>
</table>
INFECTIONAL VULVOVAGINITIS

Table 15. Infectious Vulvovaginitis

| Organisms        | Candi
dias          | Bacterial Vaginosis (BV)                                      | Trichomoniasis                        |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>(90%)</td>
<td>Candida glabrata (≤5%)</td>
<td>Trichomonas vaginalis (flagellated protozoan)</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>(&lt;5%)</td>
<td>Mycoplasma hominis</td>
<td></td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>(&lt;5%)</td>
<td>Anaerobes: Prevotella, Mobiluncus, Bacteroides</td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology or Transmission

<table>
<thead>
<tr>
<th>Predisposing factors include:</th>
<th>Replacement of vaginal Lactobacillus with organisms above</th>
<th>Sexual transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressed host (DM, AIDS, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent antibiotic use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased estrogen levels (e.g. pregnancy, OCP)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discharge

| Whitish, “cottage cheese,” minimal | Grey, thin, diffuse | Yellow-green, malodorous, diffusely frothy |

Other

| 20% asymptomatic | 50-75% asymptomatic | 25% asymptomatic |

Signs/Symptoms

<table>
<thead>
<tr>
<th>Intense pruritus</th>
<th>Swollen, inflamed genitals</th>
<th>Fishy odour especially after coitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvar burning, dysuria, dyspareunia</td>
<td>Absence of vulvar/vaginal irritation</td>
<td>Petechiae on vagina and cervix</td>
</tr>
<tr>
<td>Fishy odour especially after coitus</td>
<td>Occasional irritated tender vulva</td>
<td></td>
</tr>
<tr>
<td>Dysuria, frequency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

pH

| ≤4.5 | ≥4.5 | ≥4.5 |

Saline Wetmount

<table>
<thead>
<tr>
<th>KOH wetmount reveals hyphae and spores</th>
<th>&gt;20% clue cells = squamous epithelial cells dotted with coccobacilli (Gardnerella)</th>
<th>Motile flagellated organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paucity of WBC</td>
<td>Many WBC</td>
</tr>
<tr>
<td></td>
<td>Paucity of Lactobacilli</td>
<td>Inflammatory cells (PMNs)</td>
</tr>
<tr>
<td></td>
<td>Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)</td>
<td>Can have positive whiff test</td>
</tr>
</tbody>
</table>

Treatment

<table>
<thead>
<tr>
<th>Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments</th>
<th>No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure</th>
<th>Treat even if asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment in pregnancy is usually topical</td>
<td>Oral Metronidazole 500 mg PO bid x 7 d</td>
<td>Metronidazole 2 g PO single dose or 500 mg bid x 7 d (alternative)</td>
</tr>
<tr>
<td>Fluconazole 150 mg PO in single dose (can be used in pregnancy)</td>
<td>Topical Metronidazole gel 0.75% x 5 d OD (may be used in pregnancy)</td>
<td>Symptomatic pregnant women should be treated with 2 g metronidazole once</td>
</tr>
<tr>
<td>Clindamycin 2% 5 g intravaginally at bedtime for 7 d</td>
<td>Clindamycin 2% 5 g intravaginally at bedtime for 7 d</td>
<td></td>
</tr>
<tr>
<td>Probiotics (lactobacillus sp.): oral or topical alone or as adjuvant</td>
<td>Probiotics (lactobacillus sp.): oral or topical alone or as adjuvant</td>
<td></td>
</tr>
</tbody>
</table>

Other

<table>
<thead>
<tr>
<th>Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole</th>
<th>Associated with recurrent preterm labour, preterm birth, and postpartum endometritis</th>
<th>Warnings accompanying metronidazole use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine treatment of partner(s) not recommended (not sexually transmitted)</td>
<td>Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)</td>
<td></td>
</tr>
<tr>
<td>Routine treatment of partner(s) not recommended (not sexually transmitted)</td>
<td>Routine treatment of partner(s) not recommended (not sexually transmitted)</td>
<td></td>
</tr>
</tbody>
</table>

Sexually Transmitted Infections

- see Family Medicine, FM42
TRICHOMONIASIS
• see Infectious Vulvovaginitis, Table 15

CHLAMYDIA

Etiology
• Chlamydia trachomatis

Epidemiology
• most common bacterial STI in Canada
• often associated with N. gonorrhoeae

Clinical Features
• asymptomatic (80% of women)
• muco-purulent endocervical discharge
• urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
• pelvic pain
• postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
• symptomatic sexual partner

Investigations
• cervical culture or nucleic acid amplification test
• obligate intracellular parasite: tissue culture is the definitive standard
• urine and self vaginal tests now available which are equally or more effective than cervical culture

Treatment
• doxycycline 100 mg PO bid for 7 d or azithromycin 1 g PO in a single dose (may use in pregnancy)
• also treat gonorrhea because of high rate of co-infection
• treat partners
• reportable disease
• test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

Screening
• high risk groups
• during pregnancy
• when initiating OCP if sexually active (independent risk factor)

Complications
• PID – low grade salpingitis and adhesions resulting in tubal obstruction
• infertility
• ectopic pregnancy
• chronic pelvic pain
• Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
• reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
• perinatal infection: conjunctivitis, pneumonia

GONORRHEA

Etiology
• Neisseria gonorrhoeae
• symptoms and risk factors same as with chlamydia

Investigations
• Gram stain shows Gram-negative intracellular diplococci
• cervical, rectal, and throat culture (if clinically indicated)

Treatment
• single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
• if pregnant: above regimen or 2 g spectinomycin IM plus azithromycin 1 g PO (avoid quinolones)
• also treat chlamydia, because of high rate of co-infection
• treat partners
• reportable disease
• screening as with chlamydia
HUMAN PAPILLOMAVIRUS

Etiology
- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

Investigations
- cytology
- koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
- patient administered
  - podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  - imiquimod (Aldara*) 5% cream 3x/wk qhs x 16 wk
- provider administered
  - cryotherapy with liquid nitrogen: repeat q1-2wk
  - podophyllin resin in tincture of benzoin: weekly
  - trichloroacetic acid (TCA) (80-90%) or bichloroacetic acid weekly X4-6wks; safe in pregnancy
  - surgical removal/laser
  - intralesional interferon

Prevention
- vaccination: Gardasil® 9, Gardasil®, Cervarix® see Table 25, GY43
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

HERPES SIMPLEX VIRUS OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: present 2-21 d after contact
- prodromal symptoms: tingling, burning, pruritus
- multiple painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent and shorter in duration (usually only HSV-2)

Investigations
- viral culture preferred in patients with ulcer present, however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear) shows multinucleated giant cells, acidophilic intranuclear inclusion bodies
- HSV DNA PCR
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)
Treatment
• first episode
  - acyclovir 400 mg PO tid x 7-10 d or acyclovir 200 mg PO five times daily x 7-10 d or valacyclovir 1g PO bid x 7-10 d or famciclovir 250 mg PO tid x 7-10 d
• recurrent episode
  - acyclovir 400 mg PO tid x 5 d or acyclovir 800 mg PO bid x 5 d or acyclovir 800 mg PO tid x 2 d or valacyclovir 500 mg PO bid x 3 d or valacyclovir 1 g PO OD x 5 d or famciclovir 125 mg PO bid x 5 d or famciclovir 1 g PO bid x 1 d or famciclovir 500 mg PO x 1 d followed by 250 mg PO bid x 2 d
• daily suppressive therapy
  - consider for >6 recurrences per yr or one every 2 mo
  - acyclovir 400 mg PO bid or valacyclovir 500 mg PO OD or valacyclovir 1 g PO OD or famciclovir 250 mg PO bid
  - severe disease: IV acyclovir 5-10 mg/kg IV q8h x 2-7 d or until clinical improvement observed followed by oral antiviral therapy to complete 10 d of therapy total
  - education regarding transmission
  - avoid contact from onset of prodrome until lesions have cleared
  - use barrier contraception

SYPHILIS
Etiology
• Treponema pallidum

Classifications
• primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
• secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based fleshy grey lesions
  - serological tests usually positive
• latent syphilis
  - no clinical manifestations; detected by serology only
• tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate and become necrotic (rare)
• congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

Investigations
• aspiration of ulcer serum or node
• darkfield microscopy (most sensitive and specific diagnostic test for syphilis)
• spirochetes
• non-treponemal screening tests (VDRL, RPR); non-reactive after treatment, can be positive with other conditions
• specific anti treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment
• treat partners
• reportable disease
• treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
• treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
• treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
• screening
  - high risk groups
  - in pregnancy (see Obstetrics, Table Infections During Pregnancy, OB29)

Complications
• if untreated, 1/3 will experience late complications

HIV
• see Infectious Diseases, ID27
Bartholin Gland Abscess

**Etiology**
- often anaerobic and polymicrobial
- *U. urealyticum*, *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *P. mirabilis*, *Streptococcus* spp., *S. aureus* (rare)
- blockage of duct

**Clinical Features**
- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

**Treatment**
- sitz baths, warm compresses
- antibiotics: cephalexin x 1 wk
- incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk (or as long as stays in situ)
- marsupialization under general anesthetic – more definitive treatment
- rarely treated by removing gland

Pelvic Inflammatory Disease

**Etiology**
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
    - gonorrhea and chlamydia often co-exist
  - endogenous flora: anaerobic, aerobic, or both
    - *E. coli*, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Bacteroides*, *Peptostreptococcus*, *H. influenzae*, *G. vaginalis*
  - cause of recurrent PID
  - associated with instrumentation
  - *Actinomyces israelii* (Gram-positive, non acid-fast anaerobe)
    - 1-4% of PID cases associated with IUDs
    - others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

**Risk Factors**
- age <30 yr
- risk factors as for chlamydia and gonorrhea
- vaginal douching
- IUD (within first 10 d after insertion)
- invasive gynecologic procedures (D&C, endometrial biopsy)

**Clinical Presentation**
- up to 2/3 asymptomatic: many subtle or mild symptoms
- common: fever >38.3°C, lower abdominal pain and tenderness, abnormal discharge: cervical or vaginal
- uncommon: N/V, dysuria, AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

**Investigations**
- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for *N. gonorrhoeae*, *C. trachomatis*
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrocolpos (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

**PID Diagnosis**
- Must have
  - Lower abdominal pain
  - Plus one of
    - Cervical motion tenderness
    - Adnexa tenderness
  - Plus one or more of
    - High risk partner
    - Temperature >38°C
    - Mucopurulent cervical discharge
    - Positive culture for *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, or other vaginal flora
    - Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
    - Leukocytosis
    - Elevated ESR or CRP (not commonly used)
Treatment

- must treat with polymicrobial coverage
- inpatient if:
  - moderate to severe illness
  - atypical infection
  - adnexal mass, tubo-ovarian mass, or pelvic abscess
  - unable to tolerate oral antibiotics or failed oral therapy
  - immunocompromised
  - pregnant
  - adolescent – first episode
  - surgical emergency cannot be excluded (e.g. ovarian torsion)
  - PID is secondary to instrumentation
  - recommended treatment
    - Regimen A: cefoxitin 2 g IV q6h PLUS doxycycline 100 mg IV/PO q12h
    - Regimen B: clindamycin 900 mg IV q8h PLUS gentamicin loading dose 2 mg/kg IV/IM followed by 1.5 mg/kg IV/IM q8h
    - continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO bid to complete 14 d
    - percutaneous drainage of abscess under U/S guidance
    - when no response to treatment, laparoscopic drainage
    - if failure, treatment is surgical (salpingectomy, TAH/BSO)
- outpatient if:
  - typical findings
  - mild to moderate illness
  - oral antibiotics tolerated
  - compliance ensured
  - follow-up within 48-72 h (to ensure symptoms not worsening)
  - recommended treatment (Regimen A OR Regimen B)
    - Regimen A, 1 of:
      - ceftriaxone 250 mg IM x 1 PLUS doxycycline 100 mg PO bid x 14 d ± metronidazole 500 mg PO bid x 14 d
      - cefoxitin 2 g IM PLUS probenecid 1 g PO x 1 PLUS doxycycline 100 mg PO bid x 14 d ± metronidazole 500 mg PO bid x 14 d
    - Regimen B, 1 of:
      - ofloxacin 400 mg PO bid x 14 d ± metronidazole 500 mg PO bid x 14 d
      - levofloxacin 500 mg PO bid OD x 14 d ± metronidazole 500 mg PO BI bid D x 14 d
  - consider removing IUD after a minimum of 24 h of treatment
  - reportable disease
  - treat partners
  - consider re-testing for C. trachomatis and N. gonorrhoeae 4-6 wk after treatment if documented infection

Complications of Untreated PID

- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID → 13% infertility
  - 2 episodes of PID → 36% infertility
- bacteremia
- septic arthritis, endocarditis

Toxic Shock Syndrome

[see Infectious Diseases, ID23]

Risk Factors

- tampon use
- diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

Clinical Presentation

- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness
Sexual Abuse

Treatment
- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics, e.g. cloxacillin
- steroid use controversial but if started within 72 h, may reduce severity of symptoms and duration of fever

Surgical Infections

Post-Operative Infections in Gynecological Surgery
- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, discharge involving vaginal cuff
  - treat if fever and leukocytosis with broad spectrum antibiotics, i.e. clindamycin and gentamicin
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see General Surgery, Post-Operative Fever, GS7

Sexual Abuse

- see Family Medicine, FM26, Emergency Medicine, ER27

Sexuality and Sexual Dysfunction

SEXUAL RESPONSE
1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

SEXUAL DYSFUNCTION

Etiology
- psychological or emotional: depression, abuse
- hormonal: menopause
- neurologic dysfunction: spinal cord injury
- vascular insufficiency: DM
- drug side effects: β-blockers
- trauma: episiotomy

Classification
- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but now unable to
- dyspareunia (3-6%): painful intercourse, superficial or deep
  - vaginismus (15%)
  - vulvodynia
  - vaginal atrophy
  - vulvar vestibulitis: associated with history of frequent yeast infections
  - PID

Treatment
- lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
- dyspareunia
  - Kegel and reverse Kegel exercises
  - dilator treatment
  - comfort with self-exam
  - psychotherapy, other behavioural techniques
  - female on top position: allows for control of speed and duration
  - vestibulitis: remove local irritants, change in contraceptive methods, dietary changes (increased citrate, decreased oxalate), and vestibulectomy (rare)
  - vulvodynia: local moisturization, cold compresses, systemic nerve blocking therapy (amitriptyline, gabapentin) orally or topically, topical anesthetics, estrogen cream
  - pain clinic
  - removal of environmental factors – bubble baths, soaps, perfumes, sanitary pads with plastic lining

Kegel Exercises
- Regular contraction and relaxation to strengthen pelvic floor muscles
- Reverse Kegel Exercises
  - 1 s contraction then 5 s of relaxation
Menopause

• see Family Medicine, FM40

Definitions

• lack of menses for 1 yr

• types of menopause
  • physiological; average age 51 yr (follicular atresia)
  • primary ovarian insufficiency; before age 40 (autoimmune disorder, infection, Turner’s syndrome)
  • iatrogenic (surgical/radiation/chemotherapy)

Clinical Features

• associated with estrogen deficiency
  • vasomotor instability (tends to dissipate with time)
    • hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, palpitations
  • urogenital atrophy involving vagina, urethra, bladder
    • dyspareunia, pruritus, vaginal dryness, bleeding, post-coital bleeding, urinary frequency, urgency, incontinence
    • inspection may reveal: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  • skeletal
    • osteoporosis, joint and muscle pain, back pain
  • skin and soft tissue
    • decreased breast size, skin thinning/loss of elasticity
  • psychological
    • mood disturbance, irritability, fatigue, decreased libido, memory loss

Investigations

• increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
• FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
• decreased levels of estradiol (later)

Treatment

• goal is for individual symptom management
  • vasomotor instability
    • HRT (first line), SSRIs, venlafaxine, gabapentin, propranolol, clonidine
  • acupuncture
  • vaginal atrophy
    • local estrogen: cream (Premarin*), vaginal suppository (VagiFem*), ring (Estring*)
    • lubricants (Replens*)
    • oral or transdermal hormone replacement therapy (if treatment for systemic symptoms is desired)
    • intravaginal laser
  • urogenital health
    • lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery
  • osteoporosis
    • 1,000-1,500 mg calcium OD, 800-1,000 IU vitamin D, weight-bearing exercise, smoking cessation
    • bisphosphonates (e.g. alendronate)
    • selective estrogen receptor modifiers (SERMs): raloxifene (Evista*) – mimics estrogen effects on bone, avoids estrogen-like action on breast and uterine cancer; does not help hot flashes
    • HRT: second-line treatment (unless for vasomotor instability as well)
  • decreased libido
    • vaginal lubrication, counselling, androgen replacement (testosterone cream or the oral form Androli*)
  • cardiovascular disease
    • management of cardiovascular risk factors
  • mood and memory
    • antidepressants (first line), HRT (augments effect)
  • alternative choices (not evidence-based, safety not established)
    • black cohosh, phytoestrogens, St. John’s wort, gingko biloba, valerian, evening primrose oil, ginseng, Don Quai

Menopause

Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins)

“Being in menopause”
Lack of menses for 1 yr

Perimenopause
Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset

• 85% of women experience hot flashes
• 20-30% seek medical attention
• 10% are unable to work

Menopause Pathophysiology

Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)

Less estrogen is produced

Decreased negative feedback on hypothalamic-pituitary-adrenal axis

Increased FSH and LH

Stromal cells continue to produce androgens as a result of increased LH stimulation

Osteoporosis is the single most important health hazard associated with menopause

Cardiovascular disease is the leading cause of death post-menopause

Increased risk of breast cancer (RR 1.3) is associated with estrogen+progesterone HRT, but not with estrogen-only HRT

All women taking HRT should have periodic surveillance and counselling regarding its benefits and risks
Hormone Replacement Therapy

- see Family Medicine, FM40
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin\textsuperscript{®}) and duration of treatment short (<5 yr)

HRT Components

- estrogen
- oral or transdermal (e.g. patch, gel)
- transdermal preferred for women overall, especially with hypertriglyceridemia or impaired hepatic function, smokers, and women who suffer from headaches associated with oral HRT
- low-dose (preferred dose: 0.3 mg Premarin\textsuperscript{®}/25 µg Estradot\textsuperscript{®} patch, can increase if necessary)
- progestin
- given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

Table 16. Examples of HRT Regimens

<table>
<thead>
<tr>
<th>HRT Regimen</th>
<th>Estrogen Dose</th>
<th>Progestin Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed</td>
<td>CEE 0.625 mg PO OD</td>
<td>None</td>
<td>If no intact uterus</td>
</tr>
<tr>
<td>Standard-Dose</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 2.5 mg PO OD, or micronized progestrone 100 mg PO OD</td>
<td>Withdrawal bleeding may occur in a spotty, unpredictable manner Usually abates after 6-8 mo due to endometrial atrophy Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy)</td>
</tr>
<tr>
<td>Standard-Dose</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 5-10 mg PO days 1-14 only, or micronized progestrone 200 mg PO OD days 1-14 only</td>
<td>Bleeding occurs monthly after day 14 of progestin (can continue for years) PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT</td>
</tr>
<tr>
<td>Cyclic</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA low-dose</td>
<td>3 d on, 3 d off</td>
</tr>
<tr>
<td>Pulsatile</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA low-dose</td>
<td>Use patch twice weekly Can use oral progestins (Estrodern\textsuperscript{®}) Combined patches available (Estalis\textsuperscript{®})</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Estrodern\textsuperscript{®}-Estradiol 0.05 mg/d or 0.1 mg/d Estalis\textsuperscript{®}-Estradiol 140 µg/d or 250 µg/d</td>
<td>Estrodern\textsuperscript{®}-MPA 2.5 mg PO OD Estalis\textsuperscript{®} NEA 50 µg/d</td>
<td>Use patch twice weekly Can use oral progestins (Estrodern\textsuperscript{®}) Combined patches available (Estalis\textsuperscript{®})</td>
</tr>
<tr>
<td>Topical</td>
<td>Estrace\textsuperscript{®} 2-4 g/d x 1-2 wk, 1 g/d maintenance Premarin\textsuperscript{®} 0.5-2 g/d for 21 d then off 7 d for vaginal atrophy, 0.5 g/d for 21 d then off 7 d or twice/wk for dyspareunia Estragyn\textsuperscript{®} 2-4 g/d</td>
<td>Crinone\textsuperscript{®} 4% or 8% (45 or 90 mg applicator)</td>
<td>If simultaneously taking oral estrogen tablet, may need to adjust dosing If intact uterus, also take progesterone</td>
</tr>
</tbody>
</table>

CEE = conjugated equine estrogen (e.g. Premarin\textsuperscript{®}); MPA = medroxyprogesterone acetate (e.g. Provera\textsuperscript{®}); NEA = norethindrone acetate
Consider lower dose regimens, PREMPRO\textsuperscript{®} 0.45/1.5 (Premarin\textsuperscript{®} 0.45 mg and Provera\textsuperscript{®} 1.5 mg), Estrace\textsuperscript{®} (topical 17β-estradiol) = 0.1 mg active ingredient/g; Premarin\textsuperscript{®} (topical CEE) = 0.625 mg active ingredient/g; Estragyn\textsuperscript{®} (topical estrone) = 1 mg active ingredient/g

Side Effects of HRT

- abnormal uterine bleeding
- mastodynia: breast tenderness
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

Contraindications to HRT

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - history of breast cancer
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - DM (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

Absolute Contraindications to HRT

<table>
<thead>
<tr>
<th>ABCD</th>
<th>Acute liver disease</th>
<th>Undiagnosed vaginal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>Cancer (breast/uterine)</td>
<td>Cardiovacular disease</td>
</tr>
<tr>
<td>BD</td>
<td>DVT (thromboembolic disease)</td>
<td></td>
</tr>
</tbody>
</table>
WOMEN'S HEALTH INITIATIVE (launched in 1991)

- two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old
  - continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
  - estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy
- both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE, and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm
- the apparent increase in CHD was in disagreement with results of previous observational trial
- results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results
- benefits and risks reported as number of cases per 10,000 women each year

<table>
<thead>
<tr>
<th>Benefits/Effects</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Symptoms: less frequent and severe with use of either combined or estrogen-alone HRT</td>
<td>Stroke: 8 additional cases with combined HRT, and 12 additional cases for estrogen alone (WHI)</td>
</tr>
<tr>
<td>Osteoporosis: 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT; 6 fewer cases of hip fractures with estrogen alone</td>
<td>DVT/PE: 18 additional cases with combined HRT, and 9 additional cases for estrogen-alone (WHI)</td>
</tr>
<tr>
<td>Colon Cancer: 6 fewer cases with combined HRT (WHI)</td>
<td>CHD: 7 additional MIs with combined HRT (WHI); secondary analysis suggests greater absolute risk for women aged &gt;70 yr and for women who start HRT &gt;10 yr post-menopause</td>
</tr>
<tr>
<td>One additional case with estrogen-alone</td>
<td>Breast Cancer: 8 additional cases with combined HRT (WHI); risk only increased after &gt;5 yr of combined HRT use; no increased risk for estrogen-alone</td>
</tr>
<tr>
<td>Dementia and Mild Cognitive Impairment: 50% greater risk of developing dementia in women taking estrogen alone after age 65; risk is greater for women taking combined HRT; risk of developing dementia was reduced for women taking HRT before age 65</td>
<td></td>
</tr>
</tbody>
</table>

Table 17. HRT Benefits vs Risks

Figure 21. Pelvic anatomy
Prolapse

Etiology
• relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
• related to:
  ■ vaginal childbirth
  ■ aging
  ■ decreased estrogen (post-menopause)
  ■ following pelvic surgery
  ■ increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  ■ congenital (rarely)
  ■ ethnicity (Caucasian women > Asian or African women)
  ■ collagen disorders

GENERAL CONSERVATIVE TREATMENT
(for pelvic relaxation/prolapse and urinary incontinence)
• Kegel exercises
• local vaginal estrogen therapy
• vaginal pessary (intravaginal suspension disc)

Table 18. Pelvic Prolapse

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystocele</td>
<td>(protrusion of bladder into the anterior vaginal wall)</td>
<td>Frequency, urgency, nocturia Stress incontinence Incomplete bladder emptying ± associated increased incidence of UTIs – may lead to renal impairment</td>
</tr>
<tr>
<td>Enterocele</td>
<td>(prolapse of small bowel in upper posterior vaginal wall)</td>
<td>Straining/digitation to evacuate stool Constipation</td>
</tr>
<tr>
<td>Rectocele</td>
<td>(protrusion of rectum into posterior vaginal wall)</td>
<td>Straining/digitation to evacuate stool Constipation</td>
</tr>
<tr>
<td>Uterine Prolapse</td>
<td>(protrusion of cervix and uterus into vagina)</td>
<td>Groin/back pain (stretching of uterosacral ligaments) Feeling of heaviness/pressure in the pelvis Worse with standing, lifting Worse at the end of the day Relieved by lying down Ulceration/bleeding (particularly if hypoestrogenic) ± urinary incontinence</td>
</tr>
<tr>
<td>Vault Prolapse</td>
<td>(protrusion of apex of vaginal vault into vagina, post-hysterectomy)</td>
<td></td>
</tr>
</tbody>
</table>

Urinary Incontinence

• see Urology, U5

STRESS INCONTINENCE

Definition
• involuntary loss of urine with increased intra-abdominal pressure (coughing, laughing, sneezing, walking, running)

Risk Factors for Stress Incontinence in Women
• pelvic prolapse
• pelvic surgery
• vaginal delivery
• hypoestrogenic state (post-menopause)
• age
• smoking
• neurological/pulmonary disease
Treatment
- see Prolapse, General Conservative Treatment, GY37
- surgical
  - tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

URGE INCONTINENCE

Definition
- urine loss associated with an abrupt, sudden urge to void
- “overactive bladder”
- diagnosed based on symptoms

Etiology
- idiopathic (90%)
- detrusor muscle overactivity (“detrusor instability”)

Associated Symptoms
- frequency, urgency, nocturia, leakage

Treatment
- behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
- Kegel exercises
- medications
  - anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  - tricyclic antidepressants: imipramine

Gynecological Oncology

Uterus

ENDOMETRIAL CARCINOMA

Epidemiology
- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5 yr survival for stage I disease
- 70-80% 5 yr survival for all stages

Clinical Classifications
- Type I is usually characterized as estrogen-related (i.e. excess/unopposed estrogen)
  - includes well-differentiated endometrioid adenocarcinoma
- Type II is usually characterized as non-estrogen related
  - includes serous, clear cell, grade 4 endometrioid and undifferentiated carcinomas as well as carcinosarcoma
  - more aggressive histologic subtypes; prognosis typically worse than type I, with a poorer 5 yr survival
- note: types above have been classified based on typical estrogen dependence. Type II tumours also associated with estrogen factors, but to a lesser degree than Type I

Risk Factors
- general: increasing age and FHx
- Type I, commonly known as “estrogen-related”
  - PCOS
  - Diabetes mellitus
  - unbalanced HRT (balanced HRT is protective)
  - nulliparity
  - late menopause (>55 yr), early menarche
  - estrogen-producing ovarian tumours (e.g. granulosa cell tumours)
  - HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome
  - tamoxifen
- Type II, commonly known as “non-estrogen related”
  - obesity (though stronger association with Type I)
  - early menarche
  - nulliparity
  - diabetes mellitus
  - increasing age of menarche and number of children not significantly associated with reduced risk in clear-cell endometrial carcinoma
  - has been associated with p53 mutations

Incidence of Malignant Gynecological Lesions in North America
- endometrium > ovary > cervix > vulva > vagina > fallopian tube

Risk Factors for Endometrial Cancer
- COLD NUT
  - Cancer (ovarian, breast, colon)
  - Obesity
  - Late menopause
  - Diabetes mellitus
  - Nulliparity
  - Unopposed estrogen: PCOS, anovulation, HRT
  - Tamoxifen: chronic use

Postmenopausal bleeding = endometrial cancer until proven otherwise (95% present with vaginal bleeding)

An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding
Screening
• no known benefit for mass screening
• routine pelvic ultrasound should not be used as screening test (high false positives)

Clinical Features
• Type I (well-differentiated endometrioid adenocarcinoma) ~80% of cases
  • postmenopausal bleeding in majority, abnormal uterine bleeding in majority of affected premenopausal women (menorrhagia, intermenstrual bleeding)
• Type II (serous, clear cell carcinoma, grade 3 endometrioid, undifferentiated, carcinosarcoma) ~15% of cases
  • may not present with bleeding in early stage, more likely to present with advanced stage disease with symptoms like ovarian cancer (i.e. bloating, bowel dysfunction, pelvic pressure)
  • pelvic exam usually shows normal sized uterus unless there are fibroids, sarcomas or other uterine pathologies associated

Investigations
• endometrial sampling
  • office endometrial biopsy
  • D&C ± hysteroscopy
• ± pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
  • not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

Table 19. FIGO Staging of Endometrial Cancer (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to corpus</td>
<td>IIIC</td>
<td>Metastasis to pelvic ± para-aortic LNs</td>
</tr>
<tr>
<td>IA</td>
<td>No or less than half myometrial invasion</td>
<td>IIIC1</td>
<td>Positive pelvic LN</td>
</tr>
<tr>
<td>IB</td>
<td>Invades through ≥1/2 of myometrium</td>
<td>IIIC2</td>
<td>Positive para-aortic LN ± positive pelvic LNs</td>
</tr>
<tr>
<td>II</td>
<td>Tumour invades cervical stroma, but does not extend beyond uterus*</td>
<td>IV</td>
<td>Invasion of bladder ± bowel mucosa ± distant metastases</td>
</tr>
<tr>
<td>III</td>
<td>Local and/or regional spread of tumour</td>
<td>IVA</td>
<td>Invasion of bladder ± bowel mucosa</td>
</tr>
<tr>
<td>IIIA</td>
<td>Invasion of serosa, corpus uteri ± adnexae</td>
<td>IVB</td>
<td>Distant mets, including intra-abdominal mets ± inguinal LNs</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal ± parametrical involvement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

Treatment
• surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
  • goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
  • laparoscopic approach associated with improved quality of life (optimal for most patients)
• adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
• chemotherapy: often used for recurrent disease (especially if high grade or aggressive histology)
• hormonal therapy: progestins can be used for recurrent disease (especially if low grade)

UTERINE SARCOMA
• rare; 2-6% of all uterine malignancies
• arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
• behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5-yr survival is 35%
• vaginal bleeding is most common presenting symptom
Protective Factors (for epithelial ovarian cancers)

Table 21. FIGO Staging of Uterine Sarcoma (2009)

<table>
<thead>
<tr>
<th>Type</th>
<th>Epidemiology</th>
<th>Features</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURE TYPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1. Leiomyosarcoma         | Most common type of uterine sarcoma  
                              Average age of presentation is 55 yr but may present in pre-menopausal women  
                              Often coexists with benign leiomyomatosis (fibroids)                      | Histologic distinction from leiomyoma  
                              1. Increased mitotic count (>10 mitoses/10 high power fields)  
                              2. Tumour necrosis  
                              3. Cellular atypia  
                              Rapidly enlarging fibroids in a pre-menopausal woman  
                              Enlarging fibroids in a postmenopausal woman                      | Often post-operatively after uterus removed for presumed fibroids  
                              Stage using FIGO 2009 staging for leiomyosarcomas and ECC          | Hysterectomy/BSO usually  
                              No routine pelvic lymphadenectomy  
                              Chemotherapy is used in cases of metastatic disease  
                              Radiation therapy does not improve local control or survival  
                              Poor outcomes overall, even for early stage disease            |
| 2. Endometrial Stromal Sarcoma (ESS) | Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding | Abnormal uterine bleeding  
                              Good prognosis                                                                 | Diagnosed by histology of endometrial biopsy or D&C  
                              Stage using FIGO 2009 staging for leiomyosarcomas and ECC          | Hysterectomy & BSO (remove ovaries as ovaries may stimulate growth)  
                              No routine pelvic lymphadenectomy  
                              Adjunct therapy based on stage and histologic features (hormones and/or radiation)  
                              Hormonal therapy (progestins) may be used for metastatic disease |
| 3. Undifferentiated Sarcoma | Rare; less common than leiomyosarcoma, endometrial stromal sarcoma         | Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack smooth muscle or endometrial stromal differentiation  
                              Poor prognosis                                                                 | Often found incidentally post-operatively for abnormal bleeding      | Treatment primarily surgical  
                              Radiation and/or chemotherapy for advanced diseased or unresctectable disease |
| MIXED TYPE                |                                                                              |                                                                          |                                                                          |                                                                          |
| 4. Adenosarcoma           | The rarest of the uterine sarcoma  
                              Mixed tumour of low malignant potential                                    | Present with abnormal vaginal bleeding  
                              Polypoid mass in uterine cavity                                      | Mixture of benign epithelium with malignant low grade sarcoma         | Treatment is surgical with hysterectomy and BSO                           |

Table 20. Summary of Uterine Sarcoma Subtypes and Features

<table>
<thead>
<tr>
<th>Type</th>
<th>Epidemiology</th>
<th>Features</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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                              1. Increased mitotic count (>10 mitoses/10 high power fields)  
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                              3. Cellular atypia  
                              Rapidly enlarging fibroids in a pre-menopausal woman  
                              Enlarging fibroids in a postmenopausal woman                      | Often post-operatively after uterus removed for presumed fibroids  
                              Stage using FIGO 2009 staging for leiomyosarcomas and ECC          | Hysterectomy/BSO usually  
                              No routine pelvic lymphadenectomy  
                              Chemotherapy is used in cases of metastatic disease  
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                              Poor outcomes overall, even for early stage disease            |
| 2. Endometrial Stromal Sarcoma (ESS) | Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding | Abnormal uterine bleeding  
                              Good prognosis                                                                 | Diagnosed by histology of endometrial biopsy or D&C  
                              Stage using FIGO 2009 staging for leiomyosarcomas and ECC          | Hysterectomy & BSO (remove ovaries as ovaries may stimulate growth)  
                              No routine pelvic lymphadenectomy  
                              Adjunct therapy based on stage and histologic features (hormones and/or radiation)  
                              Hormonal therapy (progestins) may be used for metastatic disease |
| 3. Undifferentiated Sarcoma | Rare; less common than leiomyosarcoma, endometrial stromal sarcoma         | Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack smooth muscle or endometrial stromal differentiation  
                              Poor prognosis                                                                 | Often found incidentally post-operatively for abnormal bleeding      | Treatment primarily surgical  
                              Radiation and/or chemotherapy for advanced diseased or unresctectable disease |
| MIXED TYPE                |                                                                              |                                                                          |                                                                          |                                                                          |
| 4. Adenosarcoma           | The rarest of the uterine sarcoma  
                              Mixed tumour of low malignant potential                                    | Present with abnormal vaginal bleeding  
                              Polypoid mass in uterine cavity                                      | Mixture of benign epithelium with malignant low grade sarcoma         | Treatment is surgical with hysterectomy and BSO                           |

Ovary

**BENIGN OVARIAN TUMOURS**
- see Table 22
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
  - peritoneal irritation may result from an infarcted tumour – rare

**MALIGNANT OVARIAN TUMOURS**
- see Table 22

**Epidemiology**
- lifetime risk 1.4%  
  - in women >50 yr, more than 50% of ovarian tumours are malignant
  - causes more deaths in North America than all other gynecologic malignancies combined
  - 4th leading cause of cancer death in women
  - 85% epithelial; 15% non-epithelial
  - 10-15% of epithelial ovarian cancers are related to hereditary predisposition

**Risk Factors (for epithelial ovarian cancers)**
- personal history of breast, colon, endometrial cancer
- family history of breast, colon, endometrial, ovarian cancer
- use of fertility drugs

**Protective Factors (for epithelial ovarian cancers)**
- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
- pregnancy/breastfeeding
- salpingectomy (prophylactic)
- BSO (prophylactic surgery performed for this reason in high risk women – i.e. BRCA mutation carriers)
### Screening
- no effective method of mass screening
- routine CA-125 level measurements or U/S not recommended
- high false positive rates
- controversial in high risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
  - familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
  - other cancers (e.g. endometrial, breast, colon)
  - BRCA-1 or BRCA-2 mutation: recommendation is prophylactic bilateral oophorectomy after age 35 or when child-bearing is completed

### Clinical Features
- most women with epithelial ovarian cancer present with advanced stage disease since often “asymptomatic” until disseminated disease (symptoms with early stage disease are vague and non-specific)
- when present, symptoms may include
  - abdominal symptoms (nausea, bloating, dyspepsia, anorexia, early satiety)
  - symptoms of mass effect
    - increased abdominal girth – from ascites or tumour itself
    - urinary frequency
    - constipation

### Low Malignant Potential (also called “Borderline”) Tumours
- a subcategory or epithelial ovarian cancer (~15% of all epithelial ovarian tumours)
- pregnancy, OCP, and breastfeeding are protective factors
- tumour cells with histologically malignant characteristics arise from the ovarian surface, but do not invade ovarian stroma.
- able to metastasize, but not commonly
- treated primarily with surgery (BSO/omentectomy ± hysterectomy)
  - NO proven benefit of chemotherapy
  - generally slow growing, excellent prognosis
  - 5yr survival >99%
  - recurrences tend to occur late, may be associated with low grade serous carcinoma

### Table 22. Ovarian Tumours

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNCTIONAL TUMOURS</strong> (all benign)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular Cyst</td>
<td>Follicle fails to rupture during ovulation</td>
<td>Usually asymptomatic</td>
<td>4-8 cm mass, unilocular, lined with granulosa cells</td>
<td>Symptomatic or suspicious masses warrant surgical exploration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May rupture, bleed, tort, infant causing pain ± signs of peritoneal irritation</td>
<td></td>
<td>Ovarian suppression – will prevent development of new cysts</td>
</tr>
<tr>
<td>Corpus Luteum Cyst</td>
<td>Corpus luteum fails to regress after 14 d. becoming cystic or hemorrhagic</td>
<td>More likely to cause pain than follicular cyst</td>
<td>Larger (10-15 cm) and firmer than follicular cyst</td>
<td>Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)</td>
</tr>
<tr>
<td>Theca-Lutein Cyst</td>
<td>Due to atretic follicles stimulated by abnormal β-hCG levels</td>
<td>Associated with molar pregnancy, ovulation induction with clomiphene</td>
<td></td>
<td>Conservative Cyst will regress as β-hCG levels fall</td>
</tr>
<tr>
<td>Endometrioma</td>
<td>See Endometriosis, GY13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic Ovaries</td>
<td>See Polycystic Ovarian Syndrome, GY24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BENIGN CYSTIC TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign Cystic Teratoma (dermoid)</td>
<td>Single most common ovarian germ cell neoplasm</td>
<td>Usually children and young women (&lt; 30 yr)</td>
<td>Surgical resection (often conservative unilateral salpingo- oophorectomy ± nodes) ± chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)</td>
<td>May rupture, twist, infant 20% bilateral 20% occur outside of reproductive yr</td>
<td>Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic</td>
<td>Treatment usually laparoscopic cystectomy, may recur</td>
</tr>
<tr>
<td><strong>MALENGNANT GERM-CELL TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Rapidly growing, 2-3% of all ovarian cancers</td>
<td>Usually children and young women (&lt; 30 yr)</td>
<td>Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>Produces LDH</td>
<td>10% bilateral</td>
<td>When diagnosed at stage IA – no adjuvant treatment is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure</td>
<td></td>
</tr>
<tr>
<td>Immature Teratoma</td>
<td>No tumour marker identified</td>
<td>Almost always unilateral</td>
<td>When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated Grade 2-3: either adjuvant chemo or surgical staging If diagnosed at advanced stage very responsive to chemotherapy, therefore complete resection is not necessary for cure</td>
<td></td>
</tr>
</tbody>
</table>
### Table 22. Ovarian Tumours (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPITHELIAL OVARIAN TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(malignant or borderline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Derived from mesothelial cells lining peritoneal cavity</td>
<td></td>
<td>Varies depending on subtype</td>
<td>Borderline</td>
</tr>
<tr>
<td></td>
<td>Classified based on histologic type</td>
<td></td>
<td></td>
<td>Cystectomy vs. unilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td></td>
<td>80-85% of all ovarian neoplasms (includes malignant)</td>
<td></td>
<td></td>
<td>Malignant</td>
</tr>
<tr>
<td>Serous</td>
<td>Most common ovarian tumour</td>
<td>20-30% bilateral</td>
<td>Lining similar to fallopian tube epithelium</td>
<td>Resembles endocervical epithelium</td>
</tr>
<tr>
<td></td>
<td>50% of all ovarian cancers</td>
<td></td>
<td>Often multilocular</td>
<td>Often multilocular</td>
</tr>
<tr>
<td></td>
<td>75% of epithelial tumours</td>
<td></td>
<td>Histologically contain</td>
<td>Histologic hallmark of cancer is small groups of</td>
</tr>
<tr>
<td></td>
<td>70% benign</td>
<td></td>
<td>Psamomma bodies</td>
<td>cells known as Call-Exner bodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>20% of epithelial tumours</td>
<td></td>
<td>Poor response to chemotherapy</td>
<td>If mucinous, remove appendix as well to rule out possible source of primary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SEX CORD STROMAL OVARIAN TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibroma/Thecoma</strong></td>
<td>From mature fibroblasts in ovarian stroma</td>
<td></td>
<td>Non-functioning</td>
<td>Surgical resection of tumour</td>
</tr>
<tr>
<td>(benign)</td>
<td>Occasionaly associated with Meig’s syndrome</td>
<td></td>
<td>Firm, smooth rounded tumour with interlacing fibrocytes</td>
<td>Chemotherapy may be used for unresectable metastatic disease</td>
</tr>
<tr>
<td><strong>Granulosa-Theca</strong></td>
<td>Can be associated with endometrial cancer</td>
<td></td>
<td>Estrogen producing → feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding)</td>
<td>Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies</td>
</tr>
<tr>
<td><strong>Cell Tumours</strong></td>
<td>Inhibin is tumour marker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(benign or malignant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sertoli-Leydig</strong></td>
<td>Can measure elevated androgens as tumour markers</td>
<td></td>
<td>Androgen-producing → virilizing effects (hirsutism, deep voice, recession of front hairline)</td>
<td></td>
</tr>
<tr>
<td><strong>Cell Tumour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(benign or malignant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>METASTATIC OVARIAN TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From GI</td>
<td>4-8% of ovarian malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tract, Breast, Endometrium, Lymphoma</td>
<td>4-8% of ovarian malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Knuebenberg tumour – metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>with “signet-ring” cells</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Investigation of Suspicious Ovarian Mass
- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
- bimanual examination
  - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
- RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynecologic oncology referral (see sidebar, GY??)
- physical exam findings largely dependent on stage of disease
- blood work: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
- radiology
  - transvaginal ultrasound best to visualize ovaries
  - CT abdomen and pelvis to look for metastatic disease
  - bone scan or PET scan not indicated
- try to rule out other primary source if suspected, based on:
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms: gastroscopy ± upper GI series
  - abnormal vaginal bleeding: endometrial biopsy to rule out concurrent endometrial cancer; abnormal cervix: need to biopsy cervix (NOT pap smear) breast lesion identified or risk factors present: mammogram

![Effects of Screening on Ovarian Cancer Mortality: The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Randomized Controlled Trial](image)
Malignant Cervical Lesions

- **Etiology**
  - at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
  - during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from columnar to squamous)
  - a new squamocolumnar junction forms as a result
  - the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction
  - the majority of dysplasias and cancers arise in the TZ of the cervix
  - must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
  - dysplasia → carcinoma in situ (CIS) → invasion
  - slow process (~10 yr on average)
  - growth is by local extension
  - metastasis occurs late

**Risk Factors**
- HPV infection
  - see Sexually Transmitted Infections, GY27
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
  - high risk behaviours (risk factors for HPV infection)
    - multiple partners
    - other STIs (HSV, trichomonas)
    - early age at first intercourse
    - high risk male partner

### Table 23. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2014)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>Extension ± implants to uterus/tubes</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension to other pelvic structures</td>
</tr>
<tr>
<td>IIIA</td>
<td>Positive retroperitoneal LN's and/or microscopic metastasis beyond pelvis</td>
</tr>
<tr>
<td>IIIC</td>
<td>Same as above but peritoneal metastasis &gt; 2 cm</td>
</tr>
<tr>
<td>IVB</td>
<td>Metastasis to extra-abdominal organs (inguinal LNs and LNs outside of abdominal cavity)</td>
</tr>
<tr>
<td>IVC</td>
<td>Distant metastasis beyond peritoneal cavity</td>
</tr>
<tr>
<td>IVA</td>
<td>Pleural effusion with positive cytology</td>
</tr>
<tr>
<td>IVB</td>
<td>Hepatic and/or splenic parenchymal metastasis or metastasis to extra-abdominal organs (inguinal LNs and LNs outside of abdominal cavity included)</td>
</tr>
<tr>
<td>IIIB</td>
<td>Macroscopic peritoneal metastasis beyond pelvis ±2 cm, ± positive retroperitoneal LN's</td>
</tr>
<tr>
<td>IIIC</td>
<td>Same as above but peritoneal metastasis &gt; 2 cm</td>
</tr>
</tbody>
</table>

**Cervix**

**Benign Cervical Lesions**
- Nabothian cyst/inclusion cyst
- no treatment required
- endocervical polyps
- treatment is polypectomy (office procedure)

**Malignant Cervical Lesions**

**Epidemiology**
- majority are SCC (70%); adenocarcinomas increasing (25%); rare subtypes include small cell, adenosquamous
- 8,000 deaths annually in North America
- annual Pap test reduces a woman's chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

**Figure 22. The cervix**

Cervical cancer is most prevalent in developing countries and therefore is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies, such as CT and MRI.
Cervical Cancer Screening Guidelines (Pap Test)

- see Family Medicine, FM5

Clinical Features

- SCC: exophytic, fungating tumour
- adenocarcinoma: endophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
- postcoital bleeding
- late
  - 80-90% present with bleeding; either postcoital, postmenopausal or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix

Diagnosis

- colposcopy is a clinical procedure that facilitates identification and biopsy of suspicious cells
- in colposcopy:
  - apply acetic acid and identify acetowhite lesions, punctuation, mosaicism, and abnormal blood vessels to guide cervical biopsy
  - endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
  - diagnostic excision (LEEP) if:
    - unsatisfactory colposcopy (poor visualization/access to transformation zone)
    - discrepancy between cytology, colposcopy, and histological findings
    - positive findings/glandular abnormalities in endocervical curettage
    - suspicious for adenocarcinoma in situ (consider cold-knife conization)
    - recurrence of lesion post-ablation or excision
    - inability to rule out invasive disease, i.e. large lesions (lesions extending into endocervical canal, extending widely on cervix, or onto vaginal epithelium)
- consider cold knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including examination under anesthesia), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, IVP, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

Figure 23. Decision making chart for Pap test (not applicable for adolescents)
Adapted from: Ontario Cervical Screening Practice Guidelines. May 2012. Cervical screening guidelines unique to each province

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. Cervical intraepithelial neoplasia (CIN) or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

CA-125 is indicated for monitoring response to treatment

Causes of Elevated CA-125

- Age influences reliability of test as a tumour marker
- 50% sensitivity in early stage ovarian cancer (poor) – therefore not good for screening
  - Malignant
    - Gyn: ovary, uterus
    - Non-Gyn: pancreas, stomach, colon, rectum
  - Non-Malignant
    - Gyn: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
    - Non-Gyn: cr hoss, pancreatitis, renal failure

• smoking
• poor screening uptake is the most important risk factor for cervical cancer in Canada
• at-risk groups include:
  - immigrant Canadians
  - First Nations Canadians
  - geographically isolated Canadians
  - sex-trade workers
  - low socioeconomic status
Table 24. FIGO Staging Classification of Cervical Cancer (Clinical Staging) (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to cervix</td>
</tr>
<tr>
<td>IA</td>
<td>Microinvasive (diagnosed only by microscopy)</td>
</tr>
<tr>
<td>IA1</td>
<td>Stromal invasion not &gt;3 mm deep, not &gt;7 mm wide</td>
</tr>
<tr>
<td>IA2</td>
<td>3-5 mm deep; not &gt;7 mm wide</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically visible lesion confined to cervix, or micoscopic lesion &gt;IA</td>
</tr>
<tr>
<td>IB1</td>
<td>Clinically visible lesion ≤4 mm in greatest dimension</td>
</tr>
<tr>
<td>IB2</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>II</td>
<td>Beyond uterus but not to the pelvic wall or lower 1/3 of vagina</td>
</tr>
<tr>
<td>IIA</td>
<td>No obvious parametrical involvement</td>
</tr>
<tr>
<td>IIA1</td>
<td>Clinically visible lesion ≤4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIA2</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>Obvious parametrical involvement</td>
</tr>
<tr>
<td>III</td>
<td>Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IIIA</td>
<td>Involves lower 1/3 vagina but no extension into pelvic side wall</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IV</td>
<td>Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread of the growth to adjacent organs (bladder or rectum)</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

Treatment: Prevention and Management

Prevention: HPV Vaccine
- two vaccines currently approved (Gardasil®, Cervarix®)

Table 25. Comparison of Two Vaccines against Human Papillomavirus (HPV)

<table>
<thead>
<tr>
<th></th>
<th>Gardasil®</th>
<th>Cervarix®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Strains Covered</td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>Schedule of Dosing</td>
<td>0, 2, 6 mo</td>
<td>0, 1, 6 mo</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Local: redness, pain, swelling General: headache, low grade fever, GI upset</td>
<td>Local: redness, pain, swelling General: headache, low grade fever, GI upset</td>
</tr>
<tr>
<td>Approved Age</td>
<td>Females age 9-45, males age 9-26</td>
<td>Females age 10-25</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnant women and women who are nursing (limited data)</td>
<td></td>
</tr>
</tbody>
</table>

*Gardasil-9 also covers types 31, 33, 45, 52, and 58; also used to prevent genital warts

- should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
- may be given at the same time as hepatitis B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 d after last dose of vaccination
Table 26. Management of Patients Abnormal Cervical Histology and Cervical Cancer

<table>
<thead>
<tr>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CIN I</strong></td>
</tr>
<tr>
<td>Preferred option for biopsy-proven CIN I is observation</td>
</tr>
<tr>
<td>Repeat assessment and cytology in 12 mo</td>
</tr>
<tr>
<td>Management according to cytology results</td>
</tr>
<tr>
<td>If after HSIL or ASC:</td>
</tr>
<tr>
<td>Cytology and histology should be reviewed</td>
</tr>
<tr>
<td>If discrepancy remains, excisional biopsy may be considered</td>
</tr>
<tr>
<td><strong>CIN II and CIN III</strong></td>
</tr>
<tr>
<td>Women ≥25 yr:</td>
</tr>
<tr>
<td>CIN II or III should be treated</td>
</tr>
<tr>
<td>Excisional procedures preferred for CIN III</td>
</tr>
<tr>
<td>Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage</td>
</tr>
<tr>
<td>Women &lt;25 yr:</td>
</tr>
<tr>
<td>Same treatment for CIN II and CIN III: observe with colposcopy at 6-mo intervals for up to 24 mo before treatment considered</td>
</tr>
<tr>
<td>During pregnancy:</td>
</tr>
<tr>
<td>CIN II or III suspected or diagnosed during pregnancy, repeat colposcopy and treatment delayed until 8-12 wk after delivery</td>
</tr>
<tr>
<td><strong>Stage IA1 (no LVS1)</strong></td>
</tr>
<tr>
<td>LEEP if future fertility desired (and lesion ≤2 cm)</td>
</tr>
<tr>
<td>Simple hysterectomy if future fertility is not desired</td>
</tr>
<tr>
<td><strong>Stage IA2 IB1</strong></td>
</tr>
<tr>
<td>Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study)</td>
</tr>
<tr>
<td>If high chance of adjuvant radiation then consider primary chemoradiation as more morbidity occurs from double modality treatment (surgery and radiation) (Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted ad. vant therapy)</td>
</tr>
<tr>
<td>Advantage is that ovaries can be spared if pre menopausal</td>
</tr>
<tr>
<td>For fertility preservation (if tumour &lt; 2cm), may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease</td>
</tr>
<tr>
<td>Chemoradiation therapy if adverse high risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins or adverse cervical factors (2 or more): deep stromal invasion, size &gt; 4 cm, LVS1</td>
</tr>
<tr>
<td><strong>Stages IB2 (&gt;4 cm), II, III, IV</strong></td>
</tr>
<tr>
<td>Primary chemoradiation therapy</td>
</tr>
<tr>
<td>CT assess extent of disease: evaluate pelvic and para-aortic nodes</td>
</tr>
<tr>
<td>For positive nodes on PET: primary chemoradiation with extended field RT</td>
</tr>
<tr>
<td>Hysterectomy generally not suggested following primary treatment with curative intent</td>
</tr>
</tbody>
</table>

Abnormal Pap Tests in Pregnancy
- incidence: 1/2,200
- Pap test at all initial prenatal visits
  - if abnormal Pap or suspicious lesion, refer to colposcopy
  - if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
  - if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
  - if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
    - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
    - recommendations in T2/T3: delay of therapy until viable fetus and C/S for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium
- biopsy is necessary to make diagnosis and/or rule out malignancy
- hyperplastic dystrophy (squamous cell hyperplasia)
  - surface thickened and hyperkeratotic
  - pruritus most common symptom
  - typically postmenopausal women
  - treatment: 1% fluorinated corticosteroid ointment bid for 6 wk
- lichen sclerosis
  - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
  - pruritus, dyspareunia, burning
  - figure of 8’ distribution
  - most common in postmenopausal women but can occur at any age
  - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down, can consider long term suppression twice a week
- mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
  - hyperkeratotic areas with areas of thin, shiny epithelium
  - treatment: fluorinated corticosteroid ointment
**Tumours**
- papillary hidradenoma, nevus, fibroma, hemangioma

**MALIGNANT VULVAR LESIONS**

**Epidemiology**
- 5% of genital tract malignancies
- 90% SCC; remainder melanomas, basal cell carcinoma, Paget’s disease, Bartholin’s gland carcinoma
  - Type I disease: HPV-related (50-70%)
    - more likely in younger women
    - 90% of vulvar intraepithelial neoplasia (VIN) contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    - usually postmenopausal women

**Risk Factors**
- HPV infection
- VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  - progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)

**Clinical Features**
- many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
  - localized pruritus or lesion most common
- less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal → pelvic nodes)
  - hematogenous

**Investigations**
- ± colposcopy
- ALWAYS biopsy any suspicious lesion
  - do not remove entire lesion so if malignant, site can be identified for sentinel LN injection

**Prognosis**
- depends on stage – particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

**Treatment**
- T1 lesions (tumour confined to vulva; no extension to adjacent perineal structures): Radical local excision
- T2 lesions (tumour of any size with extension to adjacent perineal structures): modified radical vulvectomy
- T3 lesions (extension to any of: proximal 2/3 of urethra, proximal 2/3 of the vagina, bladder mucosa, rectal mucosa or fixed to pelvic bone): chemoradiation followed by selective resection of residual primary
- node positive disease: adjuvant chemoradiation or radiation therapy

**Vagina**

**BENIGN VAGINAL LESIONS**
- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct, seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic
MALIGNANT VAGINAL LESIONS

Epidemiology
- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are SCC
- more than 50% diagnosed between 70-90 yr old

Risk Factors
- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations
- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy!)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are actually metastatic from one of these sites)
- staging

Clinical Features

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Intra-Epithelial Neoplasia (VAIN)</td>
<td>Grades: analogous to cervical dysplasia</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma (SCC)</td>
<td>Most common site is upper 1/3 of posterior wall of vagina&lt;br&gt;Asymptomatic&lt;br&gt;Painless discharge and bleeding&lt;br&gt;Vaginal discharge (often foul-smelling)&lt;br&gt;Vaginal bleeding especially during/post-coitus&lt;br&gt;Urinary and/or rectal symptom 2° to compression</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Most are metastatic, usually from cervix, endometrium, ovary, or colon&lt;br&gt;Most primaries are clear cell adenocarcinomas&lt;br&gt;2 types: non-DES and DES syndrome</td>
</tr>
</tbody>
</table>

Treatment
- Stage I
  - radiation therapy: for tumours >2 cm diameter or tumour involvement of the mid to lower vagina
  - surgical excision: radical hysterectomy, upper vaginectomy and bilateral pelvic lymphadenectomy
- Stage II - IV: chemoradiation

Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)
- usually serous epithelial carcinoma
- new evidence shows that some serous ovarian cancers originate in the fallopian tube
- more common in fifth and sixth decade

Clinical Features
- classic triad present in minority of cases, but very specific
  - watery discharge (most specific) = “hydrops tubae profluens”
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain
  - most patients present with a pelvic mass (see Ovarian Tumours, GY40 for guidelines regarding diagnosis/investigation)

Treatment
- as for malignant epithelial ovarian tumours
Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast

**Epidemiology**
- 1/1,000 pregnancies
- marked geographic variation – as high as 1/125 in Taiwan
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

**HYDATIDIFORM MOLE (Benign GTD)**

**Complete Mole**
- most common type of hydatidiform mole
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues, or membranes present
- 46XX or 46XY, chromosomes completely of paternal origin (90%)
- 2 sperm fertilize empty egg or 1 sperm with reduplication
- 15-20% risk of progression to malignant sequelae
- risk factors
  - geographic (South East Asia most common)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency) – not proven
- clinical features
  - often present during apparent pregnancy with abnormal symptoms/findings
  - vaginal bleeding (97%)
  - excessive uterine size for LMP (51%)
  - theca-lutein cysts >6 cm (50%)
  - preeclampsia (27%)
  - hyperemesis gravidarum (26%)
  - hyperthyroidism (7%)
  - β-hCG >100,000 IU/L
  - no fetal heart beat detected

**Partial (or Incomplete) Mole**
- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXY XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
- low risk of progression to malignant sequelae (<4%)
- associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations
- clinical features
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

**Investigations**
- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
- U/S findings
  - if complete: no fetus (classic “snow storm” due to swelling of villi)
  - if partial: molar degeneration of placenta ± fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - β-hCG >100,000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts

**Treatment**
- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- consider hysterectomy (if patient no longer desires fertility)
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

**Follow-Up**
- contraception required to avoid pregnancy during entire follow-up period
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of β-hCG indicates GTN → patient needs chemotherapy

With development of hypertonion early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease
GTN (MALIGNANT GTD)

Invasive Mole or Persistent GTN
- diagnosis made by rising or plateau in β-hCG, development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

Choriocarcinoma
- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

Placental-Site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

CLASSIFICATION of GTN
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - lungs (80%): cough, hemoptysis, CXR lesion(s)
    - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
    - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - liver (10%): elevated LFTs, U/S or CT findings
    - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
  - highly vascular tumour → bleeding → anemia
  - all have rising or plateau of β-hCG
  - classification of metastatic GTN
    - divided into good prognosis and bad prognosis
      - features of bad prognosis
        - long duration (>4 mo from antecedent pregnancy)
        - high pre-treatment β-hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood
        - brain or liver metastases
        - prior chemotherapy
        - metastatic disease following term pregnancy
      - good prognosis characterized by the absence of each of these features

Investigations – For Staging
- blood work: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis, CT abdo/pelvis, CT brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG
- ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases

Table 28. FIGO Staging and Management of Malignant GTN

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Management</th>
</tr>
</thead>
</table>
| I     | Disease confined to uterine corpus | Single agent chemotherapy for low risk disease (WHO score ≤ 6)  
  - 1st line: pulsed – actinomycin D (Act-D) IV q2wk  
  - Alternatives: MTX-based regimen  
  - 20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal  
  - Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single agent chemotherapy  
  - Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour |
| II    | Metastatic disease to genital structures | As above |
| III   | Metastatic disease to lungs with or without genital tract involvement | As above |
| IV    | Distant metastatic sites including brain, liver, kidney, GI tract | Usually high risk (EMA-CO) with surgical resection of sites of disease  
  - Persistence/resistance to chemotherapy  
  - Consider radiation for brain mets |
### Table 29. WHO Prognostic Score for GTD (2011)

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age</td>
<td>&gt;40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antecedent Pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval (end of Antecedent Pregnancy to chemotherapy in months)</td>
<td>&lt;4</td>
<td>4 6</td>
<td>7-13</td>
<td>&gt;13</td>
</tr>
<tr>
<td>HCG IU/1</td>
<td>&lt;103</td>
<td>103-104</td>
<td>104-105</td>
<td>&gt;105</td>
</tr>
<tr>
<td>Number of Metastases</td>
<td>0</td>
<td>1-4</td>
<td>5-8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Site of Metastases</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>GI tract</td>
<td>Brain, liver</td>
</tr>
<tr>
<td>Largest Tumour Mass</td>
<td>3-5 cm</td>
<td></td>
<td>&gt;5 cm</td>
<td></td>
</tr>
<tr>
<td>Prior Chemotherapy</td>
<td>Single drug</td>
<td></td>
<td>Two drug</td>
<td></td>
</tr>
</tbody>
</table>

### Follow-up (for GTN)
- Contraception for all stages to avoid pregnancy during entire follow-up period
  - stage I, II, III
    - weekly β-hCG until 3 consecutive normal results
    - then monthly x 12 mo
  - stage IV
    - weekly β-hCG until 3 consecutive normal results
    - then monthly x 24 mo

### GTN Diagnosis
- β-hCG plateau: <10% drop in β-hCG over four values in 3 wk (e.g. days 1, 7, 14, and 21) OR
- β-hCG rise >20% in any two values over two wk or longer (e.g. measure at days 1, 7, 14) OR
- β-hCG persistently elevated >6 mo OR
- metastases on workup

### Common Medications

#### Table 30. Common Medications

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Action</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acyclovir (Zovirax®)</td>
<td>Antiviral; inhibits DNA synthesis and viral replication</td>
<td>First Episode: 400 mg PO tid x 7-10 d Recurrence: 400 mg PO tid x 5 d</td>
<td>Genital herpes</td>
<td>S/E: headache, GI upset</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D/I: didoxuridine, probenecid</td>
</tr>
<tr>
<td>bromocriptine (Parlodel®)</td>
<td>Dopaminomimetic Agonist at D2R Antagonist at D1R</td>
<td>Initial: 1.25-2.5 mg PO qhs with food Then: increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response</td>
<td>Galactorrhea + amenorrhea</td>
<td>S/E: N/V, headache, postural hypotension, somnolence</td>
</tr>
<tr>
<td></td>
<td>Acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin</td>
<td>Usual Range: 1.5-15 mg DD For IF: Initial: 1.25 mg/d PO be ween days 4-6 of follicular phase Then: 2.5 mg/d until 3 d after onset menstruation</td>
<td>Prolactin-dependent menstrual disorders and infertility</td>
<td>C/I: uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolactin-secreting adenomas</td>
<td>D/I: domperidone, macrolides, octreotide</td>
</tr>
<tr>
<td>clomiphene citrate</td>
<td>Increases output of pituitary gonadotropins which induces ovulation</td>
<td>50 mg OD x 5 d Try 100 mg or 160 mg OD if ineffective 3 courses = adequate trial</td>
<td>Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS)</td>
<td>S/E: Common – hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz, menorrhagia, endometriosis, hyperplasia, polycystic ovarian syndrome, multiple pregnancy, visual blurring, birth defects</td>
</tr>
<tr>
<td>(Clomid®)</td>
<td></td>
<td></td>
<td>who desire pregnancy</td>
<td>C/I: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding</td>
</tr>
<tr>
<td>clotrimazole (Canesten®)</td>
<td>Antifungal; disrupt fungal cell membrane</td>
<td>Tablet: 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose Cream (1 or 2%) 1 applicator intravaginally ghs x 3-7 d</td>
<td>Vulvovaginal candidiasis</td>
<td>S/E: vulvar/vaginal burning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>danazol (Cyclomen® – CAN) (Danocrine® – US)</td>
<td>Synthetic steroid that inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties</td>
<td>200-800 mg in 2-3 divided doses Used for 3-8 mo Biannual hepatic U/S required if &gt;6 mo use</td>
<td>Endometriosis 1° menorrhagia/DUB</td>
<td>S/E: weight gain, acne, mild hirsutism, hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C/I: unplanned pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, nephrotic syndrome, liver disease, thromboembolic disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D/I: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives</td>
</tr>
<tr>
<td>Drug Name (Brand Name)</td>
<td>Action</td>
<td>Dosing Schedule</td>
<td>Indications</td>
<td>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------</td>
<td>-----------------</td>
<td>-------------</td>
<td>----------------------------------------------------------</td>
</tr>
</tbody>
</table>
| doxycycline | Tetracycline derivative; inhibit protein synthesis | 100 mg PO bid x ≥7 d | Chlamydia, gonococcal infection, syphilis | S/E: GI upset, hepatotoxicity  
C/I: pregnancy, severe hepatic dysfunction  
D/I: warfarin, digoxin |
| fluconazole (Diflucan<sup>®</sup>) | Antifungal; disrupt fungal cell membrane | 150 mg PO x 1 dose | Vulvovaginal candidiasis unresponsive to clotrimazole | S/E: headache, rash, N/V, abdominal pain, diarrhea  
C/I: tetracycline, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin |
| leuprolide (Lupron<sup>®</sup>) | Synthetic GnRH analog  
Induces reversible hypoestrogenic state | 3.75 mg IM q1 mo or 11.25 mg IM q3 mo  
Usually ≤6 mo, check bone density if >6 mo  
Retreatment with Lupron<sup>®</sup> alone not recommended because of effects on bone density | Endometriosis  
Leiomyomata  
DUB  
Precocious puberty | S/E: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset  
C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding |
| menotropin (Pergonal<sup>®</sup>) | Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development | 75-150 U of FSH and LH IM OD x 7 12 d, then 10,000 U HCG one day after last dose | Infertility | S/E: blushing, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy  
C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding |
| metronidazole (Flagyl<sup>®</sup>) | Bactericidal; forms toxic metabolites which damage bacterial DNA | 2 g PO x 1 dose or 500 mg PO bid x 7 d | Bacterial vaginosis, trichomonas vaginitis | S/E: headache, diziness, N/V, diarrhea, disulfiram-like reaction (flushing, tachycardia, N/V)  
C/I: pregnancy (1st trimester)  
D/I: cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine |
| oxybutinin (Ditropan<sup>®</sup>) | Anticholinergic – relaxes bladder smooth muscle, inhibits involuntary detrusor contraction | 5 or 10 mg/d PO  
May increase doses by 5 mg weekly to a max of 30 mg/d | Overactive bladder (urge incontinence) | S/E: dry mouth/eyes, constipation, palpitations, urinary retention, diziness, headache  
C/I: glaucoma, GI ischa, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function |
| tolterodine (Detrol<sup>®</sup>) | Anticholinergic | 1-2 mg PO bid | Overactive bladder (urge incontinence) | S/E: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain  
C/I: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function |
| tranexamic acid (Cyklokapron<sup>®</sup>) | Anti-fibrinolytic, reversibly inhibits plasminogen activation | 1-1.5 g tid-qid for first 4 d of cycle  
Max 4 g/d  
Ophthalmic check if used for several wk | Menorrhagia | S/E: N/V, diarrhea, diziness, rare cases of thrombosis, abdominal pain, MI/MIK pain  
C/I: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age <15 yr |
| ulipristal acetate (Fibristal<sup>®</sup>) | Selective progesterone receptor modulator (SPRM) | 5 mg PO OD for max 3 mo; first tablet taken anytime during first 7 days of menstruation | Leiomyoma (pre-operative) | S/E: headache, hot flushes, constipation, vertigo, endometrial thickening  
C/I: pregnancy, undiagnosed vaginal bleeding, any gynae cancer |
| urofollitropin (Metrodin<sup>®</sup>) | FSH | 75 U/d SC x 7-12d | Ovulation induction in PCOS | S/E: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy  
C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding |

**Table 30. Common Medications (continued)**
Acronyms .................................................. 2
Basics of Hematology ................................. 2
Complete Blood Count
Blood Film Interpretation
Bone Marrow Aspiration and Biopsy
Common Presenting Problems .................. 6
Anemia
Erythrocytosis
Thrombocytopenia
Thrombocytosis
Pancytopenia
Neutrophilia
Neutropenia
Lymphocytosis
Lymphopenia
Eosinophilia
Agranulocytosis
Leukemoid Reaction
Approach to Lymphadenopathy ............... 12
Approach to Splenomegaly ......................... 13
Microcytic Anemia .................................. 13
Iron Metabolism
Iron Deficiency Anemia
Anemia of Chronic Inflammation
Sideroblastic Anemia
Lead Poisoning
Normocytic Anemia ................................. 17
Aplastic Anemia
Normocytic Anemia ................................. 18
Thalassemia
β-Thalassemia Minor (Thalassemia Trait)
β-Thalassemia Major
β-Thalassemia Intermedia
α-Thalassemia
Sickle Cell Disease
Autoimmune Hemolytic Anemia
Microangiopathic Hemolytic Anemia/
Thrombotic Microangiopathy
Hereditary Spherocytosis
Hereditary Elliptocytosis
Glucose-6-Phosphate Dehydrogenase Deficiency
Macrocytic Anemia ................................ 23
Vitamin B12 Deficiency
Folate Deficiency
Hemostasis .............................................. 25
Stages of Hemostasis
Disorders of Primary Hemostasis ............ 27
Immune Thrombocytopenia
Thrombotic Thrombocytopenic Purpura
and Hemolytic Uremic Syndrome
von Willebrand Disease
Disorders of Secondary Hemostasis .......... 31
Hemophilia A (Factor VIII Deficiency)
Hemophilia B (Factor IX Deficiency)
Factor XI Deficiency
Liver Disease
Vitamin K Deficiency
Disseminated Intravascular Coagulation
Hypercoagulable Disorders ..................... 33
Venous Thromboembolism ....................... 35
Approach to Treatment of Venous
Thromboembolism
Hematologic Malignancies and
Related Disorders ................................. 37
Myeloid Malignancies .............................. 37
Acute Myeloid Leukemia
Myelodysplastic Syndromes
Myeloproliferative Neoplasms ............... 40
Chronic Myeloid Leukemia
Polycythemia Vera
Idiopathic Myelofibrosis
Essential Thrombocytemia
Lymphoid Malignancies ......................... 44
Acute Lymphoblastic Leukemia
Lymphomas ............................................ 45
Hodgkin Lymphoma
Non-Hodgkin Lymphoma
Malignant Clonal Proliferations of
Mature B-Cells ..................................... 48
Chronic Lymphocytic Leukemia
Multiple Myeloma
Monoclonal Gammapathy of Unknown
Significance
Lymphoplasmacytic Lymphoma
(Waldenstrom's Macroglobulinemia)
Complications of Hematologic Malignancies .. 51
Hyperviscosity Syndrome
Tumour Lysis Syndrome
Blood Products and Transfusions ............. 52
Red Blood Cells
Platelets
Coagulation Factors
Acute Blood Transfusion Reactions
Delayed Blood Transfusion Reactions
Common Medications ............................. 56
Antiplatelet Therapy
Anticoagulant Therapy
Chemotherapeutic and Biologic Agents Used
in Oncology
Landmark Hematology Trials .................. 59
References .......................................... 60
Hematopoiesis

- over $10^{11}$ blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies, cranium
- lifespan of mature cells in blood
  - erythrocytes (90-120 d), neutrophils (~1 d), platelets (7-10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - spleen: part of reticuloendothelial system, sequesters aged RBCs, removes opsonized cells, site of antibody production
  - thymus: site of T-cell maturation, invovles with age
- lymph nodes: sites of B and T-cell activation (adaptive immune response)
### Complete Blood Count

#### Table 1. Common Terms Found in the CBC

<table>
<thead>
<tr>
<th>Test</th>
<th>Definition</th>
<th>Normal Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red Blood Cell (RBC) Count</strong></td>
<td>The number of RBCs per volume of blood</td>
<td>4.2-6.9 x 10⁶/mm³</td>
</tr>
<tr>
<td><strong>Hemoglobin (Hb)</strong></td>
<td>Amount of oxygen-carrying protein in the blood</td>
<td>130-180 g/L (male)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120-160 g/L (female)</td>
</tr>
<tr>
<td><strong>Hematocrit (Hct)</strong></td>
<td>Percentage of a given volume of whole blood occupied by packed RBCs</td>
<td>45%-62% (male)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37%-48% (female)</td>
</tr>
<tr>
<td><strong>Mean Corpuscular Volume (MCV)</strong></td>
<td>Measurement of RBC size</td>
<td>80-100 µm³</td>
</tr>
<tr>
<td><strong>Mean Corpuscular Hb (MCH)</strong></td>
<td>Amount of oxygen-carrying Hb inside RBCs</td>
<td>27-32 pg/cell</td>
</tr>
<tr>
<td><strong>Concentration (MCHC)</strong></td>
<td>Average concentration of Hb inside RBCs</td>
<td>32% 36%</td>
</tr>
<tr>
<td><strong>RBC Distribution Width (RDW)</strong></td>
<td>Measurement of variance in RBC size</td>
<td>11.0%-15.0%</td>
</tr>
<tr>
<td><strong>White Blood Cell (WBC) Count</strong></td>
<td>The number of WBCs per volume of blood</td>
<td>4.3-10.8 x 10⁹/mm³</td>
</tr>
<tr>
<td><strong>WBC Differential</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>1.8-7.8 x 10³/mm³</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>0.7-4.5 x 10³/mm²</td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
<td>0.1-1.0 x 10³/mm³</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td>0.0-0.6 x 10³/mm³</td>
</tr>
<tr>
<td>Basophils</td>
<td></td>
<td>0.0-0.2 x 10³/mm³</td>
</tr>
<tr>
<td><strong>Platelet Count</strong></td>
<td>The number of platelets per volume of blood</td>
<td>150-400 x 10⁹/mm³</td>
</tr>
<tr>
<td><strong>Mean Platelet Volume (MPV)</strong></td>
<td>Measurement of platelet size</td>
<td>7.2-11.7 FL</td>
</tr>
<tr>
<td><strong>Reticulocytes</strong></td>
<td>Immature RBCs that contain no nucleus but have residual RNA</td>
<td>Normally make up 1% of total RBC count</td>
</tr>
</tbody>
</table>

*Normal values may vary depending on site and age

---

**Approach to Interpreting a CBC**

1. **consider values in the context of individual’s baseline:**
   - up to 5% of population without disease may have values outside “normal” range
   - an individual may display a clinically significant change from their baseline without violating “normal” reference range

2. **is one cell line affected or are several?**
   - if all lines are low: pancytopenia (see Pancytopenia, H8)
   - if RBCs and platelets are low: consider a MAHA/TMA (see Microangiopathic Hemolytic Anemia/Thrombotic Microangiopathy, H22)
   - if single cell line affected: see Common Presenting Problems, H6

---

**Blood Film Interpretation**

**RED BLOOD CELLS**

**Size**
- microcytic (MCV <80 µm³), normocytic (MCV = 80-100 µm³), macrocytic (MCV >100 µm³)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, hemolytic anemias, myelofibrosis, blood transfusion, MDS

**Colour**
- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
- iron deficiency anemia, anemia of chronic disease sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
- increased RBC production by bone marrow

**Shape**
- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, myelofibrosis, severe B₁₂ deficiency, MDS, burns
### Table 2. Common Erythrocyte Shapes

<table>
<thead>
<tr>
<th>Shape</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discocyte</td>
<td>Biconcave disc</td>
<td>Normal RBC</td>
</tr>
<tr>
<td>Spherocyte</td>
<td>Spherical RBC (due to loss of membrane)</td>
<td>Hereditary spherocytosis, immune hemolytic anemia, post-transfusion</td>
</tr>
<tr>
<td>Elliptocyte/Ovalocyte</td>
<td>Oval-shaped, elongated RBCs</td>
<td>Hereditary elliptocytosis, megaloblastic anemia, iron-deficiency, MDS (myelodysplastic syndrome)</td>
</tr>
<tr>
<td>Schistocyte (helmet cell, fragment)</td>
<td>Fragmented cells (due to traumatic disruption of membrane)</td>
<td>Microangiopathic hemolytic anemia (HUS, aHUS, TTP, DIC, preeclampsia, HELLP, malignant HTN, vasculitis, glomerulonephritis, prosthetic heart valve)</td>
</tr>
<tr>
<td>Sickle Cell</td>
<td>Sickle-shaped RBC (due to polymerization of hemoglobin S)</td>
<td>Sickle cell disorders: HbSC, HbSS</td>
</tr>
<tr>
<td>Codocyte (target cell)</td>
<td>“Bull’s eye” on dried film</td>
<td>Liver disease, hemoglobin SC, thalassemia, iron deficiency, asplenia</td>
</tr>
<tr>
<td>Dacrocyte (teardrop cell)</td>
<td>Single pointed end, looks like a teardrop</td>
<td>Myelofibrosis, thalassemia major, megaloblastic anemia, bone marrow infiltration</td>
</tr>
<tr>
<td>Acanthocyte (spur cell)</td>
<td>Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids)</td>
<td>Severe liver disease (spur cell anemia), starvation/anorexia, post-splenectomy</td>
</tr>
<tr>
<td>Echinocyte (bur cell)</td>
<td>RBC with numerous regularly spaced, small spiny projections</td>
<td>Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, storage artifact</td>
</tr>
<tr>
<td>Rouleaux Formation</td>
<td>Aggregates of RBC resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)</td>
<td>Pregnancy is most common cause (due to physiological increase in fibrinogen) Inflammatory conditions (due to polyclonal immunoglobulins) Plasma cell dyscrasias (due to monoclonal paraproteinemia, e.g. multiple myeloma, macroglobulinemia) Storage artifact</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, and low platelet count; HUS = hemolytic uremic syndrome; aHUS = atypical HUS; TTP = thrombotic thrombocytopenic purpura

Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

### Table 3. RBC Inclusions

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus</td>
<td>Present in erythroblasts (immature RBCs)</td>
<td>Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, MPNs (MF)</td>
</tr>
<tr>
<td>Heinz Bodies</td>
<td>Denatured and precipitated hemoglobin</td>
<td>G6PD deficiency (post-exposure to oxidant), thalassemia, unstable hemoglobins</td>
</tr>
<tr>
<td>Howell-Jolly Bodies</td>
<td>Small nuclear remnant resembling a pyknotic nucleus</td>
<td>Post-splenectomy, hyposplenism (sickle cell disease), neonates, megaloblastic anemia</td>
</tr>
<tr>
<td>Basophilic Stippling</td>
<td>Deep blue granulations indicating ribosome aggregation</td>
<td>Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, hereditary (pyrimidine 5’nucleotidase deficiency)</td>
</tr>
<tr>
<td>Sideroblasts</td>
<td>Erythrocytes with Fe containing granules in the cytoplasm</td>
<td>Hereditary, idiopathic, drugs, hypothyroidism (see Sideroblastic Anemia, H183), myelodysplastic syndrome, toxins (lead)</td>
</tr>
</tbody>
</table>

BM = bone marrow; MF = myelofibrosis; MPN = myeloproliferative neoplasm

Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012
WHITE BLOOD CELLS

• lymphocytes
  • comprise 30-40% of WBCs; great variation in “normal” lymphocyte morphology

• neutrophils
  • normally, only mature neutrophils (with 3-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
  • hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B12 or folate deficiency)
  • left shift (increased granulocyte precursors)
    • seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, myeloproliferative neoplasms (CML, MF)

• blasts
  • immature, undifferentiated precursors; associated with acute leukemia, MDS, G-CSF (growth factor that stimulates neutrophil production) use

Table 4. Abnormal White Blood Cells on Film

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed-Sternberg Cell</td>
<td>Giant, multinucleated B-lymphocyte, (classic 'owl-eye' morphology)</td>
<td>Primarily Hodgkin lymphoma, also seen in some non-Hodgkin lymphoma, CLL, and EBV infection</td>
</tr>
<tr>
<td>Smudge Cell</td>
<td>Lymphocytes damaged during blood film preparation indicating cell fragility</td>
<td>CLL and other lymphoproliferative disorders Pathognomonic in EBV infection</td>
</tr>
<tr>
<td>Auer Rod</td>
<td>Cytoplasmic inclusions that form long needles in the cytoplasm of myeloblasts</td>
<td>Pathognomonic for acute myeloid leukemia (AML)</td>
</tr>
<tr>
<td>Atypical Lymphocyte</td>
<td>Pale blue cytoplasm following RBC edges with pink granules</td>
<td>Viruses (particularly EBV) T-cell large granular lymphocyte leukemia (T-LGL)</td>
</tr>
</tbody>
</table>

EBV = Epstein-Barr virus; CLL = chronic lymphocytic leukemia
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012 and Danielle Sayeau 2017

PLATELETS

• small, purple, anuclear cell fragments

Bone Marrow Aspiration and Biopsy

• sites: posterior iliac crest, sternum
• analyses: most often done together
  • aspiration: takes a fluid marrow sample for cellular morphology, flow cytometry, cytogentic studies, microbiology (C&S, acid-fast bacilli, PCR)
    • note: differential diagnosis for a “dry tap”: MF, hairy cell leukemia, bone marrow infiltration
  • biopsy: takes a sample of intact bone marrow to assess histology (architecture) and immunohistochemistry
    • only aspirates, not biopsies, can be obtained from the sternal site

Indications

• unexplained CBC abnormalities
• diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, solid tumours
• diagnosis and staging of lymphoma or solid tumours
• evaluate iron metabolism and stores (gold standard, but rarely done)
• evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher’s disease)
• evaluate fever of unknown origin, suspected mycobacterial, fungal/parasitic infections, or granulomatous disease
• evaluate unexplained splenomegaly
• confirm normal bone marrow in potential allogeneic hematopoietic cell donor

Important Considerations

• consult a hematologist prior to conducting a bone marrow biopsy on a patient with an inherited (e.g. hemophilia, vWF disease) or acquired (e.g. DIC, anticoagulant therapy, coagulopathy of liver disease, severe thrombocytopenia) bleeding diathesis to determine if pro-hemostatic therapy is indicated pre-procedure
• do not perform a bone marrow biopsy if there is evidence of infection over the targeted skin site

Left Shift
Refers to an increase in granulocyte precursors in the peripheral smear (myelocytes, metamyelocytes, promyelocytes, blasts). If present, implies increased marrow production of granulocytes (e.g. inflammation, infection, G-CSF administration, CML)

The presence of predominantly blasts in the peripheral smear with immature cells between mature neutrophils and blast suggests clonal cell disorder (MDS, acute leukemia)

If > 20% of the total WBC differential consists of blasts, this is acute leukemia and is a medical emergency
Common Presenting Problems

**Anemia**

**Definition**
- A decrease in RBC mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
  - Adult males: Hb $<$130 g/L or Hct $<$0.41%
  - Adult females: Hb $<$120 g/L or Hct $<$0.36% (changes with pregnancy and trimester)

**Clinical Features**
- **History**
  - Symptoms of anemia: fatigue, headache, light-headedness, malaise, weakness, decreased exercise tolerance, dyspnea, palpitations, dizziness, tinnitus, syncope
  - Acute vs. chronic, bleeding, systemic illness, diet (Fe, B12 sources), alcohol, family history
  - Menstrual history: menorrhagia, menometrorrhagia
  - Rule out pancytopenia (recurrent infection, mucosal bleeding, easy bruising)
- **Physical Signs**
  - HEENT: pallor in mucous membranes and conjunctiva at Hb $<$90 g/L (<9 g/dL), ocular bruits at Hb $<$55 g/L (<5.5 g/dL), angular cheilitis, jaundice
  - Cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
  - Dermatologic: ecchymosis, petechiae, pallor in palmar skin creases at Hb $<$75 g/L, jaundice (if due to hemolysis), nail changes (spooning), glossitis
  - Splenomegaly, lymphadenopathy

**Investigations**
- Rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential
- Reticulocyte count and blood smear/film
- Rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
- Additional laboratory investigations as indicated (see [Microcytic Anemia, H13], [Normocytic Anemia, H17], [Hemolytic Anemia, H18], and [Macrocytic Anemia, H23])
- N.B. may have a mixed picture with multiple concomitant nutritional deficiencies

**Erythrocytosis**

**Definition**
- An increase in the number of RBCs: Hb $>$185 g/L or Hct $>$52% (males); Hb $>$165 g/L or Hct $>$47% (females and African males)

**Etiology**
- Relative spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, "stress" (Gaisböck’s syndrome)
- Absolute erythrocytosis
Table 5. Etiology of Erythrocytosis

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Inappropriate Production of Erythropoietin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia Vera (PV) (see Polycythemia Vera, H41)</td>
<td>Physiologic (poor tissue oxygenation/hypoxia)</td>
<td>Tumours</td>
</tr>
<tr>
<td></td>
<td>Carbon monoxide poisoning</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Heavy smoking</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>High altitude</td>
<td>Cerebellar hemangioblastoma</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>COPD</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Sleep apnea</td>
<td>Uterine leiomyoma</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
<td>Ovarian tumour</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>R to L shunt (Eisenmenger syndrome)</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>RBC defects (Hb with increased O₂ affinity, methemoglobinemia)</td>
<td>Polycystic kidney disease</td>
</tr>
</tbody>
</table>

Clinical Features
- secondary to high red cell mass and hyperviscosity
  - headache, dyspnea, dizziness, tinnitus, visual disturbances, hypertensive symptoms, numbness/tingling
  - symptoms of angina, congestive heart failure, aquagenic pruritus (only in MPNs)
  - thrombosis (venous or arterial) or bleeding (seen with acquired vWD or acquired platelet dysfunction in MPNs)
  - physical findings
    - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

Investigations
- serum erythropoietin (EPO): differentiates primary (low/normal) from other etiologies (elevated)
  - search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
    - only send if low/normal EPO level
  - ferritin (iron deficiency can mask the diagnosis; if iron deficient with reticulocytosis, suggestive of PV)

Treatment
- if primary: see Polycythemia Vera, H41
- if secondary: treat underlying cause
  - O₂ for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours
  - often cardiologists will be hesitant to treat high Hct in cyanotic patients

Thrombocytopenia

Definition
- platelet count <150 x 10⁹/L

Clinical Features
- history: mucocutaneous bleeding (easy bruising, gingival bleeding), epistaxis, peri-operative bleeding (including dental procedures, heavy menstrual bleeding, peripartum bleeding)
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura, wet purpura
  - see Disorders of Primary Hemostasis, H27 for complications

Investigations
- CBC and differential
- blood film
  - rule out pseudo-thrombocytopenia (platelet clumping or platelet satellitism)
  - decreased production: other cell line abnormal ties, blasts, hypersegmented PMNs, leukoerythroblastic changes
  - increased destruction: large platelets (often seen in ITP), schistocytes (seen in MAHA/TMA)
  - workup for nutritional deficiencies: B₁₂, RBC folate
  - PT/INR, aPTT, and fibrinogen if DIC suspected
  - LFTs

Treatments
- life threatening bleeding: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see Immune Thrombocytopenic Purpura, H27
**Thrombocytopenia**

**Definition**
- platelet count >400 x 10⁹/L
- primary thrombocytosis (uncommon): due to myeloproliferative neoplasms (e.g. CML, polycythemia vera, primary myelofibrosis, essential thrombocytosis; rarely associated with MDS)
- reactive/secondary thrombocytosis (common): acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms, ischemic injury)

**Clinical Features**
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative neoplasms (MPNs)

**Investigations**
- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS

**Treatment**
- primary: ASA ± cytoreductive agents (e.g. hydroxyurea, anagrelide, interferon-α)
- secondary: treat underlying cause

**Pancytopenia**

**Definition**
- a decrease in all hematopoietic cell lines

**Clinical Features**
- anemia: fatigue (see Anemia, H6)
- leukopenia: recurrent infections (see Neutropenia, H9)
- thrombocytopenia: mucosal bleeding (see Thrombocytopenia, H7)

**Investigations**
- CBC, peripheral blood film, serum ferritin concentration, B₁₂, folate
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- workup as per Figure 4 and presenting symptoms/physical exam
- if reactive process has been ruled out, bone marrow biopsy may be required

*In hospitalized patients most common causes of thrombocytopenia are drugs and infection*

APS = antiphospholipid antibody syndrome; DIC = disseminated intravascular coagulation; HELLp = hemolysis, elevated liver enzymes, low platelet count; HIT = heparin induced thrombocytopenia; HUS = hemolytic uremic syndrome; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura

**Figure 3. Approach to thrombocytopenia**
Adapted from: Cecil Essentials of Medicine
Neutrophilia

**Definition**
- variable definition, but generally an absolute neutrophil count (ANC) >7.7 x 10⁹/L (WHO definition)

**Etiology**
- primary neutrophilia
  - chronic myeloid leukemia (CML)
  - other myeloproliferative disorders: PV, ET, myelofibrosis
  - hereditary neutrophilia (autosomal dominant)
  - chronic idiopathic neutrophilia in otherwise healthy patients
  - leukocyte adhesion deficiency
- secondary neutrophilia
  - stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  - obesity
  - infection: leukocytosis with left shift ± toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
  - inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, burns
  - malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  - medications: glucocorticoids, β-agonists, lithium, G-CSF

**Clinical Features**
- look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
- including lymphadenopathy and organomegaly
- examine oral cavity, teeth, peri-rectal area, genitals, and skin for signs of infection

**Investigations**
- CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
- blood film: Döhle bodies, toxic granulation, cytoplasmic vacuoles in infection
- may require bone marrow biopsy if MPN suspected

**Treatment**
- directed at underlying cause

Neutropenia

**Definition**
- mild: ANC 1.0-1.5 x 10⁹/L
- moderate: ANC 0.5-1.0 x 10⁹/L (risk of infection starts to increase)
- severe: ANC <0.5 x 10⁹/L
- profound: ANC <0.1 x 10⁹/L for >7 d

**Absolute Neutrophil Count (ANC) = WBC count x (%PMNs + %bands)
Be aware of fever + ANC <0.5 x 10⁹/L = FEBRILE NEUTROPENIA**
Etiology

Table 6. Etiology of Neutropenia

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Peripheral Destruction/Sequestration</th>
<th>Excessive Margination (Transient Neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td>Anti-neutrophil antibodies</td>
<td>Idiopathic (most common)</td>
</tr>
<tr>
<td>Viral hepatitis, EBV, HIV, TB, typhoid, malaria</td>
<td>Spleen or lung trapping</td>
<td>Overwhelming bacterial infection</td>
</tr>
<tr>
<td>Autoimmune disorders: RA (Felty’s syndrome), SLE</td>
<td>Drugs: haptens (e.g. α-methyldopa)</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Hematological Diseases</td>
<td>Granulomatosis with polyangitis (formerly Wegener’s)</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>Idiopathic, aplastic anemia, myelofibrosis, BM infiltration, cyclic, PNH, MDS, immune-mediated</td>
<td></td>
<td>Racial variation (e.g. African or Ashkenazi Jewish descent)</td>
</tr>
<tr>
<td>Drug-Induced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agents, antimetabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anticonvulsants, antipsychotics, anti-inflammatory agents, anti thyroid drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxins/Chemicals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose radiation benzene, DDT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional Deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bi₂, folate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutinal neutropenia, benign cyclic neutropenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features

- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. S. aureus, gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth, and throat following colonization by opportunistic organisms
- avoid digital rectal exam

Investigations

- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

Treatment

- regular dental care: chronic gingivitis and recurrent stomatitis major sources of morbidity
- treatment of febrile neutropenia (see Infectious Diseases, ID45)
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, methotrexate)

Lymphocytosis

**Definition**

- absolute lymphocyte count >4.0 x 10⁹/L

**Etiology**

- infection (reactive lymphocytosis)
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
  - smoking
  - physiologic response to stress (e.g. trauma, status epilepticus)
  - hypersensitivity (e.g. drugs, serum sickness)
  - autoimmune (e.g. rheumatoid arthritis)
  - neoplasm (e.g. ALL if blasts present, CLL, B cell lymphocytosis of undetermined significance)

**Investigations**

- CBC, peripheral smear assessing lymphocyte morphology

**Treatment**

- treat underlying cause
**Lymphopenia**

**Definition**
- absolute lymphocyte count <1.0 x 10⁹/L

**Etiology**
- idiopathic CD4+ lymphocytopenia
- radiation
- HIV/AIDS, hepatitis B, hepatitis C
- malignancy/chemotherapeutic agents
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)

**Clinical Features**
- opportunistic infections (see Infectious Diseases, ID34)

**Treatment**
- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see Infectious Diseases, ID30)

---

**Eosinophilia**

**Definition**
- absolute eosinophil count >0.5 x 10⁹/L

**Etiology**
- primary: due to clonal bone marrow disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome
    - 6 mo of eosinophilia (count >1.5 x 10⁹/L) with no other detectable causes and end organ damage
    - can involve heart, bone marrow, CNS
- secondary
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes
    - collagen vascular diseases (e.g. RA, polyarteritis nodosa, see Rheumatology, RH19)
    - respiratory causes (asthma, eosinophilic pneumonia, Churg-Strauss)
    - cholesterol emboli
    - hematologic malignancy: see Chronic Myeloid Leukemia, H40 and Hodgkin Lymphoma, H45
    - adrenal insufficiency, see Endocrinology, E33
    - medications (penicillins)
    - atopic dermatitis

**Treatment**
- treat underlying cause
- ensure strongyloides serology is collected to rule out infection before initiating steroids for patients at risk

---

**Agranulocytosis**

**Definition**
- severe depletion of granulocytes (neutrophils, eosinophils, basophils) from the blood and granulocyte precursors from bone marrow

**Etiology**
- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine, and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors

**Clinical Features**
- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

**Prognosis**
- high fatality without vigorous treatment

**Investigations/Treatment**
- discontinue offending drug
- pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture, and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider bone marrow aspirate and biopsy if cause unclear
- consider G-CSF
Leukemoid Reaction

- blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
- leukocytosis >50 x 10⁹/L, marked left shift (myelocytes, metamyelocytes, bands in peripheral blood smear)

Approach to Lymphadenopathy

**History**
- constitutional/B-symptoms: seen in TB, lymphoma, other malignancies
- growth pattern: acute vs. chronic
- exposures: cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), high risk behaviours (HIV)
- joint pain/swelling, rashes (connective tissue disorder)
- pruritus (seen in Hodgkin lymphoma)
- medications (can cause serum sickness → lymphadenopathy)

**Clinical Features**
- determine if lymphadenopathy is localized or generalized
- localized: typically reactive or neoplastic
  - cervical (bacterial/mycobacterial infections, ENT malignancies, metastatic cancer)
  - supravclavicular
    - right (mediastinal, bronchogenic esophageal cancer)
    - left (gastric, gall bladder, pancreas, renal, testicular/ovarian cancer)
  - axillary (cat scratch fever, breast cancer, metastatic cancer)
  - epitrochlear (infections, sarcoidosis, lymphoma)
  - check for splenomegaly, constitutional symptoms

**Investigations**
- CBC and differential, blood film
- if generalized consider tuberculin test, HIV RNA, VDRL, Monospot* / EBV serology, ANA, imaging
- if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → biopsy)
- excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
- in areas difficult to access (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
- FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (use excisional biopsy instead)
  - FNA is helpful for recurrence of solid tumour malignancy
  - imaging such as U/S or CT can provide more info, but generally adds little to diagnosis

<table>
<thead>
<tr>
<th>Table 7. Inflammatory vs. Neoplastic Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Consistency</td>
</tr>
<tr>
<td>Mobility</td>
</tr>
<tr>
<td>Tenderness</td>
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<tr>
<td>Size</td>
</tr>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8 Differential Diagnosis of Generalized Lymphadenopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Bacterial (TB, Lyme, brucellosis, cat scratch disease, syphilis)</td>
</tr>
<tr>
<td>Viral (EBV, CMV, HIV)</td>
</tr>
<tr>
<td>Parasitic (toxoplasmosis)</td>
</tr>
<tr>
<td>Fungal (histoplasmosis)</td>
</tr>
</tbody>
</table>
Table 9. Differential Diagnosis of Splenomegaly

<table>
<thead>
<tr>
<th>Increased Demand for Splenic Function</th>
<th>Congestive</th>
<th>Infiltrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
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<tr>
<td>Nutritional anemias</td>
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<tr>
<td>Hemoglobinopathies</td>
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<tr>
<td>Hemolysis</td>
<td></td>
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<tr>
<td>Spherocytosis</td>
<td></td>
<td></td>
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<tr>
<td>Sequestration crisis</td>
<td></td>
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<tr>
<td>Elliptocytosis</td>
<td></td>
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</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral e.g. EBV, HIV, CMV</td>
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<td></td>
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<tr>
<td>Bacterial e.g. endocarditis, TB</td>
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<td></td>
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<tr>
<td>Parasitic e.g. Malaria</td>
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<tr>
<td>Histoplasmosis, Leishmaniasis</td>
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<tr>
<td>Fungal</td>
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<tr>
<td>Inflammatory</td>
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<tr>
<td>SLE</td>
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<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Felty syndrome</td>
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<tr>
<td>Still's disease</td>
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<tr>
<td>Cirrhosis</td>
<td></td>
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<tr>
<td>Portal HTN</td>
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<tr>
<td>Portal vein obstruction (including right heart failure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenic vein thrombosis</td>
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<tr>
<td>Non-Malignant</td>
<td></td>
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<tr>
<td>Benign metaplasia</td>
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<tr>
<td>Cysts</td>
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</tr>
<tr>
<td>Amyloidosis, Sarcoidosis</td>
<td></td>
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</tr>
<tr>
<td>Hamartomas</td>
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</tr>
<tr>
<td>Vascular abnormalities</td>
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<tr>
<td>Lysosomal storage diseases</td>
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<tr>
<td>(Gaucher’s, Niemann-Pick)</td>
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<tr>
<td>Glycogen storage diseases</td>
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<tr>
<td>Maligant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia (CML, CLL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoproliferative disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic tumour</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The underlined conditions cause massive splenomegaly (spleen crosses midline or reaches pelvis)

History
- constitutional symptoms, feeling of fullness in LUQ, early satiety
- signs or symptoms of infection (e.g. mononucleosis) or malignancy
- history of liver disease, hemolytic anemia, or high-risk exposures

Clinical Features
- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell's sign, Traube's space, Nixon's method) and palpation
- associated lymphadenopathy or hepatomegaly
- signs of CHF

Investigations
- CBC and differential, blood film
- as indicated: liver enzymes (AST, ALT, ALP, GGT) and/or LFTs (platelet, INR, albumin, bilirubin), reticulocyte count, Monospot®/EBV, haptoglobin, LDH, infectious, and autoimmune workup
- imaging
  - ultrasound of abdomen/liver to assess for cirrhosis and portal vein thrombosis (if positive, refer to hepatology for evaluation)
  - echo for cardiac function
  - CT to rule out lymphoma and assess splenic lesions

Table 10. Iron Indices and Blood Film in Microcytic Anemia

<table>
<thead>
<tr>
<th>Lab Tests</th>
<th>Blood Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>Hypochromic, microcytic</td>
</tr>
<tr>
<td>Serum Iron</td>
<td></td>
</tr>
<tr>
<td>TIBC</td>
<td></td>
</tr>
<tr>
<td>% saturation</td>
<td></td>
</tr>
<tr>
<td>RDW</td>
<td></td>
</tr>
<tr>
<td>Iron Deficiency Anemia</td>
<td>N/↑</td>
</tr>
<tr>
<td>Anemia of Chronic Disease</td>
<td></td>
</tr>
<tr>
<td>Sideroblastic Anemia</td>
<td>N/↑</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>N/↑</td>
</tr>
</tbody>
</table>

Iron Intake (Dietary)
- average North American adult diet = 10-20 mg iron (Fe) daily
- steady state absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males have positive Fe balance; up to 20% of menstruating females have negative Fe balance
**Iron Absorption and Transport**
- dietary iron is absorbed in the duodenum (e.g. absorption impaired in IBD and Celiac disease)
- in circulation the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages of the reticuloendothelial system and hepatocytes) to RBC precursors in the bone marrow

**Iron Levels**
- hepcidin is a hormone produced by hepatocytes that regulates systemic iron levels
  - binds to iron exporter ferroportin (on duodenal enterocytes and reticuloendothelial cells) and induces its degradation, thereby inhibiting iron export into circulation (diminished absorption of iron and iron trapping in reticuloendothelial system cells)
- hepcidin production is:
  - increased in states of iron overload (inhibiting additional iron absorption) and inflammation (mediating anemia of chronic inflammation through iron trapping)
  - decreased in states where erythropoiesis is increased (e.g. hemolysis) or oxygen tension is low

**Iron Storage**
- ferritin
  - ferric iron (Fe³⁺) complexed to a protein called apoferritin (hepatocytes are main ferritin storage site)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated despite low Fe stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monooyte system is main source of hemosiderin storage

**Iron Indices**
- bone marrow aspirate: gold standard test for assessment of iron stores (rarely done)
- serum ferritin: most important blood test for iron stores
  - decreased in iron deficiency anemia
  - elevated in infection, inflammation, malignancy, liver disease, hyperthyroidism, and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
  - virtually all serum iron is bound to transferrin, only a trace is free or complexed in ferritin
- total iron binding capacity (TIBC): total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - high specificity for decreased iron, low sensitivity saturation
  - serum Fe divided by TIBC, expressed as a proportion or a percentage
- soluble transferrin receptor (sTfR)
  - reflects the availability of iron at the tissue level
  - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some is cleaved off and is present in circulation as sTfR
  - in iron deficient states more transferrin receptor is expressed on erythroblasts leading to an increase in sTfR
  - low in reduced erythropoiesis and iron overload
  - useful in determining iron deficiency in the setting of chronic inflammatory disorders (see *Iron Deficiency Anemia*)

*Figure 5. Iron metabolism*
Iron Deficiency Anemia

- see Pediatrics, P41
- most common cause of anemia in North America

Etiology
- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology in the developed world)
  - cow’s milk (infant diet), “tea and toast” diet (elderly), absorption imbalances, post-gastrectomy, malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis, H.pylori infection)
- increased losses
  - hemorrhage
    - obvious causes: menorrhagia, abnormal uterine bleeding, frank GI bleed
    - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - chronic intravascular hemolysis (e.g. PNH, cardiac valve RBC fragmentation)

Clinical Features
- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see Anemia, H6
- brittle hair, nail changes (brittle, koilonychia)
- pica (appetite for non-food substances e.g. ice, paint, dirt)
- restless leg syndrome

Investigations
- iron indices, including soluble transferrin receptor
  - low ferritin (<18 µg/L) is diagnostic of iron deficiency
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms, anisocytosis
  - target cells
- bone marrow (gold standard but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation

Patient with microcytic anemia

![Figure 6. Approach to interpreting iron indices](adapted from Am Fam Physician 2007;75:871-878)

Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.)
In males and in post menopausal women, a GI workup is always warranted (gastroscopy, colonoscopy)

Treatment
- treat underlying cause
- supplementation
  - oral (capsules, syrup)
    - ferrous sulphate 325 mg tid (65 mg elemental iron), ferrous gluconate 300 mg tid (35 mg elemental iron), or ferrous fumarate 300 mg tid (100 mg elemental iron)
  - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
  - oral iron should be taken with citrus juice (vitamin C) to enhance absorption
  - IV (iron sucrose or dextran) can be used if patient cannot tolerate or absorb oral iron
- monitoring response
  - reticulocyte count will begin to increase after one wk
  - Hb normalizes by 10 g/L per wk (if no blood loss)
Anemia of Chronic Inflammation

Etiology
- infection, malignancy, inflammatory and rheumatologic disease, chronic renal and liver disease, endocrine disorders (e.g. DM, hypothyroidism, hypogonadism, hypopituitarism)

Pathophysiology
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - hepatic hepcidin production is increased in inflammatory processes, trapping iron in enterocytes and macrophages (via ferroportin inhibition), see Figure 5
  - reduced plasma iron levels make iron relatively unavailable for new hemoglobin synthesis
  - marrow unresponsive to normal or slightly elevated EPO
  - mild hemolytic component is often present i.e. RBC survival is modestly decreased

Investigations
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen, platelets)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
  - “classic” serum iron indices
    - serum iron and TIBC low, % saturation low
    - serum ferritin is normal or increased
- bone marrow
  - normal or increased iron stores
  - decreased or absent staining for iron in erythroid precursors

Treatment
- treat underlying disease
- only treat anemia in patients who can benefit from a higher hemoglobin
- IV iron if no benefit from PO iron (overcomes sequestration in enterocytes)
- erythropoietin indicated in chronic renal failure; not to be used if patient has concomitant curative solid tumour malignancy; ensure Hb target <110 g/L

Sideroblastic Anemia

uncommon compared to iron deficiency anemia or anemia of chronic disease

Sideroblasts
- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
- “normal”: in healthy individuals, granules are small and randomly spread in the cytoplasm
- “ring”: iron deposits in mitochondria, forming large, abnormal granules that surround the nucleus
  - the hallmark of sideroblastic anemia

Etiology
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - refractory anemia with ringed sideroblasts: a subtype of MDS (see Myelodysplastic Syndromes, H39)
  - may be a preleukemic phenomenon (10% transform to AML)
- reversible
  - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, hypothyroidism

Clinical Features
- anemia symptoms (see Anemia, H6)
- hepatosplenomegaly, evidence of iron overload

Investigations
- serum iron indices
  - increased serum Fe++, normal TIBC, increased ferritin, increased sTfR
- blood film/bone marrow biopsy
  - ringed sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikilocytosis, basophilic stippling
**Normocytic Anemia**

- MCV 80-100 fL
- see Figure 2, Approach to Anemia, H6

### Aplastic Anemia

**Definition**
- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

**Etiology**

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi’s anemia</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>Often T-cell mediated</td>
</tr>
<tr>
<td>Drugs</td>
<td>Close-related (i.e. chemotherapeutics)</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic (chloramphenicol, anti-malarials, phenylbutazone)</td>
</tr>
<tr>
<td>Toxins</td>
<td>Benzene/organic solvents</td>
</tr>
<tr>
<td></td>
<td>DDTP, insecticides</td>
</tr>
</tbody>
</table>

**Clinical Features**
- can present acutely or insidiously
- symptoms of anemia (see Anemia, H6), thrombocytopenia (see Thrombocytopenia, H7), and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)

**Investigations**
- exclude other causes of pancytopenia (see Figure 4), including PNH (overlap syndrome)
- CBC
  - anemia, neutropenia or thrombocytopenia (any combination) ± pancytopenia
  - decreased reticulocytes (<1% of the total RBC count) blood film
  - decreased number of normal RBCs
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement
  - decreased cellularity

**Treatment**
- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
  - judicious use so as to not increase the risk of immune sensitization to blood products
- immunosuppression (for idiopathic aplastic anemia)
  - anti-thymocyte globulin: 50-60% of patients respond
  - cyclosporine
- allogeneic bone marrow transplant
- growth factors: e.g. Eltrombopag (TPO receptor agonist), G-CSF, and EPO not effective

### Lead Poisoning

**Definition/Etiology**
- blood lead levels greater than 80 µg/dL, possible symptomatology at 50 µg/dL
- identify source: consider occupational history, exposures history, utensil history

**Clinical Features**
- abdominal pain, constipation, irritability, difficulty concentrating

**Treatment**
- chelation therapy: dimercaprol and EDTA are first line agents

### Causes of Normocytic Anemia

**ABCD**
- Acute blood loss
- Bone marrow failure
- Chronic disease
- Destruction (hemolysis)
Hemolytic Anemia

Definition
- anemia due to a shortened survival of circulating RBCs, usually defined as <100 d
- uncommon cause for anemia (<5% of cases) with many etiologies (>200)

Classification
- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
  - immune
    - autoimmune: warm vs. cold autoimmune hemolytic anemias (AIHA), see Table 14 Classification of AIHA, H22
    - alloimmune: hemolytic disease of the fetus/newborn, post-transfusion
  - non-immune
    - MAHA/TMA, now known as TMA: thrombus in blood vessel causes RBCs to be sheared associated with DIC, HUS, aHUS, TTP, preeclampsia/HELLP, vasculitides, malignant hypertension
    - other causes: PNH, hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, mechanical heart valves
- also classified as intravascular or extravascular
  - intravascular: MAHA/TMA (e.g. TTP DIC), infections (malaria, Clostridium), and PNH
  - extravascular: RBCs are coated with antibodies (AIHA) or have an abnormal membrane structure/shape or inclusions

Clinical Features Specific to HA
- jaundice
- dark urine (hemoglobinuria, bilirubin)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

Table 12. Investigations for Hemolytic Anemia

<table>
<thead>
<tr>
<th>Screening Tests</th>
<th>Tests Specific For Intravascular Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased LDH</td>
<td>Schistocytes on blood film</td>
</tr>
<tr>
<td>Decreased haptoglobin</td>
<td>Free hemoglobin in serum</td>
</tr>
<tr>
<td>Increased unconjugated bilirubin</td>
<td>Methemalbuminemia (heme + albumin)</td>
</tr>
<tr>
<td>Increased urobilinogen</td>
<td>Hemoglobinuria (immediate)</td>
</tr>
<tr>
<td>Reticulocytosis</td>
<td>Hemoglobinuria (delayed) – most sensitive</td>
</tr>
</tbody>
</table>

Tests Specific for Extravascular Hemolysis

Direct Antiglobulin Test (direct Coombs)
- Detects IgG or complement on the surface of RBC
- Add anti-IgG or anti complement Ab to patient’s RBCs; positive if agglutination
- Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction

Indirect Antiglobulin Test (indirect Coombs)
- Detects an antibodies in serum that can recognize antigens on RBCs
- Mix patient’s serum + donor RBCs + Coombs serum (anti-human Ig Ab); positive if agglutination
- Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA

Thalassemia

Definition
- defects in production of the α or β chains of hemoglobin
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
  - clinical manifestations and treatment depends on specific gene and number of alleles affected
- common features
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film

Thalassemia

- β-Thal: prevalent in Mediterranean
- α-Thal: prevalent in South East Asia (SEA) and Africa (α = Asia, Africa)
Pathophysiology
- defect may be in any of the Hb genes
  - normally 4α genes in total; 2 on each copy of chromosome 16
  - normally 2β genes in total; 1 on each copy of chromosome 11
  - fetal hemoglobin (HbF, α2γ2), switches to adult forms HbA (α2β2) and HbA2 (α2δ2) at 3-6 mo of life
- HbA constitutes 97% of adult hemoglobin
- HbA2 constitutes 3% of adult hemoglobin

β-Thalassemia Minor (Thalassemia Trait)

Definition
- defect in single allele of β gene (heterozygous for one normal β globin allele and one β globin thalassemic allele)
- common in people of Mediterranean and Asian descent

Clinical Features
- usually asymptomatic; a palpable spleen is very rare

Investigations
- Hb (100-140 g/L), MCV (<70 fL), Fe (normal), RBC count (normal)
- peripheral blood film – microcytosis basophilic stippling
- HB electrophoresis
  - specific: HbA2 increased to 3.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

Treatment
- no treatment required
- genetic counselling for patient and family

β-Thalassemia Major

Definition
- defect in both alleles of β gene (homozygous, autosomal recessive)

Pathophysiology
- ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs, and increase in HbF

Clinical Features
- initial presentation at age 6-12 mo when HbA (α2/β2) normally replaces HbF (α2/γ2)
  - severe anemia, jaundice
  - iron overload progressing to hemochromatosis
    - secondary to repeated transfusions and ineffective erythropoiesis
    - leads to iron-induced organ damage
  - stunted growth and development (hypogonadal dwarf)
  - gross hepatosplenomegaly (due to extramedullary hematopoiesis)
  - radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
    - skull x-ray has “hair-on-end” appearance
    - pathologic fractures common
  - evidence of increased Hb catabolism (e.g. pigmented gallstones)
  - death can result from
    - untreated anemia (should transfuse)
    - infection (should identify and treat early)
    - iron overload (common); late complication from repeated transfusions and ineffective erythropoiesis

Investigations
- severe microcytic anemia (Hb <60 g/L)
- peripheral blood film: teardrop, target, hypochromatic, microcytic
- HB electrophoresis
  - HbA: 0-10% (normal >95%)
  - HbA2 >2.5%
  - HbF: 90-100%

Treatment
- lifelong regular transfusions to suppress endogenous erythropoiesis
- iron chelation (e.g. deferoxamine, deferasirox, deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)
- folic acid supplementation if not transfused
- allogeneic bone marrow transplantation (potentially curative) or cord blood transplant
- splenectomy (now performed less frequently)
**β-Thalassemia Intermedia**

**Definition**
- clinical diagnosis in patients whose clinical manifestations are too mild to be classified as thalassemia major, but too severe to be classified as thalassemia minor

**Clinical Features**
- wide variety of clinical phenotypes
- in most cases of TI, both β-globin genes affected
- three main mechanisms account for the milder phenotype compared to thalassemia major: (1) subnormal (vs. absent) β-chain synthesis, (2) increased number of γ chains, (3) coinheritance of α thalassemia (in some cases)
- complications more commonly seen in TI than thalassemia major include extramedullary hematopoiesis, leg ulcers, gallstones, thrombosis, and pulmonary hypertension, and growth retardation

**α-Thalassemia**

**Definition**
- defect(s) in α genes
- similar geographic distribution as β-thalassemia, but higher frequency among Asians and Africans

**Clinical Features**
- 1 defective α gene (aa/a-): clinically silent; normal Hb, normal MCV
- 2 defective α genes (cis: aa/-- or trans: a/a-): decreased MCV, normal Hb
  - N.B. cis 2-gene deletion more common in Asia vs. trans 2-gene deletion more common in Africa – this leads to increased risk of fetal hydrops in offspring of Asian patients vs. African patients
- 3 defective α genes (a-/-): HbH (β4) disease; presents in adults, decreased MCV, decreased Hb, splenomegaly
- 4 defective α genes (--/--): Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

**Investigations**
- peripheral blood film – screen for HbH inclusion bodies with supravital stain
- electrophoresis can be used to identify HgH disease, definitive diagnosis with DNA genotyping

**Treatment**
- depends on degree of anemia, referral for genetic/prenatal counselling
  - 1 or 2 defective α genes: no treatment required
  - HbH disease: similar to β-thalassemia intermedia
  - HbBarts: no definitive treatment, majority of pregnancies terminated (fetal/maternal mortality risk), intrauterine transfusion, stem cell transplants

**Sickle Cell Disease**

**Definition**
- autosomal recessive sickling disorders arise due to a mutant β-globin chain, most commonly caused by a Glu → Val substitution at position 6 (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)
- increased incidence of HbS allele with African or Mediterranean heritage (thought to be protective against malaria)
- sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

**Pathophysiology**
- at low pO2, deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes → ‘sickles’
- the pO2 level at which sickling occurs is related to the percentage of HbS present
- sickling aggravated by acidemia, increased CO2, increased 2,3-DPG, fever, and osmolality
- fragile sickle cells then cause injury in two main ways
  1. fragile sickle cells hemolyze (nitric oxide depletion)
  2. occlusion of small vessels (hypoxia, ischemia-reperfusion injury)

**Clinical Features**
- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first yr of life
  - retarded growth and development ± skeletal change
  - splenomegaly in childhood; splenic atrophy in adulthood

---

**Figure 7. Pathophysiology of sickling**

- Blood flow slows
- pO2 decreases
- Blood viscosity increases
- Distorted RBC sickle cells
- Deoxy Hb S polymers
- Impaction
- Infarction
- Hb S
  - ↑ H+
  - ↑ CO2

**Functional asplenism:** increased susceptibility to infection by encapsulated organisms
- S. pneumoniae
- N. meningitidis
- H. influenzae
- Salmonella (osteomyelitis)
SCD-SS often presents with acute pain episode
1. aplastic crises
   • toxins and infections (especially parvovirus B19) transiently suppress bone marrow
2. splenic sequestration crises
   • usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
   • uncommon in adults due to asplenia from repeated infarction
3. vaso-occlusive crises (infarction)
   • may affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen, and extremities), fever, and leukocytosis
   • can cause a stroke or a silent myocardial infarction
   • precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses, and alcohol
4. acute chest syndrome

SCD-SC (most common compound heterozygote)
• 1:833 live births in African-Americans, common in West Africa
• milder anemia than HbSS
• similar complications as HbSS, although typically milder and less frequent (exception is proliferative sickle retinopathy, glomerulonephritis, and avascular necrosis)
• spleen not always atrophic in adults

Investigations
• sickle cell prep (detects sickling of RBCs under the microscope in response to O2 lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS
• Hb electrophoresis distinguishes HbAS, HbSS, HbSC, and other variants
• all newborns in developed countries typically screened for SCD

Table 13. Investigations for Sickle Cell Disease

<table>
<thead>
<tr>
<th></th>
<th>HbAS</th>
<th>HbSS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBC</strong></td>
<td>Normal</td>
<td>Increased reticulocytes, decreased Hb, decreased Hct</td>
</tr>
<tr>
<td><strong>Peripheral Blood</strong></td>
<td>Normal; possibly a few target cells</td>
<td>Sickled cells</td>
</tr>
<tr>
<td><strong>Hb Electrophoresis</strong></td>
<td>HbA fraction of 0.65 (65%)</td>
<td>No HbA, only HbS and HbF (proportions change with age; normal amount of HbA2)</td>
</tr>
</tbody>
</table>

Treatment
• genetic counselling
• HbAS: no treatment required
• HbSC: treatment as per HbSS, but is dictated by symptom severity
• HbSS
  1. folic acid to prevent folate deficiency
  2. hydroxyurea to enhance production of HbF
     • mechanism of action: stops repression of Hb-γ chains and/or initiates differentiation of stem cells in which this gene is active
     • presence of HbF in the SS cells decreases polymerization and precipitation of HbS
     • N.B. hydroxyurea is cytotoxic and may cause bone marrow suppression
  3. treatment of vaso-occlusive crisis
     • supportive care: oxygen, hydration (reduces viscosity), correct acidosis, analgesics/opiates
     • indication for exchange transfusion: Hb <50-60 g/L, SCD complications (acute chest syndrome, aplastic crisis, hepatic or splenic sequestration, stroke), prevention of complications, pre-operative
     • less routinely: antimicrobials for suspected infection
  4. prevention of crises
     establish diagnosis
     • avoid conditions that promote sickling (hypoxia, acidosis, dehydration, fever)
     • vaccination in childhood (pneumococcus, meningococcus, H. influenzae b)
     • prophylactic penicillin (age 3 mo-5 yr)
     • good hygiene, nutrition, and social support
  5. screen for complications
     • regular blood work (CBC, reticulocytes, iron indices, BUN, LFTs, creatinine)
     • urinalysis annually (proteinauria, glomerulopathy)
     • transcranial doppler annually until 16 yr old (stroke prevention)
     • retinal examinations annually from 8 yr old (screen for retinopathy)
     • echocardiography once in late childhood/early adulthood (screen for pulmonary hypertension)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Ischemic or hemorrhagic stroke, vasculopathy</td>
</tr>
<tr>
<td>Eye</td>
<td>Hemorrhage, blindness</td>
</tr>
<tr>
<td>Liver</td>
<td>Infects, RUG syndrome</td>
</tr>
<tr>
<td>Lung</td>
<td>Chest syndrome, long-term pulmonary hypertension</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Stones</td>
</tr>
<tr>
<td>Heart</td>
<td>Hyperdynamic flow murmurs</td>
</tr>
<tr>
<td>Spleen</td>
<td>Enlarged (child); atrophic (adult)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Hematuria, loss of renal concentrating ability, proteinuria</td>
</tr>
<tr>
<td>Intestines</td>
<td>Acute abdomen</td>
</tr>
<tr>
<td>Placenta</td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Penis</td>
<td>Priapism</td>
</tr>
<tr>
<td>Digits</td>
<td>Dactylitis</td>
</tr>
<tr>
<td>Femoral and Humeral Head</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Bone</td>
<td>Infarction, infection</td>
</tr>
<tr>
<td>Ankle</td>
<td>Leg ulcers</td>
</tr>
</tbody>
</table>

NIH Consensus Development Conference
Statement: Hydroxyurea Treatment for Sickle Cell Disease
Ann Intern Med 2000;143:92-938

Efficacy: Strong evidence for adolescents and adults and there is emerging data supporting its use in children. In the single RCT, the Hb level was higher in hydroxyurea recipients than placebo recipients at 2 yr (difference, 6 g/L), as was HbF (absolute difference, 3.2%). The median number of painful crises was 44% lower than in the placebo arm. The 12 observational studies that enrolled adults reported a relative increase in HbF of 4-20% and a relative reduction in crisis rates by 68-84%. Hospital admissions declined by 18-32%.

Effectiveness: Data is limited. It seems to be highly effective but is currently underutilized.

Short-Term Harms (within 6 mo): Dose-related leukopenia, thrombocytopenia, anemia, and decreased reticulocyte count. Others include decreased sperm production and dry skin.

Long-Term Harms: Birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug.
Autoimmune Hemolytic Anemia

Table 14. Classification of AIHA

<table>
<thead>
<tr>
<th>Warm (75-90% cases)</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibody Allotype</strong></td>
<td>IgG</td>
</tr>
<tr>
<td><strong>Agglutination Temperature</strong></td>
<td>37°C</td>
</tr>
<tr>
<td><strong>Direct Coombs Test</strong></td>
<td>Positive for IgG ± complement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Etiology</strong></th>
<th>Warm patient/avoid cold</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin lymphoma)</td>
<td>Rituaximab regiments (1st line)</td>
<td>Secondary to infection (e.g. mycoplasma pneumonia, EBV)</td>
</tr>
<tr>
<td>Secondary to autoimmune disease (e.g. SLE)</td>
<td>Plasma exchange (2nd line for high IgM levels)</td>
<td>Secondary to lymphoproliferative disorder (e.g. macroglobulinemia, CLL)</td>
</tr>
<tr>
<td>Drug-induced (e.g. penicillin, quinine, methyldopa)</td>
<td>Folic acid</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Blood Film</strong></th>
<th>Spherocytes</th>
<th>Agglutination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Management</strong></td>
<td>Treat underlying cause</td>
<td>Treat underlying cause</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Warm patient/avoid cold</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Rituaximab regiments (1st line)</td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Plasma exchange (2nd line for high IgM levels)</td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td>Folic acid</td>
<td></td>
</tr>
<tr>
<td>Rituaximab (2nd line to steroids)</td>
<td>Low dose alkylating agents (chlorambucil, cyclophosphamide) or interferon may be useful but less effective</td>
<td></td>
</tr>
</tbody>
</table>

Microangiopathic Hemolytic Anemia
Thrombotic Microangiopathy

**Definition**
- hemolytic anemia due to intravascular fragmentation of RBCs

**Etiology**
- see Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome, H30
- see Disseminated Intravascular Coagulation, H32
- eclampsia, HELLP syndrome, AFLP (see Obstetrics, OB25)
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic antiphospholipid antibody syndrome

**Investigations**
- blood film: evidence of hemolysis, schistocytes
- hemolytic workup
- urine: hemosiderinuria, hemoglobinuria

Hereditary Spherocytosis

- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
  - spleen makes defective RBCs more spherocytotic (and more fragile) by membrane removal; also acts as site of RBC destruction
- autosomal dominant with variable penetrance

**Investigations**
- blood film (shows spherocytes), osmotic fragility (increased), molecular analysis for spectrin gene

**Treatment**
- in severe cases, splenectomy and vaccination against pneumococcus, meningococcus, and H. influenza b (avoid in early childhood)
Hereditary Elliptocytosis

Definition/Etiology
- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

Treatment
- immunizations; splenectomy for severe hemolysis

Glucose-6-Phosphate Dehydrogenase Deficiency

Definition
- deficiency in glucose-6-phosphate dehydrogenase (G6PD), corresponding to a lack of reduced glutathione (GSH) and leading to RBC sensitivity due to oxidative stress

Pathophysiology
- X-linked recessive, prevalent in individuals of African, Asian, and Mediterranean descent

Clinical Features
- frequently presents as episodic hemolysis precipitated by:
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

Investigations
- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
  - may have features of intravascular hemolysis (e.g. RBC fragments)

Treatment
- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases

Macrocytic Anemia

- MCV >100 fL
- see Figure 2. Approach to Anemia, H6

<table>
<thead>
<tr>
<th></th>
<th>Megaloblastic</th>
<th>Non-Megaloblastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Large, oval, nucleated RBC precursor</td>
<td>Large round RBC</td>
</tr>
<tr>
<td></td>
<td>Hypersegmented neutrophils</td>
<td>Normal neutrophils</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm</td>
<td>Reflects membrane abnormality with abnormal cholesterol metabolism</td>
</tr>
</tbody>
</table>

Causes of Macrocytic Anemia
- ABCDEF
  - Alcoholism (liver disease)
  - B12 deficiency
  - Compensatory reticulocytosis
  - Drugs (cytotoxic, AZT/Dysplasia
  - Endocrine (hypothyroidism)
  - Folate deficiency/Fetus (pregnancy)

Characteristics of Megaloblastic Macrocytic Anemia
- Pancytopenia
- Hypersegmented neutrophils
- Megaloblastic bone marrow
Vitamin B₁₂ Deficiency

- B₁₂ (cobalamin) see Family Medicine, Nutrition, FM6
- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

Etiology

<table>
<thead>
<tr>
<th>Diet</th>
<th>Gastric</th>
<th>Intestinal Absorption</th>
<th>Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict vegan</td>
<td>Mucosal atrophy</td>
<td>Malabsorption</td>
<td>Transcobalamin</td>
</tr>
<tr>
<td>More likely to present in</td>
<td>Gastritis, autoimmune</td>
<td>Crohn’s, celiac sprue,</td>
<td>II deficiency</td>
</tr>
<tr>
<td>pediatric population</td>
<td>Pernicious anemia (see below)</td>
<td>pancreatic</td>
<td>IF receptor defect</td>
</tr>
<tr>
<td>Vegetarian in pregnancy</td>
<td>Post-gastrectomy</td>
<td>insufficiency, H. pylori</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Stagnant bowel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blind loop, stricture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fish tapeworm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection of ileum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neomycin, biguanides, PPI, N3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>vitamin, metformin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology of Pernicious Anemia
auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize B₁₂ as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of B₁₂
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- most common in Northern European Caucasians, usually >30 yr old (median age of 60 yr old)

Clinical Features
- neurological (severity of anemia and neurological sequelae depends on deficiency)
  - peripheral neuropathy (variable reversibility)
  - usually symmetrical, affecting lower limbs more than upper limbs
  - cord (irreversible damage)
  - subacute combined degeneration
    - posterior columns: decreased vibration sense, proprioception, and 2-point discrimination, parasthesia
    - pyramidal tracts: spastic weakness, ataxia
  - cerebral (common, reversible with B₁₂ therapy)
  - confusion, delirium, dementia
  - cranial nerves (rare)
  - optic atrophy

Investigations
- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
  - MCV >110 fl
  - low reticulocyte count relative to the degree of anemia (<2%)
- serum B₁₂ and RBC folate
  - caution: low serum B₁₂ leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B₁₂
  - alternatively, can measure elevated urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils
- bone marrow
  - hypercellularity
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- Schilling test (radiolabeled B₁₂ test, rarely done) to distinguish pernicious anemia from other causes
  - anti-intrinsic factor antibody, anti-parietal cell antibody

Treatment
- vitamin B₁₂ 1,000 µg IM or 1,000-1,200 µg PO if intestinal absorption intact, route and duration depends on cause
- less frequent, higher doses may be as effective (e.g. 1,000 µg IM q3mo)
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

Table 16. Etiology of Vitamin B₁₂ Deficiency

Pathology of Pernicious Anemia

<table>
<thead>
<tr>
<th>Diet</th>
<th>Gastric</th>
<th>Intestinal Absorption</th>
<th>Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict vegan</td>
<td>Mucosal atrophy</td>
<td>Malabsorption</td>
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<td>IF receptor defect</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Stagnant bowel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blind loop, stricture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fish tapeworm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection of ileum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Neomycin, biguanides,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vitamin, metformin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oral Vitamin B₁₂ vs. Intramuscular Vitamin B₁₂ for Vitamin B₁₂ Deficiency
Cochrane DB Syt Rev 2005;3:CD004655
Study: Systematic review. 2 RCTs met inclusion criteria; total 108 patients with follow-up from 90 d-4 mo.
Intervention: One study evaluated 1,000 µg of oral B₁₂ compared to 1,000 µg IM B₁₂ on the same dosing schedule. The other compared 2,000 µg daily oral B₁₂ to 1,000 µg IM B₁₂ on a less frequent dosing schedule. Neurological and hematological end points were evaluated.
Results: Meta-analysis was not attempted due to study heterogeneity. Both studies reported improvements in hematological and neurological end points in both oral and IM groups. No significant difference was observed between groups in either study.
Conclusions: Limited data suggests high dose oral vitamin B₁₂ (1,000-2,000 µg) is equivalent to IM vitamin B₁₂ on the same or less frequent dosing schedule. This data is limited by small sample sizes and short follow-up periods. However, it suggests that a 3 to 4 month trial of oral supplementation is a reasonable first choice for patients with B₁₂ deficiency.

Schilling Test

Part 1
- Tracer dose (1 µg) of radiolabeled B₁₂, given PO
- Flowing dose (1 mg) of unlabeled B₁₂ IM 1 h later to saturate tissue binders of B₁₂, thus allowing radioactive B₁₂ to be excreted in urine
- 24 h urine radiolabeled B₁₂ measured
- Normal >5% excretion (a normal excretion will only be seen if the low B₁₂ was due to dietary deficiency)

Part 2
- Same as part 1, but radiolabeled B₁₂ given with oral intrinsic factor
- Should be done only if first stage shows reduced excretion
- Normal test result (≥5% excretion) = pernicious anemia
- Abnormal test result (<5% excretion) = intestinal causes (malabsorption)
Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation (enriched in flour)
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables and fortified cereals

Etiology

<table>
<thead>
<tr>
<th>Diet/Deficiency</th>
<th>Malabsorption</th>
<th>Drugs</th>
<th>Increased Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>Celiac sprue</td>
<td>Anti-folates (methotrexate)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>IBD</td>
<td>Anticonvulsants (phenytoin)</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>Elderly/infants</td>
<td>Infiltrative bowel disease</td>
<td>Alcohol</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Poor intake</td>
<td>Short bowel syndrome</td>
<td>Oral contraceptive</td>
<td>Exfoliative dermatitis/psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hemodialysis</td>
</tr>
</tbody>
</table>

Clinical Features

- anemia, mild jaundice, glossitis, diarrhea, confusion, pallor
- unlike B12 deficiency, folate deficiency has no neurologic manifestations
- consider social history, alcohol/drug abuse, very poor diet (e.g. elderly, depressed)

Investigations

- similar to B12 deficiency (CBC, reticulocytes, blood film, RBC folate, serum B12)
- if decreased RBC folate, rule out B12 deficiency as cause

Management

- folic acid 1-5 mg PO OD x 1-4 mo; then 1 mg PO OD maintenance if cause is not reversible

Hemostasis

1. Primary Hemostasis

- cellular defense – involves the platelet and vWF predominantly
- goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 11a)
  - adhesion: platelets adhere to subendothelium via von Willebrand factor (vWF)
  - activation: platelets are activated resulting in change of shape and release of ADP and thromboxane A2
  - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

2. Secondary Hemostasis

- platelet plug is reinforced by production of fibrin clot (Figure 11b)
- extrinsic (initiation) pathway: initiation of coagulation in vivo
- intrinsic (amplification) pathway: amplification once coagulation has started via positive feedback
- both intrinsic and extrinsic pathways converge onto the common pathway which results in thrombin generation and fibrin formation

3. Fibrin Stabilization

- conversion from soluble to insoluble and stable clot

4. Fibrinolysis

- once healing initiated, clot dissolution via action of the fibrinolytic system

Never give folate alone to an individual with megaloblastic anemia because it will mask B12 deficiency and neurological degeneration will continue

Normal hemostasis occurs as a result of the balance between procoagulant and anticoagulant factors

Phases of Hemostasis

- Primary hemostasis
  Vascular response and platelet plug formation via vWF
- Secondary hemostasis
  Fibrin clot formation
- Fibrin stabilization
  Fibrinolysis
Table 18. Commonly Used Tests of Hemostasis

<table>
<thead>
<tr>
<th>Type of Hemostasis</th>
<th>Test</th>
<th>Reference Range</th>
<th>Purpose</th>
<th>Examples of Associated Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Platelet count</td>
<td>150-400 x 10^9/L</td>
<td>To quanitate platelet number</td>
<td>Low in ITP, HUS/TTP, DIC</td>
</tr>
<tr>
<td>Secondary</td>
<td>aPTT</td>
<td>22-35 s</td>
<td>Measures intrinsic pathway (factors VIII, IX, XII) and common pathway</td>
<td>Prolonged in hemophilia A and B (if factor deficiency is below reagent threshold of detection)</td>
</tr>
<tr>
<td></td>
<td>PT</td>
<td>11-24 s</td>
<td>Measures extrinsic pathway (factor VII) and common pathway</td>
<td>Prolonged in vitamin K deficiency, vitamin K antagonist therapy, factor VII deficiency</td>
</tr>
<tr>
<td></td>
<td>INR</td>
<td>0.8-1.2</td>
<td>Used to monitor warfarin therapy and for assessment of hepatic function</td>
<td></td>
</tr>
<tr>
<td>Mixing studies</td>
<td></td>
<td></td>
<td>May differentiate inhibitors of clotting factor(s) from a deficiency in clotting factors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mix patient’s plasma with normal plasma in 1:1 ratio and repeat abnormal test</td>
<td></td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>Euglobulin lysis time</td>
<td>N &gt; 90 min</td>
<td>Looks for accelerated fibrinolysis</td>
<td>May be accelerated in DIC or factor XIII deficiency. Decreased in hereditary deficiency of fibrinogen</td>
</tr>
</tbody>
</table>

Other

- Fibrinogen
- D-dimer
- Specific factor assays (e.g. factor VIII)
- Lupus anticoagulant
- Thrombophilia tests (e.g. activated protein C resistance)
- von Willebrand tests (vWF antigen, Ristocetin cofactor activity, factor VIII)

Table 19. General Rules of Thumb: Signs and Symptoms of Disorders of Hemostasis

<table>
<thead>
<tr>
<th></th>
<th>Primary (Platelet, vWF)</th>
<th>Secondary (Coagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Cuts</td>
<td>Excessive, prolonged bleeding</td>
<td>Normal/slightly prolonged bleeding</td>
</tr>
<tr>
<td>Onset After Injury</td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td>Site of Bleeding</td>
<td>Superficial (nasal, gingival, GI tract, vaginal), skin</td>
<td>Deep i.e. joints, muscles Excessive post-traumatic</td>
</tr>
<tr>
<td>Lesions</td>
<td>Petechiae, ecchymoses</td>
<td>Hemarthroses, hematomas</td>
</tr>
</tbody>
</table>

Tests of Secondary Hemostasis

- PT/INR: Tennis is played outside (Extrinsic pathway)
- PTT: Tennis is played inside (Intrinsic pathway)

Causes of an Prolonged PTT Without Bleeding include:
1. Early contact factor (Factor XII, HMWK, PK) deficiency
2. Lupus anticoagulant
3. Inappropriate blood draw
4. Heparin contamination
5. Erythrocytosis (laboratory artifact)

Consider PTT
- IV heparin, argatroban monitoring
- Hemophilia A/B, factor XI deficiency, severe vWF
### Disorders of Primary Hemostasis

#### Definition
- Inability to form an adequate platelet plug due to
  - Disorders of blood vessels
  - Disorders of platelets: abnormal function/numbers
  - Disorders of vWF

#### Classification

<table>
<thead>
<tr>
<th>Low platelet count:</th>
<th>Normal platelet count:</th>
<th>Hereditary</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia (see H7)</td>
<td>Platelet dysfunction</td>
<td>Osler-Weber-Rendu</td>
<td>Purpura simplex (easy bruising)</td>
</tr>
<tr>
<td>Decreased production</td>
<td></td>
<td>Connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>• Aplastic anemia</td>
<td></td>
<td></td>
<td>• Purpura simplex (easy bruising)</td>
</tr>
<tr>
<td>Increased destruction</td>
<td></td>
<td></td>
<td>• Senile purpura</td>
</tr>
<tr>
<td>• ITP</td>
<td></td>
<td></td>
<td>• Dysproteinemias</td>
</tr>
<tr>
<td>• TTP/HUS</td>
<td></td>
<td></td>
<td>• HSP</td>
</tr>
<tr>
<td>• HIT</td>
<td></td>
<td></td>
<td>• Scaly</td>
</tr>
<tr>
<td>Sequestration</td>
<td></td>
<td></td>
<td>• Cushing's syndrome</td>
</tr>
<tr>
<td>• Splenomegaly</td>
<td></td>
<td></td>
<td>• Infections</td>
</tr>
<tr>
<td>Hereditary</td>
<td></td>
<td></td>
<td>• Drugs (ASA, E2OH, NSAIDs)</td>
</tr>
<tr>
<td>• Bernard Soulier syndrome (GPIb deficiency)</td>
<td></td>
<td></td>
<td>• Uremia/CRF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Myeloproliferative disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CRF** = chronic renal failure; **HSP** = Henoch-Schönlein purpura

#### Table 20. Lab Values in Disorders of Hemostasis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>PT</th>
<th>PTT</th>
<th>Platelet Count</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A/B</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>N*</td>
</tr>
<tr>
<td>vWD</td>
<td>N</td>
<td>±</td>
<td>N/4</td>
<td>N*</td>
</tr>
<tr>
<td>DIC</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N/4</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>↑</td>
<td>N/↑</td>
<td>N/4</td>
<td>N</td>
</tr>
<tr>
<td>ITP</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>TTP</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura; vWD = von Willebrand disease; * = anemia may develop from progressive iron deficiency and/or active bleeding.

#### Table 21. Features for Childhood vs. Adult Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Childhood ITP, see Pediatrics</th>
<th>Adult ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Age</td>
<td>2-6 yr</td>
<td>20-40 yr</td>
</tr>
<tr>
<td>Gender</td>
<td>None</td>
<td>F&gt;M (3:1)</td>
</tr>
<tr>
<td>History of Recent Infection</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset of Bleed</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Duration</td>
<td>Usually wk</td>
<td>Mo to yr</td>
</tr>
<tr>
<td>Spontaneous Remissions</td>
<td>80% or more</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

#### Terminology of ITP
- Primary: isolated thrombocytopenia (platelet count <100x10⁹/L) with no other cause of thrombocytopenia
- Secondary: thrombocytopenia associated with another condition (e.g. HIV, HCV, SLE, CLL)
- Drug-induced: drug-dependent platelet antibodies causing platelet destruction

#### Consider PT/INR
- Warfarin
- Liver disease
- Risk factor for vitamin K deficiency (e.g. malabsorption, cholestasis, malnutrition)

#### Consider both PTT and PT/INR
- Suspected DIC
- Trauma patient, or requiring massive transfusion protocol
- Bleeding patient
- Patient receiving thrombolytic therapy

#### Drugs Associated with Thrombocytopenia
- TMP-SMX
- Heparin
- NSAIDs
- Vancomycin
- Digezin
- Acetaminophen
- Rifampin
- Amiodarone
- Ethanol
- Ethambutol
- Guanidine
- H-antagonists
- Amphotericin B
- Quinidine
**Classification of primary ITP**
- acute: newly diagnosed (diagnosis to 3 mo)
- persistent: 3-12 mo from diagnosis
- chronic >12 mo
- refractory: post-splenectomy

**Pathophysiology**
- primary or secondary ITP
  - an acquired immune-mediated disorder (pathophysiology incompletely understood)
    - anti-platelet antibodies bind to platelet surface → increased splenic clearance
    - impaired platelet production
    - helper T-cell and cytotoxic T-cell activation also implicated in platelet destruction

**Clinical Presentation**
- variable presentation: asymptomatic, fatigue, minimal bruising, mucocutaneous bleed, intracranial bleed
- assess for symptoms/signs suggesting a secondary cause

**Investigations**
- CBC and reticulocyte count: thrombocytopenia
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets (rule out platelet clumping)
- HIV, HCV, H. pylori serology
- vitamin B12, ANA, C3, C4, depending on clinical symptoms
- bone marrow aspirate and biopsy: increased number of megakaryocytes
  - recommended in patients >60 yr of age, pre-splenectomy or have failed traditional ITP therapy, those with systemic symptoms, an abnormal blood film
- bone marrow aspirate and biopsy should be considered if there is any suspicion of diminished bone marrow function (e.g. myelodysplasia, infiltration)

**Treatment**
- rarely indicated if platelets >30 x 10⁹/L unless active bleeding, trauma, or surgery
- emergency treatment (active bleeding [CNS, GI, or GU] or in need of emergency surgery)
  - general measures: stop drugs that reduce platelet function, control blood pressure, minimize trauma
  - corticosteroids: prednisone (1 mg/kg) or dexamethasone (40 mg PO x 4 d)
  - antifibrinolytic: tranexamic acid (1 g PO tid or 1 g IV q6h) if mucosal bleeding
  - IVIg 1 g/kg/d x 2 doses
  - platelet transfusion: for refractory, major bleeding or need for urgent surgery (expect that platelet recovery will be diminished)
  - emergency splenectomy: may be considered, vaccinations prior if possible (pneumococcus, meningococcus, H. influenzae b)
  - management of intracranial bleeding: IV steroids, IVIg, platelets
- non-urgent treatment (Platelet count <20-30 x 10⁹/L and no bleeding)
  - 1st line
    - corticosteroids (dexamethasone 40 mg qd x 4 d x 1-4 cycles (not wk) or prednisone x 3 wk then taper)
    - IVIg
    - anti-D: appropriate for Rh+ non-splenectomized patients, but can cause hemolysis (avoid if low Hb at baseline or if DAT is positive)
  - 2nd line
    - splenectomy (need vaccinations prior to splenectomy: pneumococcus, meningococcus, H. influenzae b)
    - rituximab
  - 3rd line
    - thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag) – may be considered for second line therapy if funding available
    - immunomodulating therapy (azathioprine, cyclophosphamide, danazol, vincristine)

**Definitions of Response to Treatment**
- complete response: platelet >100
- partial response: platelet 30-100
- no response: platelet <30

**Prognosis**
- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- overall relatively benign, life-expectancy similar to general population (however, risk of mortality from bleeding/infection increases with advancing age)
- major concern is spontaneous intracranial hemorrhage if platelet <5 x 10⁹/L, more common in the elderly
Table 22. Heparin-Induced Thrombocytopenia (HIT)

| Pathophysiology | Immune mediated Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system |
| Diagnosis | Suspected with intermediate or high probability HIT Score (Table 23) Confirm with ELISA testing and SRA testing |
| Onset of Decreased Platelets | 5-15 d (if previously exposed to heparin within 100 d, HIT can develop in hours due to an anamnestic response) |
| Risk of Thrombosis | ~30% to 50% (25% of events are arterial) |
| Clinical Features | Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney) Heparin-induced skin necrosis (with LMWH) Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.) Transient global amnesia (rare) |
| Specific Tests | Re test clinical scoring models can help rule-out HIT: 4-Ts (see Table 23) and the HIT Expert Probability (HEP) score 14C serotonin release assay (uses donor platelets with 14C serotonin and heparin with patient’s plasma) ELISA for HIT-Ig (more sensitive, less specific than serotonin assay) Ultrasound of lower limb veins for DVT |
| Management | Clinical suspicion of HIT should prompt discontinuation of heparin and LMWH (specific tests take several days) Initiate anticoagulation with a non-heparin anticoagulant: e.g. argatroban, danaparoid, fondaparinux, bivalirudin unless there is a strong contraindication (duration of treatment at least 2-3 mo if no thrombotic event, and at least 3-6 mo if thrombotic event has occurred) Warfarin should only be restarted when platelet count >150 x 10^9/L Allergy band and alert in patient records |

Table 23. The 4-T Pre-Test Clinical Scoring Model for HIT

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thrombocytopenia</td>
<td>Platelet count fall &gt;50% AND platelet nadir ≥20 x 10^9/L</td>
<td>Platelet count fall 30-50% OR platelet nadir 10-19 x 10^9/L</td>
<td>Platelet count fall &lt;30% OR platelet nadir &lt;10 x 10^9/L</td>
</tr>
<tr>
<td>2. Timing of Platelet Count Fall</td>
<td>Clear onset between 5-10 d of heparin exposure OR platelet count fall at ≤1 d if prior heparin exposure within last 30 d</td>
<td>Consistent with fall in platelet count at 5-10 d but unclear (e.g. missing platelet counts) OR onset after day 10 OR fall ≤1 d with prior heparin exposure within 30-100 d</td>
<td>Platelet count fall after &lt;4 d of heparin exposure, and no recent heparin</td>
</tr>
<tr>
<td>3. Thrombosis or Other Sequelae</td>
<td>Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus</td>
<td>Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven</td>
<td>None</td>
</tr>
<tr>
<td>4. Other Causes for Thrombocytopenia</td>
<td>None apparent</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

6.5 points = high probability of HIT; 4.5 points = intermediate probability of HIT; 0.3 points = low probability of HIT

J Thromb Haemos 2006;4:759-765
Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Table 24. TTP and HUS

<table>
<thead>
<tr>
<th></th>
<th>TTP</th>
<th>HUS (see Pediatrics, P71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Predominantly adult</td>
<td>Predominantly children and elderly</td>
</tr>
</tbody>
</table>
| **Etiology** | Deficiency of metalloproteinase that breaks down ultra-large vWF multimers: ADAMTS13  
Congenital (genetic absence of ADAMTS-13)  
Acquired (drugs, malignancy, transplant, HIV-associated, idiopathic) | Shiga toxin (E. coli serotype O157:H7) in 90%  
Other bacteria, viruses, genetic causes, drugs |
| **Clinical Features** | 1. Thrombocytopenia  
2. MAHA/TMA  
3. Neurological symptoms: headache, confusion, focal defects, seizures  
4. Symptoms can be mild and non-specific | 1. Severe thrombocytopenia  
2. MAHA/TMA  
3. Acute kidney injury  
4. Bloody Diarrhea  
5. GI prodrome |
| **Investigations (both TTP, HUS)** | CBC and blood film: decreased platelets and schistocytes  
PT, aPTT, fibrinogen: normal  
Markers of hemolysis: increased unconjugated bilirubin, increased LDH, decreased haptoglobin  
Negative Coombs test | Creatinine and urea to follow renal function  
ADAMTS-13 gene, activity or inhibitor testing (TTP) |
| **Management** | Medical emergency  
Plasma exchange ± steroids  
Platelet transfusion avoided unless life-threatening bleed (associated with microvascular thrombosis)  
Plasma infusion if plasmapheresis is not immediately available | Supportive therapy (fluids, RBC transfusion, nutrition, etc.)  
Some evidence for plasma exchange  
Possible role of Eculizumab (C5 antibody blocks complement activation) for neurologic symptoms |

Note: atypical HUS is a complex disease with different etiology, treatment depends on genetic abnormalities.

von Willebrand Disease

**Pathophysiology**
- Most common inherited bleeding disorder (prevalence of 1%)
- Usually autosomal dominant (type 3 is autosomal recessive)
- Qualitative defect or quantitative deficiency of vWF depending on type
  - vWF needed for platelet adhesion/aggregation and acts as chaperone for Factor VIII (extending its half-life in circulation), therefore abnormality of vWF can affect both primary and secondary hemostasis
  - vWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion/aggregation
    - both large and small multimers complex with Factor VIII
    - vWF levels vary according to blood group (non-group O patients have higher levels than group O patients)

**Classification**
- Type 1: mild quantitative defect (decreased amount of vWF and proportional decrease in vWF activity) – 80% of cases
- Type 2: qualitative defect (vWF activity disproportionately lower than quantity) – 20% of cases
- Type 3: severe total quantitative defect (virtually no vWF produced), 1 per million

**Clinical Features**
- Bleeding history is the single most important predictor of an underlying bleeding disorder
- Validated, standardized bleeding assessment tools (e.g. ISTH-BAT) to facilitate exploration of the bleeding history
- Mucocutaneous bleeding (easy bruising, epistaxis, heavy menstrual bleeding, peripartum bleeding, post-dental extraction bleeding, post-operative bleeding, gastrointestinal bleeding)
- Type 3 vWD patients can experience musculoskeletal bleeding due to significant deficiency in FVIII due to lack of FVIII chaperoning as vWF is absent

**Investigations**
- CBC, platelet, vWF:Antigen (determine how much vWF is present), vWF:Ristocetin cofactor activity (determine how well vWF bind to platelet), Factor VIII (determine how well vWF chaperon with FVIII), PT
- Tests to further categorize type/subtype of vWD: multimer analysis, ristocetin induced platelet agglutination, genetic studies
Table 25. Investigations in vWD

<table>
<thead>
<tr>
<th>Test</th>
<th>Expected Result</th>
<th>Test</th>
<th>Expected Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT</td>
<td>N/†</td>
<td>von Willebrand antigen</td>
<td>↓</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>N/4</td>
<td>Blood group</td>
<td></td>
</tr>
<tr>
<td>P:1 Count</td>
<td>N/4</td>
<td>vWF multimer analysis</td>
<td>Multimer variants</td>
</tr>
<tr>
<td>Ristocetin Activity</td>
<td>↓ (cofactor for vWF-F1t binding)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**
- desmopressin (DDAVP®) is effective treatment for 85-90% of patients with type 1 vWD and for some subtypes of type 2 vWD
  - causes release of vWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs after 4 consecutive doses
  - need to document responsiveness with "DDAVP challenge"
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
- vWF:FVIII concentrate (Humate P®, Wilate®) if DDAVP unresponsive/clinically ineffective or for severe bleeding episode
  - need to monitor vWF and factor VIII levels (very high factor VIII level can be prothrombotic)
  - gynecologic focused care for heavy menstrual bleeding (NB estrogens have the added benefit of increasing vWF levels)

**Prognosis**
- patients with mild type 1 vWD have auto-correction of vWF deficiency in pregnancy
- patients are best managed by a hematologist, ideally one who works in a Hemophilia Treatment Centre (HTC)

**Disorders of Secondary Hemostasis**

**Definition**
- inability to form an adequate fibrin clot
  - disorders of clotting factors or co-factors
  - disorders of proteins associated with fibrinolysis
- characterized by delayed bleeding, deep muscular bleeding, spontaneous hemarthroses

**Table 26 Classification of Secondary Hemostasis Disorders**

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII: Hemophilia A, vWD</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Factor IX: Hemophilia B (Christmas Disease)</td>
<td>DIC</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Vitamin K deficiency</td>
</tr>
<tr>
<td>Other factor deficiencies are rare</td>
<td>Acquired inhibitors (FVIII most common)</td>
</tr>
</tbody>
</table>

**Hemophilia A (Factor VIII Deficiency)**

**Pathophysiology**
- X-linked recessive, 1/5,000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

**Clinical Features**
- see Table 19  Signs and Symptoms of Disorders of Hemostasis, H26
- older patients may also have HIV or HCV from contaminated blood products

**Investigations**
- prolonged aPTT, normal INR (PT)
- decreased Factor VIII (<40% of normal)

**Treatment**
- desmopressin (DDAVP®) in mild hemophilia A
  - Factor VIII concentrate for
    - prophylaxis
    - on-demand (i.e. to treat a bleed)
  - anti-fibrinolytic agents (e.g. tranexamic acid)

**Hemophilia B (Factor IX Deficiency)**

- X-linked recessive, 1/30,000 males; approximately half have severe disease (factor IX activity <1% of normal)
- clinical and laboratory features identical to hemophilia A (except decreased Factor IX)
- treatment: Factor IX concentrate (prophylaxis or on-demand), anti-fibrinolytic agents
**Factor XI Deficiency**

- autosomal recessive; more common in Ashkenazi Jewish population
- usually mild, often diagnosed in adulthood
- Fac or XI level does not correlate with bleeding risk – risk of bleeding correlates with a previous history or family history of bleeding
- treatment: antifibrinolytic agents, frozen plasma, Factor XI concentrate

**Liver Disease**

- see Gastroenterology, G32

**Pathophysiology**

- deficient synthesis of all factors except VIII (also made in endothelium)
- aberrant or diminished synthesis of fibrinogen (factor I)
- diminished synthesis of natural anticoagulants and altered regulation of fibrinolysis

**Investigations**

- peripheral blood film: target cells
- primary hemostasis affected
  - thrombocytopenia 2° to hypersplenism, nutritional deficiency, direct bone marrow toxicity related to alcohol, diminished production from chronic viral infections (e.g. HCV), decreased production of thrombopoietin
  - secondary hemostasis affected
  - elevated INR (PT), aPTT and TT, low fibrinogen in end-stage liver disease

**Treatment**

- supportive, treat liver disease, blood products if active bleeding (frozen plasma, platelets, cryoprecipitate)

**Vitamin K Deficiency**

**Etiology**

- drugs
  - vitamin K antagonist (e.g. Warfarin) – diminished production of functional Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
  - poor diet (especially in alcoholics) e.g. prolonged fasting or starvation
  - biliary obstruction
  - chronic liver disease (decreased stores)
  - fat malabsorption (e.g. celiac disease, disorders of bile or pancreatic secretion, intestinal disease, CF)
  - hemorrhagic disease of newborn, see Pediatrics, P42

**Investigations**

- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX, X (vitamin K-dependent)

**Treatment**

- hold anticoagulant if vitamin K antagonist on board
- vitamin K PO if no active bleeding
- if bleeding give vitamin K 10 mg IV (reversal may take up to 12 h)
- if life threatening bleeding and vitamin K antagonist used, give prothrombin complex concentrate (PCC) or FP if PCC contraindicated
- PCCs are contraindicated if there is a previous history of HIT (heparin is within the PCC product)

**Disseminated Intravascular Coagulation**

**Definition**

- excessive, dysregulated release of plasmin and thrombin leading to intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage or thromboembolism

**Etiology**

- occurs as a complication of many other severe medical, surgical or obstetrical conditions
- widespread endothelial damage and extensive inflammatory cytokine release
## Hematology

### Hypercoagulable Disorders

#### Hypercoagulability Workup – Venous Thrombosis

- workup for malignancy is suggested in the event of abnormal blood work, constitutional symptoms or physical exam suggestive of cancer
- workup for hypercoagulable state is controversial and should only be done if it will alter treatment decisions
- recommendations for a hypercoagulable workup include:
  - patients with recurrent or multiple thrombosis only if it will change management plans
  - warfarin-induced skin necrosis or neonatal purpura fulminans (protein C or S deficiency)
  - consider for patients with a family history of VTE who are considering OCP use
  - consider for patients who present with thrombosis at an unusual venous site only if it will change management plans
- arterial thrombotic events have only been proven to be associated with APLA, HIT, JAK2 MPNs, and PNH

### Table 27. Etiology of DIC

<table>
<thead>
<tr>
<th>Activation of Procoagulant Activity</th>
<th>Endothelial Injury</th>
<th>Reticuloendothelial Injury</th>
<th>Vascular Stasis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid antibody syndrome (APS)</td>
<td>Infections/sepsis</td>
<td>Liver disease</td>
<td>Hypotension</td>
<td>Acute hypoxia/acidosis (check lactate)</td>
</tr>
<tr>
<td>Intravascular hemolysis</td>
<td>Vasculitis</td>
<td>Splenectomy</td>
<td>Hypovolemia</td>
<td></td>
</tr>
<tr>
<td>Incompatible blood, malaria</td>
<td>Metastatic adenocarcinoma</td>
<td>Pulmonary embolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue injury</td>
<td>Aortic aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetric complications, trauma, burns, crush injuries</td>
<td>Giant hemangioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Solid tumors, hematologic malignancies (especially APLM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snake venom, fat embolism, heat stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Features

- presence of both hemorrhage and clotting

### Table 28. Clinical Features of DIC

<table>
<thead>
<tr>
<th>Signs of Microvascular Thrombosis</th>
<th>Signs of Hemorrhagic Diathesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological: multifocal infarcts, delirium, coma, seizures</td>
<td>Bleeding from any site in the body (2 to decreased platelets and clotting factors)</td>
</tr>
<tr>
<td>Skin: focal ischemia, superficial gangrene</td>
<td>Neurologic: intracranial bleeding</td>
</tr>
<tr>
<td>Renal: oliguria, azotemia, cortical necrosis</td>
<td>Renal: hematuria</td>
</tr>
<tr>
<td>Pulmonary: ARDS</td>
<td>Mucosal: gingival oozing, epistaxis, massive bleeding</td>
</tr>
<tr>
<td>G: acute ulceration</td>
<td></td>
</tr>
<tr>
<td>RBC: microangiopathic hemolysis</td>
<td></td>
</tr>
</tbody>
</table>

### Investigations

- primary hemostasis: decreased platelets
- secondary hemostasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
- fibrinolysis: increased FDPs or D-dimers, short euglobulin lysis time (i.e. accelerated fibrinolysis)
- extent of fibrin deposition: urine output, RBC fragmentation

### Treatment

- recognize early and treat underlying disorder - supportive measures: hemodynamic and/or ventilator support, aggressive hydration, RBC transfusion if severe bleed
- in hemorrhage: replacement of hemostatic elements with platelet transfusion, frozen plasma, cryoprecipitate
  - British Hematology Guidelines:
    - maintain platelets >50 x 10⁹/L, hemoglobin >80 g/L, calcium between 2.2-2.7 mmol/L, and avoid hypothermia
    - 4-5 units of FF if INR >1.5 or aPTT >38
    - 10 units of cryoprecipitate if fibrinogen <1 g/L
    - 1 adult dose of buffy-coat platelets if <10 x 10⁹/L (<20 if febrile, <50 before invasive procedure)
- in thrombotic phase: UFH or LMWH in critically ill, non-bleeding patients

### Table 29. Screening Test Abnormalities in Coagulopathies

<table>
<thead>
<tr>
<th>Increased INR Only</th>
<th>Increased PTT Only</th>
<th>Both Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Hemophilia A and B</td>
<td>Prothrombin deficiency</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>Heparin</td>
<td>Severe fibrinogen deficiency</td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td>Antiphospholipid Ab</td>
<td>Factor V and X deficiency</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Intrinsic factor inhibitors (e.g. FVIII)</td>
<td>Severe liver disease</td>
</tr>
<tr>
<td>Factor VII inhibitors</td>
<td>Factor XI and XII deficiency</td>
<td>Factor V and X, prothrombin, and fibrinogen inhibitors</td>
</tr>
</tbody>
</table>

### Hypercoagulable Disorders

#### Differential Diagnosis of Elevated D-Dimer

- Arterial thromboembolic disease (MI, CVA, acute limb ischemia, AFib, intracardiac thrombus)
- Venous thromboembolic disease (DVT, PE)
- DIC
- Preeclampsia and eclampsia
- Abnormal fibrinolysis; use of thrombolytic agents
- Cardiovascular disease, CHF
- Severe infection/sepsis/inflammation
- Surgery-trauma (tissue ischemia, necrosis)
- Systemic inflammatory response syndrome
- Vasocclusive episode of sickle cell disease
- Severe liver disease
- Malignancy
- Renal disease (nephrotic syndrome, acute/chronic renal failure)
- Normal pregnancy
- Venous malformation

#### Levels of fibrinogen can still be normal in DIC as it is an acute phase reactant

#### Serial fibrinogen levels should be measured to see if there is a trending decrease along with an increase in D-dimer

### Important Etiologies of DIC

- Obstetric complications
- Malignancy
- Infection
- Trauma
- Shock

### American Society of Hematology Choosing Wisely Recommendations

1. Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobilization)
2. Do not use inferior vena cava filters routinely in patients with acute venous thromboembolism
• workup
  • initial
    • CBC, blood smear, coagulation studies, liver/renal function, urinalysis, hemolysis markers (if anemic)
    • malignancy history, age appropriate cancer screening
    • serology: antiphospholipid antibodies (APLA)
  • post-treatment (or ≥26 wk, as protein levels depleted/consumed by clot)
    • antithrombin (not on heparin)
    • proteins C, S (not on warfarin)
• note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state
  • thus, more focus on the reversible/treatable causes (APLA, cancer, etc.)

SELECTED CAUSES OF HYPERCOAGULABILITY LEADING TO VENOUS THROMBOEMBOLISM

Activated Protein C Resistance (Factor V Leiden)
• most common cause of hereditary thrombophilia
  • 3–7% of European Caucasian population are heterozygotes
  • point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

Prothrombin Gene Mutation (PT) G20210A
• 1 3% of European Caucasian population are heterozygotes
  • G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Protein C and Protein S Deficiency
• protein C inactivates Factor Va and VIIIa using protein S as a cofactor
  • protein C deficiency
    • homozygous or compound heterozygous: neonatal purpura fulminans
    • heterozygous
      • type I: decreased protein C levels
      • type II: decreased protein C activity
    • acquired: liver disease, sepsis, DIC, warfarin, certain chemotherapeutic agents
    • 1/3 of patients with warfarin necrosis have underlying protein C deficiency
  • protein S deficiency
    • type I: decreased free and total protein S levels
    • type II: decreased protein S activity
    • type III: decreased free protein S levels
    • acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, warfarin

Antithrombin Deficiency
• antithrombin slowly inactivates thrombin in the absence of heparin, rapidly inactivates thrombin in the presence of heparin
  • autosomal dominant inheritance, urinary losses in nephrotic syndrome, or reduced synthesis in liver disease
  • diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
  • deficiency may result in resistance to unfractionated heparin (LMWH may be considered, with monitoring of anti-Xa levels)
  • heparin resistance: suspect if >35,000 units of UFH required during 24 h use

Elevated Factor VIII Levels
• an independent marker of increased incident and recurrent thrombotic risk, but levels can also be increased in numerous states as an acute phase reactant, therefore its clinical use is controversial

Congenital Dysfibrinogenemia
• may predispose to thromboembolic disease, bleeding or both

Disorders of Fibrinolysis
• includes congenital plasminogen deficiency, tissue plasminogen activator deficiency, although association with VTE risk is not clear

Antiphospholipid Antibody Syndrome (APS)
• definition: ≥1 clinical and ≥1 laboratory criteria
  • clinical: thrombosis, recurrent (≥3) early pregnancy losses <10 wk, one late fetal loss ≥10 wk (morphologically normal), or premature birth before 34 wk due to (pre)eclampsia or placental insufficiency
  • laboratory: must be confirmed on two occasions, tested ≥12 wk apart): anticardiolipin antibodies, anti-β2 glycoprotein-I antibody, lupus anticoagulant
  • mechanism: not well understood, antibodies interact with platelet membrane phospholipid causing increased activation; can also interfere with thrombin regulation, fibrinolysis, and inhibit the protein C pathway
• see Rheumatology, RH12
Venous Thromboembolism

Definition
- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- superficial thrombophlebitis, deep vein thrombosis (DVT), and pulmonary embolism (PE)
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- more common in lower extremity than upper extremity
- incidence ~1% if age >60 yr
- most important sequelae are pulmonary embolism (~50% chance with proximal DVT) and chronic venous insufficiency

Etiology (Virchow’s Triad)
- endothelial damage
  - exposes endothelium to prompt hemostasis
  - leads to decreased inhibition of coagulation and local fibrinolysis
- venous stasis
  - immobilization (post-MI, CHF, stroke, post-operative) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see Hypercoagulable Disorders, H33)
  - acquired
    - age (risk increases with age)
    - surgery (especially orthopedic, thoracic, GI, and GU)
    - trauma (especially fractures of spine, pelvis, femur or tibia, spinal cord injury)
    - neoplasms (especially lung, pancreas, colon, rectum, kidney, and prostate)
    - blood dyscrasias (myeloproliferative neoplasms, especially PV, ET), PNH, hyperviscosity (multiple myeloma, polycythemia, leukemia, sickle cell disease)
    - prolonged immobilization (CHF, stroke, MI, leg injury)
    - hormone related (pregnancy, OCP, HRT, SERMs)
    - APS
  - idiopathic (10-20% are later found to have cancer)

Clinical Features of DVT
- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth, and tenderness; purple-blue colour
- palpable cord (thrombosed vein)
- phlegmasia alba dolens (white appearance) and phlegmasia cerula dolens (acute pain and edema) with massive thrombosis
- Homan's sign (pain with foot dorsiflexion) is unreliable

Differential Diagnosis of DVT
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, arterial occlusive disease

Investigations for DVT
- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease and no other acute medical issues
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
- sensitivity for calf DVT ~70%
- other non invasive tests include MRA and impedance plethysmography
- venography is the gold standard, but is expensive, invasive, and higher risk
- CTPA or V/Q scan if PE suspected

Post-Thrombotic Syndrome
- development of chronic venous stasis signs and symptoms secondary to a deep venous thrombosis
- symptoms: pain, venous dilatation, edema, pigmentation, skin changes, venous ulcers
- clinical severity can be estimated based on the Villalta score
- large impact on quality of life following a DVT
- treatment: extremity elevation, exercise, continuous compression stockings, intermittent pneumatic compression therapy, skin/ulcer care
- for clinical features and treatment of PE, see Respirology, R18

Risk of VTE in Hospitalized Patients Receiving Ineffective Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 yr</td>
<td>1.79 (1.19-2.71)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.58 (1.01-2.51)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>1.67 (1.01-2.77)</td>
<td>0.06</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.94 (0.59-1.51)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>0.51 (0.38-0.70)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.10 (0.02-0.42)</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA III</td>
<td>0.33 (0.16-0.69)</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>1.44 (0.68-3.07)</td>
<td>0.27</td>
</tr>
<tr>
<td>Acute infectious disease</td>
<td>1.50 (0.94-2.46)</td>
<td>0.06</td>
</tr>
<tr>
<td>Acute rheumatic disease</td>
<td>1.45 (0.84-2.50)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Source: JAMA 2004;164:963-968

Wells’ Score for DVT

<table>
<thead>
<tr>
<th>Criteria (Score)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralysis, paresis, or recent orthopedic casting of lower extremity (1)</td>
<td></td>
</tr>
<tr>
<td>Recently bedridden (&gt;3 d) or major surgery within past 4 wk (1)</td>
<td></td>
</tr>
<tr>
<td>Localized tenderness in deep vein system (1)</td>
<td></td>
</tr>
<tr>
<td>Swelling of entire leg (1)</td>
<td></td>
</tr>
<tr>
<td>Cast swelling &gt;3 cm than other leg (measured 10 cm below the tibial tuberosity) (1)</td>
<td></td>
</tr>
<tr>
<td>Pitting edema greater in the symptomatic leg (1)</td>
<td></td>
</tr>
<tr>
<td>Collateral non-varicose superficial veins (1)</td>
<td></td>
</tr>
<tr>
<td>Active cancer or cancer treated within 6 mo (1)</td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis more likely than DVT (e.g. Baker’s cyst, cellulitis, muscle damage, superficial venous thrombosis) (2)</td>
<td></td>
</tr>
</tbody>
</table>

Total Score Interpretation
3-6: High probability 1-2: Moderate probability, 0-2: Low probability

Low Molecular-Weight Heparin vs. Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer
NEJM 2003;349:146-153

Study: RCT comparing the efficacy of LMWH (dalteparin) with an oral anti-coagulant agent (coumarin) in preventing recurrent thrombosis in patients with cancer.

Methods: Patients with cancer who had acute symptomatic proximal DVT, PE, or both were randomly assigned to either dalteparin or coumarin treatment for 6 mo.

Results: 27 of 336 patients in the dalteparin group had recurrent VTE versus 53 of 336 patients in the coumarin group (hazard ratio, 0.46; p=0.002). The probability of recurrent thromboembolism at 6 mo was 9% and 17% in dalteparin and coumarin groups respectively. There was no significant difference in bleeding rates. The mortality rate was 39% in the dalteparin group and 41% in the coumarin group.

Conclusions: In patients with cancer and acute VTE, dalteparin was more effective than coumarin in decreasing the risk of recurrent thromboembolism without increasing the risk of bleeding.
**Approach to Treatment of Venous Thromboembolism**

**Purpose**
- prevent further clot extension (3 mo duration is optimal)
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- treatment of massive iliofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications (e.g. postphlebitic syndrome, chronic venous insufficiency, and chronic thromboembolic pulmonary HTN)

**Initial Treatment**
- low molecular weight heparin (LMWH)
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; <1% HIT; safe and effective outpatient therapy
  - disadvantages: only partially reversible by protamine long-term use associated with osteoporosis co therapy
  - renal clearance
- unfractionated heparin (UFH)
  - in patient with average risk of bleed; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT or heparin levels with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- alternatives to LMWH and UFH
  - direct thrombin inhibitors (hirudin, lepirudin, argatroban)
  - direct factor Xa inhibitors (apixaban, rivaroxaban)
  - thrombolytic drugs (e.g. streptokinase, tPA) reserved for acute limb/life-threatening thrombosis, and low bleeding risk

**Long-Term Treatment**
- anticoagulation therapy
  - warfarin
    - standard treatment; should be initiated with heparin overlap: dual therapy for at least 48 hours with INR >2, due to initial prothrombotic state secondary to warfarin's inhibition of natural anticoagulants protein C/S, half-life of vitamin K factors and risk of warfarin-induced skin necrosis
  - INR: warfarin dosed to maintain INR at 2-3, monitor twice weekly for 1-2 wk. Discontinue heparin after INR =2.0 for 2 consecutive days
  - direct oral anticoagulants (DOACs)
    - apixaban or rivaroxaban; with no laboratory monitoring required, patients with CrCl > 50 ml/min
    - dabigatran (factor IIa inhibitor): LMWH or IV heparin for at least 5-10 days before initiating dabigatran, patients with CrCl >30 ml/min
    - important drug interactions to consider for DOACs (no relevant food interactions however)
    - cancer patients: LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients
  - duration of anticoagulant treatment
    - provoked VTE with transient risk factor: 3 mo
    - provoked VTE with ongoing risk factor: consider indefinite therapy with annual reassessment
    - first unprovoked VTE: at least 3 mo, subsequent reassessment
    - unprovoked proximal DVT or PE: consider indefinite therapy with annual reassessment
    - second unprovoked VTE: consider indefinite therapy
    - cancer-associated DVT: at least 3 mo, longer if continued evidence of cancer
  - IVC filters
    - temporary filter indicated only if acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (e.g. active bleeding) or if require interruption of anticoagulation (i.e. for urgent surgery)
    - must be retrieved once safe to do so as filter is pro-thrombotic in the long-term (consider anticoagulation if not retrieved)
  - special considerations
    - pregnancy: treat with LMWH during pregnancy, then LMWH or warfarin for 6 wk post-partum (minimum total anticoagulation time of 3-6 mo, but must include 6 wks post-partum, as this is a high risk period); avoid warfarin in pregnancy due to teratogenicity
    - surgery: avoid elective surgery in the first three months after a venous thromboembolic event
      - pre-operatively: IV heparin may be used up to 4-6 h pre-operatively
      - perioperatively: warfarin or DOACs discontinued for at least 3-5 d pre-operatively (consider mechanism of drug clearance)
        - surgery safe when INR <1.5 off of warfarin, normal PTT on dabigatran, drug-specific Xa level at zero for apixaban/ rivaroxaban/LMWH, normal PTT on IV unfractionated heparin

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**Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism**

Cochrane GB Syt Rev 2009;CD001367

**Study:** Meta-analysis of 8 RCTs (2,994 patients) comparing different durations of treatment with vitamin K antagonists in patients with symptomatic VTE

**Results:** In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of treatment (OR 0.18; 95% CI 0.13-0.28). In addition, there was no difference in risk of major bleeding complications (OR 2.81; 95% CI 1.49-4.82).

**Conclusion:** Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of bleeding exceeds the risk of recurrence of VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.

---

**Common Medications that Interact with Warfarin**
- Acetaminophen (interference with vitamin K metabolism)
- Aplinpranolol
- NSAIDs (GI injury)
- Fluconazole
- Metronidazole
- Sulfamethoxazole
- Tamoxifen

---

**Initiation of Warfarin Therapy Requires Bridging with Heparin Therapy for 4-5 Days**

- 10 mg loading dose (for example) of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state
- Warfarin decreases Factor VIII levels in first 48 h, INR is prolonged (most sensitive index to Factor VIII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after ~4 d)

---

**Low Risk Surgical Patients**
- <40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective abdominal, or thoracic surgery

**Moderate Risk Surgical Patients**
- >40 yr; 1 risk factor for VTE, GA >30 min

**High Risk Surgical Patients**
- >40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency or other risk factor

**High Risk Medical Patients**
- Heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have
- >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD)
**Hematologic Malignancies and Related Disorders**

**Myeloid Malignancies**

**Acute Myeloid Leukemia**

**Definition**
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

**Epidemiology**
- incidence increases with age; median age of onset is 65 yr old; 80% of acute adult leukemias
- accounts for 10-15% of childhood leukemias

**Figure 14. Overview of hematologic malignancies and related disorders**

**Table 30 Contraindications of Anticoagulant Therapy**

<table>
<thead>
<tr>
<th>Absolute Contraindications to Treatment</th>
<th>Relative Contraindications to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>Mild-moderate bleeding diathesis or thrombocytopenia</td>
</tr>
<tr>
<td>Severe bleeding diathesis or platelet count (&lt; 20 \times 10^9/L) ((&lt;20,000/mm^3))</td>
<td>Brain metastases</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Recent major trauma</td>
</tr>
<tr>
<td>Neurosurgery or ocular surgery within 10 d</td>
<td>Recent stroke</td>
</tr>
<tr>
<td>Other cell origin (\text{e.g. NK})</td>
<td>Major abdominal surgery within past 2 d</td>
</tr>
</tbody>
</table>

**Treatment of Pulmonary Embolism**
- see Respirology, R18

**Hematologic Malignancies and Related Disorders**

**Lymphoid Disorders**

**Leukemia**
- ALL
- CLL

**Lymphomas**
- B Cell
- T Cell

**Plasma Cell Dyscrasias**
- Multiple myeloma
- Waldenstrom’s macroglobulinemia

**Myeloid Disorders**

**Leukemia**
- AML
- MDS

**MPNs**
- ET
- CML
- IMF

**MDS**

**ALL** = acute lymphocytic leukemia; **AML** = acute myeloid leukemia; **CLL** = chronic lymphocytic leukemia; **CML** = chronic myeloid leukemia; **ET** = essential thrombocythemia; **IMF** = idiopathic myelofibrosis; **MDS** = myelodysplastic syndromes; **MGUS** = monoclonal gammopathy of unknown significance; **MPN** = myeloproliferative neoplasms; **PV** = polycythemia vera

**2008 WHO classification of AML (2016 Revision)**
- AML with recurrent genetic abnormalities:
  - AML with t(8;21)(q22;q22)RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16) RUNX1T1
  - AML with t(15;17)(q22;q12)CBFB-MYH11
  - APL, with PML-RARA
  - AML with t(11;16)(p13.1;q22)CBFB-MYH11
  - AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
  - AML with t(15;17)(q22;q12);CBFB-MYH11
  - AML with t(9;22)(q34;q11.2);DEK-NUP214
  - AML with t(8;21)(q22;q22);CBFB-MYH11
  - AML with t(9;22)(q34.1;q11.2);CBFB-MYH11
  - AML with inv(3)(q21.3q26.2)RUNX1T1
  - AML with t(6;9)(p23;q34.1);DEK-NUP214
  - AML with t(6;11)(p23;q23.3);MLLT3-KMT2A
  - AML with t(9;22)(q34.1;q11.2);CBFB-MYH11
  - AML with t(8;21)(q22;q22);CBFB-MYH11

**ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; MDS = myelodysplastic syndromes; MGUS = monoclonal gammopathy of unknown significance; MPN = myeloproliferative neoplasms; PV = polycythemia vera**
Risk Factors
- myelodysplastic syndromes (MDS), benzene, radiation, Down Syndrome, alkylating agents as treatment for previous malignancy

Pathophysiology
- etiology subdivided into:
  - primary: *de novo*
  - secondary: hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to:
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood – risk of leukostasis
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; tumour lysis syndrome

Clinical Features
- anemia, thrombocytopenia (associated with DIC in promyelocytic leukemia), neutropenia (even with normal WBC), leads to infections, fever
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - hepatosplenomegaly (in ALL)
  - lymphadenopathy (not marked in ALL)
  - gonads (in ALL)
  - skin: leukemia cutis or myeloid sarcoma
  - eyes: hemorrhages and/or whitish plaques, Roth spots, cotton wool spots, vision changes (uncommon)
- leukostasis/hyperleukocytosis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, priapism
  - associated with AML more than ALL
- metabolic effects; aggravated by treatment (rare)
  - increased uric acid → nephropathy, gout
  - release of phosphate → decreased Ca²⁺, decreased Mg²⁺
  - release of procoagulants → DIC (higher risk in acute promyelocytic leukemia)
  - decreased or normal K⁺ before treatment, increased K⁺ after treatment (from lysed cells)

Investigations
- blood work
  - CBC: anemia, thrombocytopenia, variable WBC
  - INR, aPTT, fibrin degradation products (FDP), fibrinogen (in case of DIC)
  - increased LDH, increased uric acid, increased PO₄³⁻ (released by leukemic blasts), decreased Ca²⁺, decreased K⁺
  - baseline renal and liver function tests
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- bone marrow aspirate for definitive diagnosis
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytochemical, and/or immunophenotypic features are used to establish lineage and maturation (see sidebar for WHO classification of AML H37)
- CXR to rule out pneumonia, ECG, MUGA scan prior to chemotherapy (cardiotoxic)

Treatment
- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
- all AML subtypes are treated similarly, except acute promyelocytic leukemia (APL) with t(15:17) translocation
- all-trans-retinoic acid (ATRA) added to induce differentiation; arsenic trioxide + ATRA combination therapy for APL is non-inferior to traditional chemotherapy
- treatment strategy
  1. *Induction*: chemotherapy to induce complete remission of AML (see sidebar)
     - several possible regimens (e.g. cytarabine with anthracycline [daunorubicin])
     - patients with poor response to initial induction therapy – worse prognosis
     - must ensure reversal of DIC, platelet transfusions if <10
  2. *Consolidation*: to prevent recurrence
     - intensive consolidation chemotherapy
     - stem cell transplantation – autologous or allogeneic (younger patients with better performance status)
- consider acceleration with hematopoietic growth factors (e.g. G-CSF) if severe infection develops
• supportive care
  • screening for infection via regular C&S of urine, stool, sputum, oropharynx, catheter sites, perianal area
  • fever: C&S of all orifices, CXR, start antibiotics
  • platelet and RBC transfusions (irradiated to prevent transfusion-related GVHD) + EPO
  • prevention and treatment of metabolic abnormalities
  • allopurinol, rasburicase for prevention of hyperuricemia

Prognosis
• achievement of first remission
  • 70-80% if ≤60 yr old, 50% if >60 yr old
  • median survival 12-24 mo
  • prognosis is most related to 1) cytogenetics; classified as favourable, intermediate, or adverse and 2) molecular studies (i.e. NPM1+/FLT3- mutations)
  • prognosis depends on cytogenetics, age, performance status, prior cytotoxic agents or radiation therapy

Myelodysplastic Syndromes

Definition
• heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias, and a variable risk of transformation to acute leukemias
• syndromes defined according to World Health Organization (WHO) classifications (see sidebar)

Pathophysiology
• disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular); formed elements sometimes exhibit qualitative functional defects
• intramedullary apoptosis: programmed cell death within bone marrow
  • both processes lead to reduced mature cells in periphery
  • <30% develop AML

Risk Factors
• elderly, post-chemotherapy, exposures (benzene, tobacco, radiation), inherited genetic abnormalities
• occurs in 4/100,000 patients >60 yr old

Clinical Features
• insidious onset: associated with pancytopenia; most patients asymptomatic at diagnosis
• infections and bleeding out of proportion with peripheral blood counts

Investigations
• diagnosed by:
  • anemia ± thrombocytopenia ± neutropenia
  • CBC and peripheral blood film
  • RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  • WBC: decreased granulocytes and abnormal morphology (e.g. bi-lobed or unsegmented nuclei = Pelger abnormality)
  • platelets: thrombocytopenia, abnormalities of size and cytoplasm (e.g. giant hypogranular platelets)
• bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
• bone marrow: dysplastic and often normocellular/hypercellular
• cytogenetics: high risk include partial or total loss of chromosomes 5, 7, and complex (>3 abnormalities)

Treatment
• low risk of transformation to acute leukemia (IPSS-R Very Low or Low)
  • erythropoietin stimulating agents weekly is first line in reducing transfusion requirements (EPO level must be <500)
  • If 5q deletion based on cytogenetics: lenalidomide PO
  • supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
  • high risk of transformation to acute leukemia (IPSS-R Intermediate, High or Very High)
  • supportive care
  • stem cell transplantation if age <65 yr
  • epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacytidine), histone deacetylase inhibitors

Prognosis
• Revised International Prognostic Scoring System (IPSS-R) uses 5 factors to estimate mean survival:
  • cytology, % bone marrow blasts, hemoglobin, platelets, absolute neutrophil count
  • based on the calculated score, a patient’s MDS prognostic risk is “Very Low,” “Low,” “Intermediate,” “High,” or “Very High” with a mean survival of 8.7, 5.3, 3.0, 1.6, and 0.8 yr, respectively
Myeloproliferative Neoplasms

Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets, and other cells of myeloid lineage)

Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)

Prognosis
- may develop marrow fibrosis with time
- all disorders may progress to AML

Table 31. Chronic Myeloproliferative Disorders

<table>
<thead>
<tr>
<th></th>
<th>CML</th>
<th>PV</th>
<th>IMF</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct</td>
<td>4/N</td>
<td>††</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>WBC</td>
<td>††</td>
<td>†</td>
<td>†/↓</td>
<td>N</td>
</tr>
<tr>
<td>Ph</td>
<td>†/↓</td>
<td>†</td>
<td>†/↓</td>
<td>†↑</td>
</tr>
<tr>
<td>Marrow Fibrosis</td>
<td>±</td>
<td>±</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Genetic Association</td>
<td>bcr-abl mut. (95%)</td>
<td>JAK2 mut. (96%)</td>
<td>JAK2 mut. (≈50%)</td>
<td>CALR mut (~30%)</td>
</tr>
</tbody>
</table>

CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; PV = polycythemia vera; CALR = Calreticulin

Chronic Myeloid Leukemia

Definition
- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

Epidemiology
- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

Pathophysiology
- Philadelphia chromosome (Ph)
  - translocation between chromosomes 9 and 22
  - the c-Abl proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (BCR) of chromosome 22 to produce BCR-Abl fusion gene, an active tyrosine kinase

Clinical Features
- 3 clinical phases
  - chronic phase: 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - accelerated phase: impaired neutrophil differentiation
    - circulating blasts (10-19%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytoopenia <100 x 10⁹/L
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
    - blast crisis: more aggressive course, blasts fail to differentiate
  - blast crisis: blasts (>20%) in peripheral blood or bone marrow; reflective of acute leukemia (1/3 ALL, 2/3 AML)
- clinical presentation
  - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
  - nonspecific symptoms
    - fatigue, weight loss, malaise, excessive sweating, fever
    - secondary to splenic involvement
    - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
    - splenomegaly (most common physical finding)
  - anemia
  - bleeding: secondary to platelet dysfunction
  - pruritus, PUD secondary to increased blood histamine
  - leukostasis, priapism, encephalopathy (rare): secondary to very elevated WBC (rare)

Investigations
- elevated WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
- WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
• peripheral blood film
  • leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  • presence of different mid-stage progenitor cells differentiates it from AML.
• bone marrow
  • myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
• molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
• abdominal imaging for spleen size

Treatment
• symptomatic
  • allopurinol and antihistamines
• chronic phase
  • imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for bcr abl
  • if loss of response or intolerance (~40%), trial of 2nd generation TKIs: dasatinib, nilotinib, or bosutinib
  • dasatinib and nilotinib may also be considered for first line management
• interferon-α: may improve response to tyrosine kinase inhibitors; typically now only used for pregnant patients
• hydroxyurea in palliative setting to reduce WBC
• accelerated phase or blast phase
  • refer for clinical trial or 2nd/3rd generation TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard AML induction
  • stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones
• treatment success is monitored based on therapeutic milestones
  • hematologic: improved WBC and platelet counts, reduced basophils
  • cytogenetic: undetectable Philadelphia-chromosome in the bone marrow
• molecular: reduction/absence of bcr-abl transcripts in periphery and marrow

Prognosis
• survival dependent on response
  • those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  • those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
• acute phase (blast crisis – usually within 3-5 yr)
  • 2/3 develop a picture similar to AML
  • unresponsive to remission induction
  • 1/3 develop a picture similar to ALL
• remission induction (return to chronic phase) achievable

Polycythemia Vera

Definition
• stem cell disorder characterized by elevated RBC mass (erythrocytosis) ± increased white cell and platelet production
• diagnosis (WHO 2016) requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion
  • Major Criteria
    1. hemoglobin >165 g/L in men, >160 g/L in women, OR Hct >49% in men or >48% in women, OR increased red cell mass (>25% above mean normal predicted value)
    2. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
    3. presence of JAK2 V617F or JAK2 exon 12 mutation
  • Minor Criteria
    1. serum erythropoietin level below reference range for normal (must have at least two major criteria if using erythropoietin level)

Clinical Features
• symptoms are secondary to high red cell mass and hyperviscosity (see Erythrocytosis, H6)
• thrombotic complications: DVT, PE, Budd-Chiari (hepatic vein thrombosis), portal vein thrombosis, thrombopelbitis, increased incidence of stroke, MI
• due to increased blood viscosity, increased platelet number and/or activity
• bleeding complications: epistaxis, gingival bleeding, ecchymoses, and GI bleeding
• if high platelet counts with associated acquired vWD
• erythromelalgia (burning pain in hands and feet and erythema of the skin)
  • associated with platelets >800 x 10^9/L
• pathognomonic microvascular thrombotic complication in PV and ET
• urtis, especially after warm bath or shower (40%) due to cutaneous mast cell degranulation and histamine release
• epigastric distress, PUD
• due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

Nejm 2013;368:22-33

Study: Prospective, RCT, mean follow-up of 28.9 mo. Binding not described.

Population: 365 patients with JAK2-positive polycythemia vera being treated with phlebotomy, hydroxyurea, or both.

Intervention: Patients were randomized to a target hematocrit <45% (low-hematocrit group) or 45-50% (high-hematocrit group).

Outcome: Composite of time until death from cardiovascular causes of major thrombotic events.

Results: The hazard ratio (HR) for the primary outcome was 3.9 (95% CI 1.45-10.3, p=0.007), while the HR for the primary outcome plus superficial veinous thrombosis was 2.69 (95% CI 1.19-6.12, p=0.022) for the high-hematocrit vs. low-hematocrit group.

Conclusions: The hematocrit target of <45% was associated with a lower incidence of CV death, major thrombotic events, and superficial veinous thrombosis in patients with polycythemia vera.
H42 Hematology

Myeloproliferative Neoplasms

- gout (hyperuricemia)
  - due to increased cell turnover
- characteristic physical findings
  - plethora (ruddy complexion) of face (70%), palms
  - splenomegaly (70%), hepatomegaly (40%)

Investigations
- see Erythrocytosis, H6
- must rule out secondary polycythemia if high Epo level

Treatment
- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- low-dose Aspirin® (for antithrombotic prophylaxis, will also treat erythromelalgia)
- allopurinol: as needed
- antihistamines: as needed

Prognosis
- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)

Idiopathic Myelofibrosis

Definition
- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

Epidemiology
- rare, median age at presentation is 65 yr

Pathophysiology
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
  - increasing fibrosis causes early release of hematopoietic precursors leading to:
    - leukoerythroblastic blood film (primitive RBCs and WBCs present in blood)
    - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

Clinical Features
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

Investigations
- CBC: anemia variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease) increased LDH (2ª to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B12 (2º to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets, and megakaryocyte fragments
- JAK2 PCR and calreticulin PCR
- bone marrow aspirate: “dry tap” in as many as 50% of patients (no blood cells aspirated)
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

Treatment
- allogeneic stem cell transplant is potentially curative
- JAK2 inhibitors (Ruxolitinib)
- symptomatic treatment
  - transfusion for anemia
  - erythropoietin: 30-50% of patients respond
  - androgens for anemia (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, systemic symptoms
    - nterferon-a (as second line therapy)
    - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis, symptomatic splenomegaly

Efficacy and Safety of Low-dose Aspirin® in Polycythemia Vera

Study: Double-blind, placebo-controlled, RCT
Participants: 518 patients with polycythemia vera (PV) with no clear indication for, or contraindication to, ASA therapy.
Intervention: Patients received either low-dose ASA 100 mg daily (n=263) or placebo (n=255) and were followed for up to 5 yr.
Primary Outcome: Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus PE and major venous thrombosis.
Results: Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41, p = 0.03 and RR 0.4, p = 0.03, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.
Conclusion: Low-dose ASA can safely prevent thrombotic complications in patients with PV.

Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PV or ET

A “leukoerythroblastic” blood film (RBC and granulocyte precursors) implies bone marrow infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF)

IMF typically has a dry BM aspirate and teardrop RBCs (aspiration gives no blood cells)

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis

Study: Double-blind RCT of 309 patients with myelofibrosis randomized to ruxolitinib or placebo
Outcome: Primary outcome was reduction in spleen volume of >35% at 24 wk. Secondary outcomes were durability of response, symptom burden, and overall survival.
Results: A greater proportion of patients on ruxolitinib had reduction in spleen volume >35% (41.9% vs. 0.7%) and this was sustained in 67% at 48 wk. Ruxolitinib also led to greater symptom improvement (46% vs. 5.5%) and less mortality (13 vs 24). There was no difference in rate of discontinuation due to adverse events (11.0% vs. 10.6%) but anemia and thrombocytopenia were more common with ruxolitinib.
Conclusions: Ruxolitinib reduced spleen size, improved symptoms and improved survival, compared with placebo.
Prognosis
- Dynamic International Prognostic Scoring System (DIPSS) Plus for IMF uses 5 risk factors along with karyotype, platelet count, and transfusion status to predict survival
  - presence of constitutional symptoms; age >65; hemoglobin <100 g/L; leukocyte count >25,000/mm³; circulating blast cells ≥1%
  - based on the calculated score, a patient's IMF is categorized as "low", "intermediate 1", "intermediate 2", or "high" with a mean survival of 185, 78, 35, and 16 mo, respectively
- risk of transformation to AML (8-10%)

Essential Thrombocythemia

Definition
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocythemia

Epidemiology
- increases with age; F:M = 2:1, but F=M at older age

Diagnosis (2008 WHO Criteria) requires meeting all four criteria:
1. sustained platelet count >450 x 10⁹/L
2. bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. not meeting WHO criteria for PV, primary myelofibrosis, bcr-abl CML, or myelodysplastic syndrome or other myeloid neoplasms
4. demonstration of JAK2 V617F or calreticulin (or in its absence another clonal marker), no evidence for reactive thrombocytosis

Clinical Features
- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation → microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding often GI; associated with platelets >1,000 x 10⁹/L
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

Investigations
- CBC: increased platelets; may have abnormal platelet aggregation studies or vWD studies
- JAK2 PCR assay; if negative, CALR PCR assay
- bone marrow hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased K⁺, increased PO₄³⁻ (2⁺ to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

Treatment
- low dose ASA if previous history of thrombotic event, ≥1 cardiovascular risk factors, older, or symptomatic
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st line therapy), anagrelide, interferon-α, or 32P (age >80 or lifespan <10 yr)

Etiology of Secondary Thrombocythemia
- Infection
- Inflammation (IBD, arthritis)
- Malignancy
- Hemorrhage
- Iron deficiency
- Hemolytic anemia
- Post splenectomy
- Post chemotherapy

Anagrelide vs. Hydroxyurea for Essential Thrombocythemia: ANAHYDRET Study, A Randomized Controlled Trial
Blood 2013;121:1720-8
Study: Prospective, non-inferiority, RCT. Majority of patients followed beyond 1 yr
Population: 259 previously untreated, high-risk patients with essential thrombosis as per the WHO guidelines.
Intervention: Patients were randomized to receive either non-immediate release formulation of anagrelide or hydroxyurea.
Outcome: Examined platelet counts, hemoglobin levels, leukocyte count, and occurrence of ET-related events.
Results: The hazard ratio (HR) of developing thrombocytemia was 1.19 (95% CI 0.61-2.30). The HR for a reduction of hemoglobin was 1.63 (95% CI 0.57-4.81), and 0.92 (95% CI 0.37-1.48) for leukocytosis. There was no statistical difference in occurrence of major or minor arterial or venous thrombosis, severe or minor bleeding events, or rate of discontinuation between the two arms.
Conclusions: In patients with ET, anagrelide is non-inferior to hydroxyurea in the prevention of thrombotic complications.
Lymphoid Malignancies

Acute Lymphoblastic Leukemia

Definition
- malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
  - 1. B-cell: precursor B lymphoblastic leukemia
  - 2. T-cell: precursor T lymphoblastic leukemia
- the French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged, as morphology is not prognostic

Clinical Features
- see Acute Myeloid Leukemia, H37 for full list of symptoms
- distinguish ALL from AML based on Table 32
- clinical symptoms usually secondary to:
  - bone marrow failure: anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), thrombocytopenia
  - organ infiltration: tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations
- CBC: increased leukocytes >10 x 10⁹/L (occurs in 50% of patients); neutropenia, anemia, or thrombocytopenia
- may have increased uric acid, K⁺, PO₄³⁻, Ca²⁺, LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- cytogentics: Philadelphia (Ph) chromosome in ~25% of adult ALL cases
- CXR: patients with ALL may have a mediastinal mass
- LP prior to systemic chemotherapy to assess for CNS involvement (ensure adequate platelet count and PT/PTT)

Treatment
- eliminate abnormal clonal cells
  1. induction chemotherapy: to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
  2. consolidation and/or intensification of chemotherapy
    - consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
    - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. maintenance chemotherapy: low dose intermittent chemotherapy over prolonged period (2-3 yr) to prevent relapse
  4. prophylaxis: CNS radiation therapy or methotrexate (intrathecal or systemic)
- hematopoietic stem cell transplantation: potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

Prognosis
- depends on response to initial induction or if remission is achieved following relapse
- good prognostic factors: young, WBC <30 x 10⁹/L, T cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 75% long-term remission (>5 yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of BCR-Abl fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5 yr survival

Table 32. Differentiating AML From ALL

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big people (adults)</td>
<td>Small people (kids)</td>
</tr>
<tr>
<td>Big blasts</td>
<td>Small blasts</td>
</tr>
<tr>
<td>Big mortality rate</td>
<td>Small mortality rate (kids)</td>
</tr>
<tr>
<td>Lots of cytoplasm</td>
<td>Less cytoplasm</td>
</tr>
<tr>
<td>Lots of nucleoli (3-5)</td>
<td>Few nucleoli (1-3)</td>
</tr>
<tr>
<td>Lots of granules and Auer rods</td>
<td>No granules</td>
</tr>
<tr>
<td>Myeloperoxidase, Sudan black stain</td>
<td>PAS (periodic acid-Schiff)</td>
</tr>
<tr>
<td>Maturation defect beyond myeloblast or promyelocyte</td>
<td>Maturation defect beyond lymphoblast</td>
</tr>
</tbody>
</table>

75% of ALL occurs in children < 6 yr old; second peak at age 40
**Lymphomas**

**Definition**
- collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease, and constitutional symptoms

**Table 33. Ann Arbor System for Staging Lymphomas**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region OR extralymphatic organ/site (Stage IE)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymphnode regions on both sides of the diaphragm; may or may not be accompanied by single extra lymphatic site or splenic involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse involvement of one or more extralymphatic organs including bone marrow</td>
</tr>
</tbody>
</table>

- subtypes
  - A = absence of B-symptoms (see *Approach to Lymphadenopathy*, H12)
  - B = presence of B-symptoms

**Table 34. Chromosome Translocations**

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Gene Activation</th>
<th>Associated Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(2;5)</td>
<td>ALK1 mutation</td>
<td>Anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>t(8;14)</td>
<td>c-myc activation</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>bcl-2 activation</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Overexpression of cyclin D1 protein</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>t(11;18)</td>
<td>MALT1 activation</td>
<td>Mucosa-associated lymphoid tissue (MALT)</td>
</tr>
</tbody>
</table>

**Hodgkin Lymphoma**

**Definition**
- malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal centre B-cells)

**Epidemiology**
- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases, causal role not determined

**Clinical Features**
- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
  - splenomegaly (50%) ± hepatomegaly
  - mediastinal mass
    - found on routine CXR, may be symptomatic (cough)
    - rarely may present with SVC syndrome, pleural effusion
  - systemic symptoms
    - B symptoms (especially in widespread disease; fever in 30%), pruritus
  - non-specific/paraneoplastic
    - alcohol-induced pain in nodes, nephrotic syndrome
  - starts at a single site in lymphatic system (node), spreads first to adjacent nodes
    - disease progresses in contiguity with lymphatic system

**Investigations**
- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, lymphopenia, platelets normal or increased early, decreased in advanced disease
- biochemistry
  - HIV serology
  - liver enzymes and/or LFTs (liver involvement)
  - renal function tests (prior to initiating chemotherapy)
  - ALP, Ca²⁺ (bone involvement)
  - ESR, LDH (monitor disease progression)
- imaging
  - CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement)
  - PET scans have replaced gallium scans

American Society of Hematology Choosing Wisely Recommendation
Limit surveillance CT scans in asymptomatic patients after curative-intent treatment for aggressive lymphoma

- Ann Arbor staging can be used for both Hodgkin and non-Hodgkin lymphoma, but grade/histology is more important for non-Hodgkin lymphoma because the outcome differs significantly depending on type of lymphoma
- Prognostic scores are different for indolent versus aggressive lymphomas
- Highly aggressive lymphomas act like acute leukemias

Hodgkin lymphoma is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells

Hodgkin lymphoma classically presents as a painless, non-tender, firm, rubbery enlargement of superficial lymph nodes, most often in the cervical region
• cardiac function assessment (MUGA scan or echocardiography): for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA, malnourished), treatment can be cardiotoxic
  • PFTs: if history of lung disease (COPD, smoking, previous radiation to lung)
  • excisional lymph node or core biopsy confirms diagnosis
  • bone marrow biopsy to assess marrow infiltration (only necessary if B-symptoms, stage III or IV, bulky disease or cytopenia)

Treatment
  • stage I-II: chemotherapy (ABVD) followed by involved field or involved site radiotherapy (XRT)
  • stage III-IV: chemotherapy (ABVD) with XRT for bulky disease
  • relapse, resistant to therapy: high dose chemotherapy, autologous stem cell transplant
  • PET scan results essential in clarifying disease response

Complications of Treatment
  • cardiac disease: secondary to XRT, adriamycin is also cardiotoxic
  • pulmonary disease secondary to bleomycin (interstitial pneumonitis)
  • infertility: recommend sperm banking
  • secondary malignancy in irradiated field
    • <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
    • solid tumours of lung, breast; >8 yr after treatment
  • non-Hodgkin lymphoma
  • hypothyroidism: post XRT

Prognosis
  • Hasenclever adverse prognostic factors:
    1. serum albumin <40 g/L
    2. hemoglobin <105 g/L
    3. male
    4. stage IV disease
    5. age ≥45 yr
    6. leukocytosis (WBC >1.5 x 10⁹/L)
    7. lymphocytopenia (lymphocytes <0.06 x 10⁹/L or <8% of WBC count or both)
  • prognostic score
    • each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)

Non-Hodgkin Lymphoma

Definition
  • malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

Classification
  • multiple classification systems exist at present and may be used at different centres
  • can originate from both B- (85%) and T- or NK- (15%) cells
    • B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt’s lymphoma, mantle cell lymphoma
    • T-cell NHL: e.g. mycosis fungoides (skin), TCL-NOS, anaplastic large cell lymphoma
  • WHO/REAL classification system: 3 categories of NHLs based on natural history
    • indolent (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, mantle cell lymphoma
    • aggressive (~50% of NHL): e.g. diffuse large B-cell lymphoma
    • highly aggressive (~5% of NHL): e.g. Burkitt’s lymphoma

Clinical Features
  • painless superficial lymphadenopathy, usually >1 lymph node region
  • usually presents as widespread disease (exception is aggressive lymphoma)
  • constitutional symptoms not as common as in Hodgkin lymphoma
  • cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when bone marrow is involved
  • abdominal signs
    • hepatosplenomegaly
    • retroperitoneal and mesenteric involvement (second most common site of involvement)
    • oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
    • extranodal involvement: most commonly GI tract; also testes, bone, kidney
    • CNS involvement in 1% (often with HIV)

Investigations
  • CBC
    • normocytic normochromic anemia
    • autoimmune hemolytic anemia rare
    • advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic anemia
  • peripheral blood film may show lymphoma cells
• flow cytometry of peripheral blood lymphocytosis is valuable for low-grade NHL
• biochemistry
  ■ increase in uric acid
  ■ abnormal LFTs in liver metastases
  ■ increased LDH (rapidly progressing disease, poor prognostic factor)
• staging: CT neck, chest, abdomen, pelvis and bone marrow biopsy
• PET is useful for monitoring response to treatment and evaluation of residual tumour following therapy in aggressive histological disease
• diagnosed by
  ■ lymph node biopsy: excisional biopsy preferred, FNA unreliable
  ■ bone marrow biopsy: not optimal for diagnosis as BM involved in only 30% of high grade lymphomas

Treatment
• localized disease (e.g. GI, brain, bone, head and neck)
  ■ radiotherapy to primary site and adjacent nodal areas
  ■ adjuvant chemotherapy
• surgery: splenic marginal zone lymphoma
• indolent lymphoma: goal of treatment is symptom management
  ■ watchful waiting
  ■ radiation therapy for localized disease
  ■ bendamustine plus rituximab, an anti-CD20 antibody, is superior to CHOP + rituximab (CHOP R) for advanced stage disease (StiLL trial)
• aggressive lymphoma: goal of treatment is curative
  ■ combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  ■ radiation for localized/bulky disease
  ■ CNS prophylaxis with high-dose methotrexate if certain sites involved (testicular)
  ■ relapse, resistant to therapy: high dose chemotherapy, autologous SCT
• highly aggressive lymphoma
  ■ Burkitt lymphoma: short bursts of intensive chemotherapy “CODOX-M” chemotherapy regimen also often used ± IVAC with Rituximab
  ■ CNS prophylaxis and tumour lysis syndrome prophylaxis

Complications
• hypersplenism
• infection
• autoimmune hemolytic anemia and thrombocytopenia
• vascular obstruction (from enlarged nodes)
• bowel perforation
• tumour lysis syndrome (particularly in very aggressive lymphoma) see Tumour Lysis Syndrome, H52

Prognosis
• follicular lymphoma: Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60; >4 nodal areas; elevated LDH; Lugano stage III-IV; hemoglobin <120 g/L
  ■ based on calculated risk, mean 5 yr survival ranges from 53-91%
  ■ rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
• diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
  ■ based on calculated risk, mean 5 yr survival ranges from 26-73%
  ■ ~40% rate of cure

Table 35. Characteristics of Select Non-Hodgkin Lymphomas

<table>
<thead>
<tr>
<th></th>
<th>Follicular Lymphoma</th>
<th>Diffuse Large B-Cell Lymphoma (DLBCL)</th>
<th>Burkitt Lymphoma</th>
<th>Mantle Cell Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of NHLs</td>
<td>22-30%</td>
<td>33%</td>
<td>&lt;1% adult NHLs</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30% childhood</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NHLs</td>
<td></td>
</tr>
<tr>
<td>Genetic Mutation</td>
<td>Bcl-2 activation</td>
<td>Bcl-2, Bcl-6, MYC rearrangements</td>
<td>c-Myc activation</td>
<td>Overexpression of cyclin D1 (Bcl-1 activation)</td>
</tr>
<tr>
<td>Classification</td>
<td>Indolent</td>
<td>Aggressive (high-grade)</td>
<td>Very aggressive</td>
<td>Indolent</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Widespread painless LAD* ± bone marrow involvement</td>
<td>Rapidly progressive LAD and extranodal infiltration, 50% present at stage VII, 50% widely disseminated</td>
<td>Endemic to m; massive jaw LAD “Starry-sky” histology; High risk of tumour lysis syndrome upon treatment</td>
<td>Often presents Stage N with palpable LAD involvement of Gl tract (lymphomatosis polyposis), Waldeyer’s Ring 5 yr survival 25%</td>
</tr>
</tbody>
</table>

* LAD = lymphadenopathy

Common Chemotherapeutic Regimens
CHOP: cyclophosphamide, hydroxydaunorubicin (Adriamycin®), vincristine (Oncovin®), prednisone
VAD: vincristine, adriamycin, dexamethasone
ABVD: adriamycin, bleomycin, vinblastine, dacarbazine
BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone
Table 36. Characteristics of B-Cell Malignant Proliferation

<table>
<thead>
<tr>
<th></th>
<th>CLL</th>
<th>Lymphoplasmacytic Lymphoma</th>
<th>Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Type</strong></td>
<td>Lymphocyte</td>
<td>Plasmacytoid</td>
<td>Plasma cell</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>IgM if present</td>
<td>IgM</td>
<td>IgG, A, light chain (rarely M, D, or E)</td>
</tr>
<tr>
<td><strong>Lymph Nodes</strong></td>
<td>Very common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Hepatosplenomegaly</strong></td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Bone Lesions</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Renal Failure</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Immunoglobulin Complications</strong></td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Chronic Lymphocytic Leukemia**

**Definition**
- indolent disease characterized by clonal malignancy of mature B-cells

**Epidemiology**
- most common leukemia in Western world
- mainly older patients; median age 70 yr
- M>F

**Pathophysiology**
- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes, and spleen

**Clinical Features**
- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38ºC or night sweats for ≥2 wk without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (DAT positive), ITP, hypogammaglobulinemia + neutropenia
- bone marrow failure: late, secondary to marrow involvement by CLL cells

**Investigations**
- CBC: clonal population of B lymphocytes >5 x 10⁹/L
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry (CD5, CD20dim, CD23)
- cytogenetics: FISH (dictates response therapy and prognosis)
- bone marrow aspirate
  - lymphocytes >30% of all nucleated cells
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35% worse prognosis), or mixed (25%)

**Natural History and Treatment**
- natural history: indolent and incurable; most cases show slow progression
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- first line therapy is dictated by cytogenetic status and patient co-morbidities
  - observation if early, stable, asymptomatic
  - treatment options vary by region; ideal first line therapy should include a monoclonal CD20 agent (e.g. rituximab, obinutuzumab)
    - commonly fludarabine + cyclophosphamide + rituximab (FCR) in fit patients with normal CrCl; bendamustine + rituximab (BR) in less fit
    - chlorambucil + anti-CD20 obinutuzumab in the elderly
    - corticosteroids, IVIg: especially for autoimmune phenmenonradiotherapy
- molecular therapies
  - Idelalisib – PI3K inhibitor
  - Ibr timib – BTK (Bruton’s tyrosine kinase) inhibitor

Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality)

Smudge cells are artifacts of damaged lymphocytes from slide preparation.
**Prognosis**
- 9 yr median survival, but varies greatly
- prognosis predicted by Rai staging and cytogenetic status
- low risk: lymphocytosis in blood and bone marrow only
- intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
- high risk: lymphocytosis with disease-related anemia (<110 g/L) or thrombocytopenia (<100 x 10⁹/L)

**Complications**
- bone marrow failure
- immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia, impaired T-cell function)
- polyclonal or monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- 5% undergo Richter's transformation: aggressive transformation to diffuse large B-cell lymphoma (see Table 35)

**Multiple Myeloma**

**Definition**
- neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
- usually single clone of plasma cells, although biclonal myeloma also occurs; rarely non-secretory

**Epidemiology**
- incidence 3 per 100,000, most common plasma cell malignancy
- increased frequency with age; median age of diagnosis is 68 yr; M>F

**Pathophysiology**
- malignant plasma cells secrete monoclonal antibody
  - 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    - IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    - 15-20% produce free light chains or light chains alone found in either:
      - serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      - urine has Bence-Jones protein
  - <5% are non-secretors

**Clinical Features and Complications**
- bone disease: pain (usually back), bony tenderness, pathologic fractures
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
- increased bone resorption secondary to osteoclast activating factors such as PTHrP
- anemia: weakness, fatigue, pallor
  - secondary to bone marrow suppression
- weight loss
- infections
  - usually *S. pneumoniae* and Gram-negatives
  - secondary to suppression of normal plasma cell function
- hypercalcemia: N/V confusion, constipation, polyuria, polydipsia
  - secondary to increased bone turnover
- renal disease/renal failure
  - most frequently causes cast nephropathy (see Nephrology, NP32)
- bleeding
  - secondary to thrombocytopenia, may see petechiae, purpura
  - can also be caused by acquired von Willebrand disease
- extramedullary plasmacytoma
  - soft tissue mass composed of monoclonal plasma cells, purplish colour
- hyperviscosity: may manifest as headaches, stroke, angina, MI
  - secondary to increased viscosity caused by M protein
- amyloidosis
  - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
  - neurologic disease: muscle weakness, pain, paresthesias
  - radiculopathy caused by vertebral fracture, extramedullary plasmacytoma
- spinal cord compression (10-20% of patients) is a medical emergency

**Amyloid**
The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues

Found in a variety of clinical disorders and can cause systemic (e.g. MM [light chains]) or localized amyloidosis (e.g. Alzheimer disease [AB amyloid])
Investigations

- **CBC**
  - normocytic anemia, thrombocytopenia, leukopenia
- **biochemistry**
  - increased Ca\(^{2+}\), increased ESR, decreased anion gap, increased Cr, albumin, β2-microglobulin (as part of staging), proteinuria (24 h urine collection)
- **monoclonal proteins**
  - serum protein electrophoresis (SPEP): demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - urine protein electrophoresis (UPEP): demonstrates light chains in urine = Bence-Jones protein (15% secretes only light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- **bone marrow aspirate and biopsy**
  - often focal abnormality; greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for FISH or cytogenetics (prognostic implications)
- **skeletal series (X rays), MRI if symptoms of cord compression**
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
- **β2-microglobulin, LDH, and CRP are poor prognosticators**

Diagnosis

- **International Myeloma Working Group Criteria**
  1. serum or urinary monoclonal protein
  2. presence of clonal plasma cells in bone marrow (>60% without “CRAB”) or a plasmacytoma
  3. presence of end-organ damage related to plasma cell dyscrasia, such as:
     - increased serum Ca\(^{2+}\)
     - lytic bone lesions
     - anemia
     - renal failure

Treatment

- treatment is non-curative
- **treatment goals**
  - improvement in quality of life (improve anemia, reverse renal failure, bony pain)
  - prevention of progression and complications
  - increase overall survival
- **autologous stem cell transplant if <65 yr old**
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents (i.e. immunomodulatory drugs or proteasome inhibitors)
- **chemotherapy if >65 yr old or transplant ineligable**
  - melphalan, prednisone, cyclophosphamide and proteasome inhibitor (i.e. bortezomib)
  - dexamethasone and bortezomib if ARF; bortezomib ± dexamethasone in light chain amyloidosis
- **supportive management**
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia, DVT prophylaxis
- **all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities, and preferences**

Prognosis

- **ISS - International Staging System (β2-microglobulin and albumin) used to stage and estimate prognosis**
  - revised ISS for risk stratification: combination of original ISS, cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy) and LDH
  - median survival based on stage, usually 3-7 yr
Monoclonal Gammopathy of Unknown Significance

**Definition**
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr of age
  - asymptomatic

**Diagnosis**
- presence of a serum monoclonal protein (M protein) at a concentration <30 g/L
- <10% plasma cells in bone marrow
- absence of hyperCalcemia, Renal insufficiency, Anemia, Bone disease related to the plasma cell proliferative process (absence of “CRAB”)
- 0.3-1% of patients develop a hematologic malignancy each yr
  - patients with M protein peak ≥15 g/L or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with abnormal serum free light chains ratio are at increased risk of malignant transformation
- monitor with annual history, physical, CBC, Cr, calcium, albumin, serum protein electrophoresis (considered pre-malignant)

Lymphoplasmacytic Lymphoma
(Waldenstrom’s Macroglobulinemia)

**Definition**
- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein

**Clinical Features**
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
- key complication to avoid: hyperviscosity syndrome
  - because IgM (unlike IgG) confined largely to intravascular space

**Investigations and Diagnosis**
- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- blood work rarely see hypercalcemia
- cold hemagglutinin disease possible: Raynaud’s phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present

**Treatment**
- Bendamustine – R/R-CVP chemotherapy, alkylating agents (chlorambucil), nucleoside analogues (Iluadabine), rituximab, or combination therapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

**Definition**
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum IgGs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases

**Clinical Features**
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

**Treatment**
- plasmapheresis, chemotherapy
**Tumour Lysis Syndrome**

**Definition**
- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)

**Clinical Features**
- metabolic abnormalities
  - cells lyse, releasing K⁺, uric acid, PO₄³⁻ (increased levels)
  - PO₄³⁻ binds Ca²⁺ (decreased Ca²⁺)
- complications
  - lethal cardiac arrhythmia (increased K⁺)
  - acute kidney injury (formerly known as renal failure) see Nephrology, NP18

**Treatment**
- prevention
  - aggressive IV hydration
  - allopurinol or rasburicase
  - correction of pre-existing metabolic abnormalities
  - dialysis

---

**Blood Products and Transfusions**

**Blood Products**
- RBCs, platelets and coagulation factors (frozen plasma [FP], cryoprecipitate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and platelet-rich plasma
  - platelet-rich plasma is further fractionated into platelets and plasma
  - need to pool together multiple units to obtain therapeutic amounts
  - FP (previously known as FFP) is plasma frozen within 24 h of collection
  - cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures

**Specialized Products**
- irradiated blood products
  - prevent proliferation of donor T-cells in potential or actual bone marrow transplant recipients
  - used for immunocompromised patients or for patients on purine analogue chemotherapy, first-degree relatives, HLA-matched products and intrauterine transfusions, Hodgkin lymphoma
- CMV-negative blood products
  - potential transplant recipients
  - neonates
  - AIDS patients
  - seronegative pregnant women

**Blood Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Antigen (on RBC)</th>
<th>Antibody (in serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>Anti-A, anti-B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
</tr>
<tr>
<td>AB</td>
<td>A and B</td>
<td>Nil</td>
</tr>
</tbody>
</table>

In Canada, blood products are leukodepleted via filtration immediately after donation; therefore it is considered:
- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV negative (because CMV is found in leukocytes)

**Red Blood Cells**

**Packed Red Blood Cells**
- stored at 4°C
- transfuse within 42 d of collection, otherwise cell lysis may result in hyperkalemia
- infuse each unit over 2 h (max of 4 h)

**Indications for Packed RBC Transfusion**
- Hb <70 g/L; this may change as per patient's tolerance or symptoms
  - maintain Hb between 70 and 100 g/L during active bleeds
  - consider maintaining a higher Hb for patients with:
    - CAD/unstable coronary syndromes
    - uncontrolled, unpredictable bleeding
    - impaired pulmonary function
    - increased O₂ consumption

1 unit of pRBC will increase Hb by approximately 10 g/L or increase Hct by 4%

**American Society of Hematology Choosing Wisely Recommendation**
Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin range (70-80 g/L) in stable non-cardiac patients
Selection of Red Cells for Transfusion

- when anticipating an RBC transfusion, the following should be ordered:
  - group and screen: determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens in the patient's serum
  - cross-match: involves mixing the recipient's blood with potential donor blood and looking for agglutination (takes 30-45 min)
- when blood is required, several options are available
  - 1st line: fully crossmatched blood, electronic crossmatch is becoming more widely used (not always available in emergency situations)
  - 2nd line: donor blood of the same group and Rh status as the recipient
  - 3rd line: O- blood for females of reproductive age; O+ blood for all others

Table 37. Platelet Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Donor (Pooled)</td>
<td>Thrombocytopenia with bleeding</td>
</tr>
<tr>
<td>Single Donor Platelets</td>
<td>Potential BMT recipients</td>
</tr>
<tr>
<td>HLA Matched Platelets</td>
<td>Refractory to pooled or single donor platelets, presence of HLA antibodies</td>
</tr>
</tbody>
</table>

- stored at 20-24°C
  - random donor platelets are transfused from a pool of 4 units; this should increase the platelet count by \( \geq 15 \times 10^9/L \)
  - single donor platelets (transfused as single units) should increase the platelet count by 40-60 \( \times 10^9/L \)
  - if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies, consumption (bleeding, sepsis), or hypersplenism may be present

Table 38. Indications for Platelet Transfusion

<table>
<thead>
<tr>
<th>Plt (x 10^9/L)</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Non-immune thrombocytopenia</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Procedures not associated with significant blood loss</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Procedures associated with blood loss or major surgery (&gt;500 mL EBL)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>Pre-neurosurgery or head trauma</td>
</tr>
<tr>
<td>Any</td>
<td>Platelet dysfunction (or antiplatelet agents) and marked bleeding</td>
</tr>
</tbody>
</table>

Relative Contraindications of Platelet Transfusion

- TTP, HIT, post-transfusion purpura, HELLP

Coagulation Factors

Table 39. Coagulation Factor Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen plasma (FP)</td>
<td>Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease)</td>
</tr>
<tr>
<td>Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII)</td>
<td>Hemophilia A (Factor VIII deficiency) – use in emergencies von Willebrand disease – use in emergencies Hypofibrinogenemia</td>
</tr>
<tr>
<td>Humate P or Wilate</td>
<td>von Willebrand disease, Hemophilia A</td>
</tr>
<tr>
<td>Factor VIII concentrate</td>
<td>Factor VIII deficiency (Hemophilia A)</td>
</tr>
<tr>
<td>Factor IX concentrate</td>
<td>Factor IX deficiency (Hemophilia B)</td>
</tr>
<tr>
<td>Recombinant factor Vila</td>
<td>Factor VII deficiency with bleeding/surgery, Hemophilia A or B with inhibitors, Glanzmann thrombasthenia</td>
</tr>
<tr>
<td>Prothrombin complex concentrate; PCC (Octaplex®, Beriplex®)</td>
<td>Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (&lt; 6 h) surgical procedure, urgent non-specific “reversal” of direct Xa inhibitors</td>
</tr>
<tr>
<td>Activated prothrombin complex concentrate; aPCC (FEIBA)</td>
<td>Hemophilia A or B with inhibitors, urgent non specific “reversal” of direct thrombin inhibitors</td>
</tr>
</tbody>
</table>
Acute Blood Transfusion Reactions

IMMUNE

Acute Hemolytic Transfusion Reactions
ABO incompatibility resulting in intravascular hemolysis secondary to complement activation, occurs immediately after transfusion
- most commonly due to incorrect patient identification
- risk per unit of blood is <1 in 40,000
- presentation: fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

Febrile Nonhemolytic Transfusion Reactions
- due to alloantibodies to WBC, platelets or other donor plasma antigens, and release of cytokines from blood product cells
- occurs within 0-6 h of transfusion
- risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <38ºC, continue with transfusion but decrease rate and give antipyretics
  - if temperature >38ºC, stop transfusion, give antipyretics and anti-histamine

Allergic Nonhemolytic Transfusion Reactions
- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1 in 100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema, and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenydramine, steroids, epinephrine, IV fluids, and bronchodilators

Transfusion-Related Acute Lung Injury
- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
- insidious, acute onset of pulmonary insufficiency
- profound hypoxemia (PaO2/FiO2 <300 mmHg)
- bilateral pulmonary edema on CXR
- pulmonary artery wedge pressure <18 mmHg
- no clinical evidence of left atrial hypertension
- pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 h post transfusion and resolves in 24-72 h
- risk per unit of blood is 1 in 10,000
  - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
  - inform blood bank; patient and donor testing will be arranged

NONIMMUNE

Transfusion-Associated Circulatory Overload
- due to impaired cardiac function and/or excessive rapid transfusion
- presentation: dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung, and increased venous pressure
- incidence: 1 in 700 and is becoming more common
- treatment: transfuse at lower rate, give diuretics and oxygen

Bacterial Infection
- Gram-positive: S. aureus, S. epidermidis, Bacillus cereus
- Gram-negative: Klebsiella, Serratia, Pseudomonas, Yersinia
- overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids
Hyperkalemia
- due to K⁺ release from stored RBC
- risk increases with storage time and if blood is irradiated and risk decreases if given fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP13

Citrate Toxicity
- occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca²⁺ and causes signs and symptoms of hypocalcemia
- treatment: IV calcium gluconate (10 mL for every 2 units of blood)

Dilutional Coagulopathy
- occurs with massive transfusion (>10 units)
- pRBC contains no clotting factors, fibrinogen, cryoprecipitate, or platelets
- treatment: FFP, cryoprecipitate, and platelets

Delayed Blood Transfusion Reactions

**IMMUNE**

Delayed Hemolytic
- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
- occurs 5-7 d after transfusion
- presentation: anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion
- N.B. serologic transfusion reactions are the development of alloantibodies in the absence of frank hemolysis

Transfusion-Associated Graft Versus Host Disease
- transfused T-lymphocytes recognize and react against “host” (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- presentation: fever, diarrhea, liver function abnormalities and pancytopenia
- can be prevented by giving irradiated blood products

**NONIMMUNE**

Iron Overload
- due to repeated transfusions over long period of time (e.g. β-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if no longer requiring blood transfusion and not anemic

Viral Infection Risk
- HBV 1 in 1.1 to 1.7 million
- HCV 1 in 5 to 7 million
- HIV 1 in 8 to 12 million
- Human T-lymphotropic virus (HTLV) 1 in 1 to 1.3 million
- other infections include EBV, CMV, WNV (West Nile virus)
**Common Medications**

### Antiplatelet Therapy

- see Figure 11a, Platelet Activation Cascade, H26

![Image of mechanisms of action of antiplatelet therapy](Image)

**Figure 15. Mechanisms of action of antiplatelet therapy**

**Table 40. Antiplatelet Therapy**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| **Aspirin® (ASA)** | Irreversibly acetylates COX, inhibiting TXA2 synthesis, thus inhibiting platelet aggregation | Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily | Onset: 5-30 min Peak: 0-25-3 h Duration: 3-6 h | GI ulcer/bleeding Tinnitus Bronchospasm Angioedema Reye’s syndrome in pediatric patients | - Indicated for stroke/MI prophylaxis
- Reduce incidence of recurrent MI
- Decrease mortality in post-MI patients
- Contraindicated in patients with GI ulcers |
| **Aggrenox® (ASA + Dipyridamole)** | Dipyridamole increases intracellular cAMP levels, which inhibits TXA2 synthesis, leading to decreased platelet aggregation | 1 capsule PO bid Peak: 75 min | | Dyspepsia N/V Abdominal pain Cardiac failure Hemorrhoids | - More effective than ASA in secondary prevention of stroke
- Dipyridamole potentiates antiplatelet action of ASA |
| **Clopidogrel (Plavix®)** | Irreversibility inhibit ADP binding to platelets, thus decreased platelet aggregation | 75-300 mg PO daily | Onset: 2 h Peak: 1 h | URI Chest pain Flu-like syndrome Depression UTI GI hemorrhage Pancytopenia | Prevention of cardiovascular events in high-risk patients
Clopidogrel is a prodrug requiring two-step activation to active metabolite CYP2C19 poor metabolizers have diminished response to clopidogrel
Cautions with hepatic/renal impairment |
| **Prasugrel (Effient®)** | Same as clopidogrel | 5-10 mg PO daily | Onset: 30 min | Dizziness H/A Nervousness Blurry vision | Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients
Higher potency compared to clopidogrel
No significant drug-drug interaction, although more data is required |
Table 40. Antiplatelet Therapy (continued)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Reversing Agent</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor (Brilinta&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Reversibly inhibit ADP binding to platelets</td>
<td>90 mg PO daily</td>
<td>Onset: 1.5 h for prof. Induction, 2.5 h for active metabolite</td>
<td>Difficulty or laboured breathing, Shortness of breath, Tightness in chest, Dizziness</td>
<td>Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients Higher potency compared to clopidogrel Ticagrelor is a prodrug that requires CYP3A4-mediated activation to active metabolite Drug drug interactions with CYP3A4 inhibitors and inducers</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa Inhibitors (Reopro&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Blocking GP IIb/IIIa receptor inhibits fibrinogen and von Willebrand factor binding, leading to decreased platelet aggregation</td>
<td>Variable IV</td>
<td>Variable</td>
<td>Hypotension, Back pain, N/V, Chest pain, Abdominal pain, Thrombocytopenia</td>
<td>Used most commonly in cardiac catheterization Contraindicated in PUD Monitoring aPTT/activated clotting time</td>
</tr>
</tbody>
</table>

Anticoagulant Therapy

Table 41. Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Reversing Agent</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Accelerates inhibitory activity of antithrombin</td>
<td>As per hospital nomogram</td>
<td>Onset: 20-60 min Peak: 2-4 h</td>
<td>Protamine sulfate</td>
<td>aPTT (intrinsic pathway), UFH (anti-Xa) levels</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K antagonist: inhibits production of II, VII, IX, X, proteins C and S</td>
<td>Individualized dosing by monitoring PT/INR or ID</td>
<td>Onset: 36-48 h Peak: 1.5-3 d</td>
<td>IV vitamin K</td>
<td>PT/INR maintain 2.3 (2.5-3.5 for mechanical valves)</td>
</tr>
<tr>
<td>LMWH (enoxaparin, dalteparin, tinzaparin)</td>
<td>Inhibits FXa</td>
<td>Variable SC/IV</td>
<td>Onset: 3-5 h Peak: 3-5 h Duration: 12 h</td>
<td>Partial reversibility with protamine sulfate, FXa in pediatrics, pregnancy and weight &gt;150 kg</td>
<td>Hemorrhage, Fever, Increased liver enzymes &lt;1% HIT</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Indirect inhibitor of FXa (through antithrombin)</td>
<td>Variable SC daily</td>
<td>Onset: 2 h Peak: 2-3 h</td>
<td>Not reversible</td>
<td>None</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct FXa inhibitor</td>
<td>PO</td>
<td>Peak: 2-4 h</td>
<td>Not reversible</td>
<td>None</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct FXa inhibitor</td>
<td>PO</td>
<td>Onset: 3-4 h Peak: 3-4 h</td>
<td>Not reversible</td>
<td>None</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Direct thrombin inhibitor</td>
<td>Variable IV</td>
<td>Onset: 5-10 min Duration: 20-40 min</td>
<td>Not reversible</td>
<td>aPTT</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>150 mg PO bid</td>
<td>Peak: 1 h</td>
<td>Not reversible</td>
<td>None (prolonged aPTT can suggest residual drug on board)</td>
</tr>
</tbody>
</table>

Adverse Reactions of Heparin
- Hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- Heparin-induced thrombocytopenia: associated with venous or arterial thrombosis (see Table 22, H29)
- Osteoporosis: with long-term use

Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)
- Increased bioavailability compared to normal heparin
- Increased duration of action
- SC route of administration
- Do not need to monitor aPTT
- Adverse reactions less common than UFH
- Patients with renal failure (CrCl <30 mL/min) can accumulate LMWH, therefore must adjust dose
- Only partially reversible with protamine sulfate
- HIT is less common
Table 42. Recommended Therapeutic INR Ranges of Common Indications for Oral Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Most cases of thrombosis with antiphospholipid antibody syndrome</td>
<td></td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td></td>
</tr>
<tr>
<td>AMI (to prevent systemic embolism)</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Bileaflet mechanical valve in aortic position</td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthetic mitral valves (high risk)</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>AMI = acute myocardial infarction</td>
<td></td>
</tr>
</tbody>
</table>

Table 43. Recommended Management of a Supratherapeutic INR

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding Present</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;Therapeutic to 4.5</td>
<td>No</td>
<td>Lower warfarin dose OR Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range OR No dose reduction needed if INR is minimally prolonged</td>
</tr>
<tr>
<td>4.5 to 10.0</td>
<td>No</td>
<td>Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range OR Omit a dose and administer 1 to 2.5 mg oral vit K in patients with increased risk of bleeding</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>No</td>
<td>Hold warfarin and administer 5 to 10 mg oral vit K, monitor INR more frequently and administer more vit K as needed; resume warfarin at a lower dose when INR is in therapeutic range</td>
</tr>
<tr>
<td>Any</td>
<td>Serious or life threatening</td>
<td>Hold warfarin and administer 10 mg vit K by slow IV infusion; supplement with four-factor prothrombin complex concentrate; monitor and repeat as needed</td>
</tr>
</tbody>
</table>

Adapted from: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;132 suppl.e1S

Chemotherapeutic and Biologic Agents Used in Oncology

Table 44. Selected Chemotherapeutic and Biologic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism of Action or Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating Agent</td>
<td>chlorambucil, cyclophosphamide, melphalan (nitrogen mustards)</td>
<td>Damage DNA via alkylation of base pairs leads to cross-linking of bases, abnormal base-pairing, DNA breakage</td>
</tr>
<tr>
<td></td>
<td>carboplatin, cycloplatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dacarbazine, procarbazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>busulfan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bendamustine</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>methotrexate (folic acid antagonist)</td>
<td>Inhibit DNA synthesis</td>
</tr>
<tr>
<td></td>
<td>6-mercaptopurine, fludarabine (purine antagonist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil (5-FU) (pyrimidine antagonist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hydroxyurea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cytarabine</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>adriamycin (anthracycline)</td>
<td>Interfere with DNA and RNA synthesis</td>
</tr>
<tr>
<td></td>
<td>bleomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mitomycin C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>paclitaxel</td>
<td>Stabilize microtubules against breakdown once cell division complete</td>
</tr>
<tr>
<td></td>
<td>docetaxel</td>
<td></td>
</tr>
<tr>
<td>Vinca-alkaloids</td>
<td>vinblastine</td>
<td>Inhibit microtubule assembly (mitotic spindles), blocking cell division</td>
</tr>
<tr>
<td></td>
<td>vincristine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vinorelbine</td>
<td></td>
</tr>
<tr>
<td>Topoisomerase Inhibitors</td>
<td>irinotecan, topotecan (topo I)</td>
<td>Interfere with DNA unwinding necessary for normal replication and transcription</td>
</tr>
<tr>
<td></td>
<td>etoposide (topo II)</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>prednisone</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>dexamethasone</td>
<td></td>
</tr>
<tr>
<td>Purine Analogues</td>
<td>fludarabine</td>
<td>Interferes with DNA synthesis</td>
</tr>
<tr>
<td></td>
<td>cladribine</td>
<td></td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>trastuzumab (Herceptin®)</td>
<td>HER2 antagonist</td>
</tr>
<tr>
<td></td>
<td>bevacizumab (Avastin®)</td>
<td>VEGF antagonist</td>
</tr>
<tr>
<td></td>
<td>rituximab (Rituxan®), olatumumab (Arzerra®), obinutuzumab (Gazyva®)</td>
<td>CD20 antigen, EGFR antagonist</td>
</tr>
<tr>
<td></td>
<td>cetuximab (Erbitux®)</td>
<td></td>
</tr>
<tr>
<td>Small Molecule Inhibitors</td>
<td>imatinib mesylylate (Gleevec®)</td>
<td>Bcr-Abl inhibitor</td>
</tr>
<tr>
<td></td>
<td>dasatinib</td>
<td>Bcr-Abl inhibitor</td>
</tr>
<tr>
<td></td>
<td>nilotinib</td>
<td>Bcr-Abl inhibitor</td>
</tr>
<tr>
<td></td>
<td>gefitinib (Iressa®)</td>
<td>EGFR antagonist</td>
</tr>
<tr>
<td></td>
<td>erlotinib (Tarceva®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>geftinib (Iressa®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bortezomib (Velcade®)</td>
<td>26S proteasome inhibitor</td>
</tr>
<tr>
<td></td>
<td>suntitib (Sutent®)</td>
<td>VEGFR, PDGFR antagonist</td>
</tr>
<tr>
<td></td>
<td>brivanib (Imbruvica®)</td>
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<tr>
<td></td>
<td>idekabib (Cywidig®)</td>
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<td></td>
<td>ruxolitinib (Jakavi®)</td>
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<tr>
<td></td>
<td>idelalisib (Zyedilig®)</td>
<td>P13K inhibitor</td>
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<td></td>
<td>rivinistin</td>
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<td></td>
<td>sorafenib (Nexavar®)</td>
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<td></td>
<td>vandetanib (Infinitor®)</td>
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<td>volitinib (Tafinlar®)</td>
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<td></td>
<td>nilotinib (Diphenylbutamides)</td>
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<td></td>
<td>ponatinib (Iclusig®)</td>
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<td>dasatinib (Sprycel®)</td>
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<td>bosutinib (Bosulif®)</td>
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<td>nilotinib (Sprycel®)</td>
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<td>imatinib (Gleevec®)</td>
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<td>dasatinib (Sprycel®)</td>
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<td>gefitinib (Iressa®)</td>
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<td>erlotinib (Tarceva®)</td>
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<td>bortezomib (Velcade®)</td>
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<td>bortezomib (Velcade®)</td>
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</tbody>
</table>
# Landmark Hematology Trials

## Hematologic Malignancies and Related Disorders

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin Lymphoma: ABVD vs. MOPP</td>
<td>NEJM 1992;327:1478-84</td>
<td>In Hodgkin lymphoma, ABVD regimen has equal or better free and overall survival to MOPP + ABVD, but less myelotoxicity; ABVD is standard chemotherapy for Hodgkin lymphoma.</td>
</tr>
<tr>
<td>CHOP</td>
<td>NEJM 1993;328:1002-6</td>
<td>In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival; CHOP is the standard for advanced NHL.</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>NEJM 2002;346:235-42</td>
<td>Addition of rituximab to CHOP increases complete response rate and prolongs event-free survival and overall survival in elderly with DLBCL.</td>
</tr>
<tr>
<td>CML: Imatinib vs. IFN + Cytarabine</td>
<td>NEJM 2003;349:994-1004</td>
<td>In patients with chronic-phase CML, imatinib was more effective than IFNα + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis.</td>
</tr>
<tr>
<td>CLL8</td>
<td>Lancet 2010;376:1164-74</td>
<td>Rituximab plus fludarabine and cyclophosphamide (FRD) improves progression-free and overall survival compared with fludarabine and cyclophosphamide alone (FC) in the treatment of CLL.</td>
</tr>
<tr>
<td>VISTA</td>
<td>JCO 2010;28:2259-66</td>
<td>Bortezomib plus melphalan and prednisone (MPV) is superior to melphalan and prednisone (MP) in overall survival of non-transplant-eligible multiple myeloma patients.</td>
</tr>
<tr>
<td>MInT Group</td>
<td>Lancet 2011;12:1013-1022</td>
<td>Rituximab added to CHOP-like chemotherapy improved long-term outcomes for young patients with good-prognosis DLBCL.</td>
</tr>
<tr>
<td>StIL</td>
<td>Lancet 2013;381(9873):1203-10</td>
<td>Bendamustine plus rituximab is superior to R CHOP in terms of progression-free survival and fewer toxic effects in patients with previously untreated indolent lymphoma.</td>
</tr>
<tr>
<td>Ibrutinib vs. Ofatumumab in previously treated CLL</td>
<td>NEJM 2014;371:213-223</td>
<td>Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL.</td>
</tr>
</tbody>
</table>

## Thrombosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOT</td>
<td>NEJM 2003;349:146-53</td>
<td>In patients with cancer and acute venous thromboembolism, LWMH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.</td>
</tr>
<tr>
<td>PT1</td>
<td>NEJM 2005;353:35-6</td>
<td>Hydroxyurea plus low-dose ASA is superior to anagrelide plus low-dose ASA for patients with essential thrombocythemia at high risk for vascular events.</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>Lancet 2006;367:1665-73</td>
<td>ASA plus dipyridamole is recommended over ASA alone as antithrombotic therapy after cerebral ischemia of arterial origin.</td>
</tr>
<tr>
<td>Dabigatran vs. Warfarin in VTE</td>
<td>NEJM 2009;361:2342-52</td>
<td>In the treatment of venous thromboembolism, dabigatran is as effective as warfarin and also has a similar safety profile; note: many problems in the trial, making it less pivotal in having drug approval.</td>
</tr>
<tr>
<td>E NSTEIN-PE</td>
<td>NEJM 2012;366:1287-1297</td>
<td>Among patients with acute PE, rivaroxaban is noninferior to warfarin in preventing recurrent VTE, and is associated with similar bleeding rates.</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>NEJM 2013;369:799-808</td>
<td>In patients with VTE who have completed 6-12 months of anticoagulation, long-term apixaban treatment reduces recurrent VTE or all-cause mortality without increasing rates of major bleeding.</td>
</tr>
<tr>
<td>RE-VERSE AD</td>
<td>NEJM 2015;373:511-520</td>
<td>Idarucizumab for dabigatran reversal.</td>
</tr>
</tbody>
</table>

## Blood Products and Transfusion

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Transfusion Threshold</td>
<td>NEJM 1997;337:1870-5</td>
<td>The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10; use of the lower threshold reduced platelet usage by 21.5%.</td>
</tr>
<tr>
<td>TRICC BP</td>
<td>NEJM 1999;340:409-17</td>
<td>A restrictive strategy of red-cell transfusion (when Hb &lt;70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb &lt;100) in ICU patients; one possible exception is patients with an acute MI or unstable angina.</td>
</tr>
<tr>
<td>Dose of Platelet Transfusion</td>
<td>NEJM 2010;362:600-13</td>
<td>Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions but not incidence of bleeding in patients with hypoproliferative thrombocytopenia.</td>
</tr>
<tr>
<td>Transfusion in High-Risk Patients after Hip Surgery</td>
<td>NEJM 2011;365:2453-2462</td>
<td>A liberal transfusion strategy (Hb &lt;100), as compared with a restrictive strategy (anemia symptoms or at physician discretion for Hb &lt;80), did not reduce rates of death or inability to walk independently on 60-day follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk.</td>
</tr>
<tr>
<td>Therapeutic Platelet Transfusion</td>
<td>Lancet 2012;380:1309-16</td>
<td>Therapeutic platelet transfusions (when bleeding occurs) may be used if severe bleeding can be identified early in autologous stem-cell transplant patients; prophylactic transfusion (when platelets &lt;10) should remain standard of care in AML patients.</td>
</tr>
<tr>
<td>Transfusion Strategies for Acute Upper GI Bleeding</td>
<td>NEJM 2013;368:11-21</td>
<td>As compared with a liberal transfusion strategy (Hb &lt;90), a restrictive strategy (Hb &lt;70) significantly improved outcomes in patients with acute upper gastrointestinal bleeding.</td>
</tr>
</tbody>
</table>

## Other

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSH</td>
<td>NEJM 1995;332:1317-22</td>
<td>Hydroxyurea is effective in reduction of complications and clinical manifestations of sickle cell disease.</td>
</tr>
<tr>
<td>ITP: Dexamethasone</td>
<td>NEJM 2003;349:831-6</td>
<td>A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura.</td>
</tr>
<tr>
<td>CRASH-2</td>
<td>Health Technol Assess 2013;17(10):1-79</td>
<td>Early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost-effective. Treatment beyond 3 hours of injury is unlikely to be effective.</td>
</tr>
</tbody>
</table>
Infectious Diseases

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<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronyms</td>
<td>2</td>
</tr>
<tr>
<td>Principles of Microbiology</td>
<td>2</td>
</tr>
<tr>
<td>Bacteriology</td>
<td></td>
</tr>
<tr>
<td>Virology</td>
<td></td>
</tr>
<tr>
<td>Mycology</td>
<td></td>
</tr>
<tr>
<td>Parasitology</td>
<td></td>
</tr>
<tr>
<td>Transmission of Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td>Nosocomial Infections</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory Infections</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
</tr>
<tr>
<td>Skin and Soft Tissue Infections</td>
<td>10</td>
</tr>
<tr>
<td>Cellulitis</td>
<td></td>
</tr>
<tr>
<td>Necrotizing Fasciitis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Infections</td>
<td>11</td>
</tr>
<tr>
<td>Acute Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Traveller’s Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td>Chronic Diarrhea</td>
<td>G16</td>
</tr>
<tr>
<td>Peptic Ulcer Disease (H. pylori)</td>
<td>G11</td>
</tr>
<tr>
<td>Bone and Joint Infections</td>
<td>14</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td></td>
</tr>
<tr>
<td>Diabetic Foot Infections</td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Cardiac Infections</td>
<td>16</td>
</tr>
<tr>
<td>Infective Endocarditis</td>
<td></td>
</tr>
<tr>
<td>CNS Infections</td>
<td>18</td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td></td>
</tr>
<tr>
<td>Generalized Tetanus</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td></td>
</tr>
<tr>
<td>Systemic Infections</td>
<td>21</td>
</tr>
<tr>
<td>Sepsis and Septic Shock</td>
<td></td>
</tr>
<tr>
<td>Leprosy (Hansen’s Disease)</td>
<td></td>
</tr>
<tr>
<td>Lyme Disease</td>
<td></td>
</tr>
<tr>
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<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>26</td>
</tr>
<tr>
<td>HIV and AIDS</td>
<td>27</td>
</tr>
<tr>
<td>Epidemiology</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Modes of Transmission</td>
<td></td>
</tr>
<tr>
<td>Natural History</td>
<td></td>
</tr>
<tr>
<td>Anti-Retroviral Treatment</td>
<td></td>
</tr>
<tr>
<td>Prevention of HIV Infection</td>
<td></td>
</tr>
<tr>
<td>Types of Testing</td>
<td></td>
</tr>
<tr>
<td>HIV Pre- and Post-Test Counselling</td>
<td></td>
</tr>
<tr>
<td>Fungal Infections</td>
<td>33</td>
</tr>
<tr>
<td>Skin and Subcutaneous Infections</td>
<td></td>
</tr>
<tr>
<td>Superficial Fungal Infections</td>
<td></td>
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<tr>
<td>Parasitic Infections</td>
<td>36</td>
</tr>
<tr>
<td>Protozoa – Intestinal/Genitourinary Infections</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica (Amoebas)</td>
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<tr>
<td>Cryptosporidium spp.</td>
<td></td>
</tr>
<tr>
<td>Blood and Tissue Infections</td>
<td>38</td>
</tr>
<tr>
<td>Plasmodium spp. (Malaria)</td>
<td></td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td></td>
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<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Travel Medicine</td>
<td>42</td>
</tr>
<tr>
<td>General Travel Precautions</td>
<td></td>
</tr>
<tr>
<td>Fever in the Returned Traveller</td>
<td></td>
</tr>
<tr>
<td>Fever of Unknown Origin</td>
<td>44</td>
</tr>
<tr>
<td>Infections in the Immunocompromised Host</td>
<td>45</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Infections in Solid Organ Transplant Recipients</td>
<td></td>
</tr>
<tr>
<td>Immune Reconstitution Syndrome</td>
<td></td>
</tr>
<tr>
<td>A Simplified Look at Antibiotics</td>
<td>47</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>48</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Antivirals</td>
<td>53</td>
</tr>
<tr>
<td>Antifungals</td>
<td>53</td>
</tr>
<tr>
<td>Antiparasitics</td>
<td>55</td>
</tr>
<tr>
<td>Quick Reference: Common Infections and Their Antibiotic Management</td>
<td>FM49</td>
</tr>
<tr>
<td>References</td>
<td>56</td>
</tr>
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</table>
**Acronyms**

<table>
<thead>
<tr>
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<th>Meaning</th>
</tr>
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<td>acid-fast bacilli</td>
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<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
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<tr>
<td>ANX</td>
<td>acute neutrophil count</td>
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<tr>
<td>AOM</td>
<td>acute otitis media</td>
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<tr>
<td>ARV</td>
<td>anti-retroviral therapy</td>
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<tr>
<td>ART</td>
<td>anti-retroviral therapy</td>
</tr>
<tr>
<td>BSL</td>
<td>bronchosclerotic lung</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette-Guérin</td>
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<tr>
<td>C &amp; S</td>
<td>culture and sensitivity</td>
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<tr>
<td>CMIA</td>
<td>chronic myelogenous leukemia</td>
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<tr>
<td>CLIA</td>
<td>clinical immunoassay</td>
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<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>DEET</td>
<td>N,N-Diethyl-meta-toluamide</td>
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<td>DVT</td>
<td>deep vein thrombosis</td>
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<td>Epstein-Barr virus</td>
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<td>EHEC</td>
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<td>EIA</td>
<td>enterotoxin: E. coli</td>
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<td>ETEC</td>
<td>enterotoxigenic E. coli</td>
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<td>FDP</td>
<td>fibrinogen degradation products</td>
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<td>FTA-ABS</td>
<td>fluorescent T. pyrogenic antiboody absorption</td>
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<td>hepatitis A virus</td>
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<td>HBc</td>
<td>hepatitis B virus</td>
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<td>HBAg</td>
<td>hepatitis B antigen</td>
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<td>HCC</td>
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<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
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<td>HEV</td>
<td>hepatitis E virus</td>
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<tr>
<td>HHV</td>
<td>human herpesvirus</td>
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<tr>
<td>Hb</td>
<td>Hbomeglobin</td>
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<tr>
<td>HIC</td>
<td>human immunodeficiency virus</td>
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<td>HPI</td>
<td>human papillomavirus</td>
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<tr>
<td>HIVE</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HKg</td>
<td>herpes simplex virus</td>
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<tr>
<td>HSV</td>
<td>herpesvirus</td>
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<td>IE</td>
<td>infective endocarditis</td>
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<tr>
<td>IFN</td>
<td>interferon</td>
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<tr>
<td>Ig</td>
<td>immunoglobulin</td>
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<td>INH</td>
<td>isoniazid</td>
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<td>IUD</td>
<td>intrauterine device</td>
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<td>IVM</td>
<td>intravitaminous medicine</td>
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<td>MERS</td>
<td>Middle Eastern respiratory syndrome</td>
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<tr>
<td>MDM</td>
<td>multidrug resistance</td>
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<td>MHA TP</td>
<td>microhemagglutination test</td>
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<td>MIR</td>
<td>muscle-inrtravenous injection</td>
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<tr>
<td>MMR</td>
<td>measles/mumps/rubella</td>
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<tr>
<td>MSN</td>
<td>meningitis/sclerosis/necrosis</td>
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<tr>
<td>N. meningitidis</td>
<td>Neisseria meningitidis</td>
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<tr>
<td>N. gonorrhoeae</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>OBP</td>
<td>ova and parasites</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>PMN</td>
<td>polymorphonuclear leukocytes</td>
</tr>
<tr>
<td>PNS</td>
<td>peripheral nervous system</td>
</tr>
<tr>
<td>PPD</td>
<td>purified protein derivative</td>
</tr>
<tr>
<td>RPR</td>
<td>rapid plasma reagin</td>
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<tr>
<td>RSV</td>
<td>respiratory syncytial virus</td>
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<tr>
<td>RTI</td>
<td>respiratory tract infection</td>
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<tr>
<td>RT-PCR</td>
<td>reverse transcription-PCR</td>
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<tr>
<td>SARS</td>
<td>severe acute respiratory syndrome</td>
</tr>
<tr>
<td>sBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>SCID</td>
<td>severe combined immunodeficiency</td>
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<tr>
<td>SDH</td>
<td>syndrome of inappropriate</td>
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<tr>
<td>SDI</td>
<td>syndrome of inappropriate</td>
</tr>
<tr>
<td>SII</td>
<td>severe insulin resistance</td>
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<td>Sn</td>
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<td>Spp</td>
<td>specificity</td>
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<tr>
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<td>tuberculosis</td>
</tr>
<tr>
<td>Tg</td>
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<tr>
<td>TIP</td>
<td>t. pallidum immunoagglutination test</td>
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<tr>
<td>TPHA</td>
<td>t. pallidum particle agglutination assay</td>
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<td>VDL</td>
<td>venereal disease research laboratory</td>
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<td>VRE</td>
<td>vancomycin-resistant Enterococcus</td>
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**Principles of Microbiology**

### Bacteriology

**Bacteria Basics**
- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on their cell wall
  - Gram positive (GP): thick, rigid layer of peptidoglycan
  - Gram negative (GN): thin peptidoglycan layer + thicker outer membrane composed of lipoproteins and lipopolysaccharides
- clinical significance: GN thick outer membrane makes it resistant to penicillin’s mechanism of action
- acid-fast bacilli (AFB): high mycolic acid content in cell wall, “acid fast” as washout phase with acid-alcohol is ineffective in acid-fast bacteria, e.g. Mycobacteria, Nocardia
- “atypical” bacteria: not seen on Gram stain and difficult to culture
  - obligate intracellular bacteria: e.g. Chlamydia, Chlamydia phila
  - bacteria lacking a cell wall: Mycoplasma
  - spirochetes: e.g. Treponema pallidum
- O2 can be either vital or detrimental to growth
  - obligate aerobes: require O2
  - obligate anaerobes: require environment without O2
  - facultative anaerobes: can survive in environments with or without O2

**Mechanisms of Bacterial Disease**
1. adherence to and colonization of skin or mucous membranes
   - fimbriae (pili): microfilaments extending through the cell wall attach to epithelial cells (e.g. E. coli in the urinary tract)
2. invasion or crossing epithelial barriers
3. evasion of host defense system through inhibition of
   - phagocytic uptake via polysaccharide capsule (e.g. S. pneumoniae, N. meningitidis, H. influenzae) or surface proteins (e.g. Staphylococcus, Streptococcus)
4. toxin production
   - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (e.g. Clostridium)
   - endotoxins are structural components of GN bacterial cell walls, and may be shed by live cells or released during cell lysis
5. intracellular growth
   - obligate intracellular: Rickettsia, Chlamydia, Chlamydia phila
   - facultative intracellular: Salmonella, Neisseria, Brucella, Mycobacteria, Listeria, Legionella
6. biofilm
   - an extracellular polysaccharide network forming mesh around the bacteria (e.g. S. epidermidis) which can coat prosthetic devices such as IV catheters
### Table 1. Common Bacteria

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<th>Gram Negative Bacteria</th>
<th>Not Seen on Gram Stain</th>
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<td><strong>Bacilli (rods)</strong></td>
<td><strong>Diplococci</strong></td>
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<td>Aerobes</td>
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<tr>
<td>Staphylococcus</td>
<td>Bacillus</td>
<td>Neisseria</td>
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<td>S. aureus</td>
<td>B. anthracis</td>
<td>N. meningitidis</td>
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<tr>
<td>S. saprophyticus</td>
<td>Listeria</td>
<td>N. gonorrhoeae</td>
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<tr>
<td>S. epidermidis</td>
<td>Nocardia (modified</td>
<td>Moraxella</td>
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<tr>
<td>Streptococcus</td>
<td>acid-fast positive)</td>
<td>E. catarrhalis</td>
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<td>S. pneumoniae (GAS)</td>
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<td>S. pyogenes (GBS)</td>
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<tr>
<td>Enterococcus</td>
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<tr>
<td>E. faecalis</td>
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</tr>
<tr>
<td>Neisseria</td>
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<tr>
<td>N. meningitidis</td>
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<td>S. pneumoniae</td>
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<tr>
<td>S. epidermidis</td>
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<td>S. pyogenes (GBS)</td>
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<tr>
<td>E. faecalis</td>
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<tr>
<td>Bacilli/Coccobacilli</td>
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<td>M. tuberculosis</td>
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<tr>
<td>M. leprae</td>
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<tr>
<td>M. avium complex</td>
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<tr>
<td>M. bovis</td>
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<tr>
<td>Nocardia</td>
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<tr>
<td>M. tuberculosis</td>
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<tr>
<td>M. leprae</td>
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<tr>
<td>M. avium complex</td>
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<tr>
<td>M. bovis</td>
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</tbody>
</table>

| Anaerobes              |                        |                        |                      |              |                      |
| Peptostreptococcus     | Clostridium            | Bacteroides            |                        |              |                      |
| C. difficile           |                        | B. fragilis            |                        |              |                      |
| C. tetani              |                        |                      |                        |              |                      |
| C. botulinum           |                        |                      |                        |              |                      |
| C. perfringens         |                        |                      |                        |              |                      |

### Table 2. Commensal Flora

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<thead>
<tr>
<th>Site</th>
<th>Organisms</th>
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<tr>
<td>Skin</td>
<td>Coagulase-negative staphylococci, Corynebacterium, Propionibacterium acnes, Bacillus, S. aureus</td>
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</tr>
<tr>
<td>Oropharynx</td>
<td>Viridans group streptococci, Haemophilus, Neisseria, anaerobes (Peptostreptococcus, Bacteroides Veillonella, Fusobacterium, Actinomyces, Prevotella)</td>
<td></td>
<td></td>
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<tr>
<td>Small Bowel</td>
<td>E. coli, anaerobes (low numbers)</td>
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<tr>
<td>Colon</td>
<td>E. coli, Klebsiella, Enterobacter, Enterococcus, anaerobes (Bacteroides, Peptostreptococcus, Clostridium)</td>
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<td></td>
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<tr>
<td>Vagina</td>
<td>Lactobacillus acidophilus, viridans group streptococci, coagulase-negative staphylococci, facultative Gram-negative bacilli, anaerobes</td>
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</table>

### Figure 2. Laboratory identification of bacterial species
Virology

Viral Basics
- Viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - Infect cells and use host metabolic machinery to replicate
  - Nucleic acid can be double stranded (ds) or single stranded (ss)
  - Can be enveloped or naked
- Virions are mature virus particles that can be released into the extracellular environment
- Host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

Viral Disease Patterns
1. Acute infections (e.g., adenovirus)
   - Host cells are lysed in the process of virion release
   - Some produce acute infections with late sequelae (e.g., measles virus induces subacute sclerosing panencephalitis)
2. Chronic infections (>6 mo): (e.g., HBV, HIV)
   - Host cell machinery is used to produce and chronically release virions
3. Latent infections
   - Viral genome remains latent in host cell nucleus
   - Can reactivate (e.g., HSV, VZV)

Table 3. Common Viruses

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Enveloped</th>
<th>Virus Family</th>
<th>Major Viruses</th>
<th>Medical Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>N</td>
<td>Adenoviridae</td>
<td>Adenovirus</td>
<td>URTI, Conjunctivitis, Gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Papillomaviridae</td>
<td>HPV1, 4</td>
<td>Plantar warts, Genital warts, Cervical/anal dysplasia and cancer</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Papillomaviridae</td>
<td>HPV6,11, HPV16,18, etc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HBl, HSV2, HSV3, EBV, CMV, HHV4, HHV5, HHV6*, HHV8</td>
<td>Oral, ocular, and genital herpes; encephalitis, Chicken pox, shingles, Mononucleosis, viral hepatitis, Retinitis, pneumonitis, hepatitis, encephalitis, Roseola, Kaposis’s sarcoma, multicentric Castleman’s disease, body cavity lymphoma</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Polyomaviridae</td>
<td>JC virus</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Hepadnaviridae</td>
<td>Hepatitis B</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Paroviridae</td>
<td>Parovirus B19</td>
<td>Enytherma infectiosum (Fifth disease)</td>
</tr>
<tr>
<td>ssDNA</td>
<td>N</td>
<td>Paroviridae</td>
<td>Parovirus B19</td>
<td>Enytherma infectiosum (Fifth disease)</td>
</tr>
<tr>
<td>(+) ssRNA</td>
<td>N</td>
<td>Caliciviridae</td>
<td>Norwalk, Hepatitis E</td>
<td>Gastroenteritis, Acute hepatitis</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Picornaviridae</td>
<td>Poliovirus, Echovirus, Rhinovirus</td>
<td>Polymyositis, URTIs, viral meningitis, URTIs</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Coronaviridae</td>
<td>Coronavirus</td>
<td>URTIs, SARS, MERS</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Flaviviridae</td>
<td>Yellow fever, Dengue fever, Hepatitis C, West Nile, Zika</td>
<td>Yellow fever, Dengue fever, Hepatitis, Encephalitis, Flaccid paralysis, Zika virus disease</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Togaviridae</td>
<td>Rubella, Chikungunya</td>
<td>Rubella (German measles), Chikungunya</td>
</tr>
<tr>
<td>(+) ssRNA-RT</td>
<td>Y</td>
<td>Retroviridae</td>
<td>HIV, HTLV-1</td>
<td>AIDS, 1-cell leukemia and lymphoma</td>
</tr>
<tr>
<td>(+) ssRNA</td>
<td>Y</td>
<td>Arenaviridae</td>
<td>Lassa</td>
<td>Lassa fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Filoviridae</td>
<td>Ebola, Marburg</td>
<td>Hemorrhagic fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Orthomyxoviridae</td>
<td>Influenza A, B, C</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>Measles, Mumps, Parainfluenza, RSV</td>
<td>Measles, Mumps, URTIs, bronchitis, pneumonia</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Rhabdoviridae</td>
<td>Rabies</td>
<td>Rabies</td>
</tr>
</tbody>
</table>

Note: __family, ___virus = genus, # = species (e.g., Retroviridae HPV-2)
Mycology

Fungal Basics
• fungi are eukaryotic organisms, they can have the following morphologies
  1. yeast (unicellular)
  2. moulds, also known as filamentous fungi (multicellular with hyphae)
  3. dimorphic fungi (found as mould at room temperature but grow as yeast-like forms at body temperature)

<table>
<thead>
<tr>
<th>Table 4. Membrane and Cell Wall Compositions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane Sterol</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Bacteria</td>
</tr>
<tr>
<td>Human Cell</td>
</tr>
<tr>
<td>Fungi</td>
</tr>
</tbody>
</table>

Mechanisms of Fungal Disease
• primary fungal infection by
  ■ overgrowth of normal flora (e.g. Candida species)
  ■ inhalation of fungal spores
  ■ traumatic inoculation into skin
• toxins produced by fungi (e.g. ingestion aflatoxins)
  ■ allergic reactions to fungi (e.g. bronchopulmonary aspergillosis)

Parasitology

Parasite Basics
• parasite: an organism that lives in or on another organism (host) and damages the host in the process
  ■ parasites with complex life cycles require more than one host to reproduce
    ■ reservoir host: maintains a parasite and may be the source for human infection
    ■ intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed through the larval stages
    ■ definitive host: allows the parasite to develop to the adult stage where reproduction occurs
• 2 major groups of parasites: protozoa and helminths
  ■ see Tables 26 and 27 for examples of clinically important parasites

<table>
<thead>
<tr>
<th>Table 5. Differences Between Protozoa and Helminths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protozoa</td>
</tr>
<tr>
<td>Uncellular</td>
</tr>
<tr>
<td>Motile trophozoite</td>
</tr>
<tr>
<td>Multiplication</td>
</tr>
<tr>
<td>Eosinophilia unusual</td>
</tr>
<tr>
<td>Indefinite life span</td>
</tr>
</tbody>
</table>

*Adult Ascaris (roundworm) does not cause eosinophilia; migratory larval phases of Ascaris, however, cause high-grade eosinophilia

Characteristics of Parasitic Disease
• symptoms are usually proportional to parasite burden
• tissue damage is due to the parasite and host immune response
• chronic infections may occur with or without overt disease
• immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
• eosinophilia may suggest a parasitic infection

Mechanisms of Parasitic Disease
1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B12 deficiency in diphyllobothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
  ■ acute hypersensitivity (e.g. pneumonitis in Loeffler's syndrome)
  ■ delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
  ■ cytokine-mediated (systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
  ■ autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
  ■ immune complex (e.g. nephritis of malaria, schistosomiasis)
Transmission of Infectious Diseases

Table 6. Mechanism of Transmission

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mode of Transmission</th>
<th>Examples</th>
<th>Preventative Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Direct physical contact, or indirect contact with a fomite</td>
<td>Skin-to-skin (MRSA) Sexual (M. gonorrhoeae, C. trachomatis, HSV, HIV) Blood-borne (HIV, HBV, HCV)</td>
<td>For patients in health care facilities: Contact precautions Barrier precautions Safe needlestick/sharp practices</td>
</tr>
<tr>
<td>Droplet/Contact</td>
<td>Respiratory droplets (&gt;5 µm) can be projected short distances (≤2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, snee ing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids</td>
<td>Influenza, mumps N. meningitidis, Bordetella pertussis</td>
<td>For patients in health care facilities: Contact/droplet precautions</td>
</tr>
<tr>
<td>Airborne</td>
<td>Airborne droplet nuclei (&lt;5 µm) remain infectious over time and distance</td>
<td>M. tuberculosis, VZV, measles</td>
<td>Prophylactic vaccinations where available Ensure clean food/water supply For patients in health care facilities: Airborne precautions</td>
</tr>
<tr>
<td>Food/Waterborne</td>
<td>Ingestion of contaminated food or water</td>
<td>V. cholerae, Salmonella, HAV, HEV</td>
<td>Prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization</td>
</tr>
<tr>
<td>Zoonotic</td>
<td>Disease transmission from animals to humans either directly or via an insect vector</td>
<td>Animals (rabies, Q fever) Arthropods (malaria, Lyme disease)</td>
<td>Prophylactic medications, vaccinations Protective clothing, insect repellent, mosquito nets, tick inspection</td>
</tr>
<tr>
<td>Vertical</td>
<td>Spread of disease from parent to offspring</td>
<td>Congenital syndromes (TORCH infections) Perinatal (HIV, HBV, GBS)</td>
<td>Prenatal screening Prolphylactic treatment</td>
</tr>
</tbody>
</table>

Nosocomial Infections

- **Definition:** Infections acquired >48 h after admission to a healthcare facility OR within 30 d from discharge risk factors: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
- Patients with nosocomial infections have higher mortality, longer hospital stays, and higher healthcare costs
- Hand hygiene is an essential precaution

Table 7. Common Nosocomial Infectious Agents

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Characteristics</th>
<th>Manifestation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methicillin-Resistant</strong></td>
<td>S. aureus (MRSA)</td>
<td>Gram positive cocci</td>
<td>Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis</td>
<td>Contact precautions For infection: vancomycin or daptomycin or linezolid To decolonize 2% chlorhexidine wash OD (+ rifampin + (doxycycline or TMP/SMX) + mupirocin cream bid to nares) x 7 d</td>
</tr>
<tr>
<td><strong>Vancomycin-Resistant</strong></td>
<td>Enterococcus (VRE)</td>
<td>Majority are E. faecium Resistant if minimum inhibitory concentration of vancomycin is ≥32 µg/mL</td>
<td>Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis</td>
<td>Rectal or perirectal swab OR stool culture for colonization Culture of infected site</td>
</tr>
<tr>
<td><strong>Clostridium difficile</strong> (C. difficile)</td>
<td>Releases exotoxins A and B Hyperpyevulent strain (NAP1/B1/027) has been responsible for increase in incidence and severity</td>
<td>Fever, nausea, abdominal pain Watery diarrhea ± occult blood Pseudoemembranous colitis Severe: toxic megacolon Risk of bowel perforation Associated with antibiotic use Leukocytosis</td>
<td>Stool PCR for toxin A and B genes Stool immunorassay for toxins A and B (less sensitive than PCR) ADR (may see colonic dilatation) Sigmoidoscopy for pseudomembranes; avoid if known colonic dilatation</td>
<td>Contact precautions Stop culprit antibiotic therapy (primarily fluoroquinolones and cephalosporins) Supportive therapy (IV fluids) Mild-moderate disease: metronidazole PO x 10-14 d Severe disease: vancomycin PO x 10-14 d Toxic megacolon: metronidazole IV + vancomycin PO (as above) and general surgery consult</td>
</tr>
<tr>
<td><strong>Extended Spectrum</strong></td>
<td>β-lactam Producers (ESBL producing E. coli, K. pneumoniae)</td>
<td>Resistant to most β-lactam antibiotics except carbapenems e.g. penicillins, streptomycin**, and cephalosporins</td>
<td>UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis</td>
<td>Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)</td>
</tr>
</tbody>
</table>

*Use of contact precautions for VRE varies depending on institutional policies.
**Not available in Canada
Respiratory Infections

Pneumonia

- see Pediatrics, P80

Definition
- infection of the lung parenchyma

Etiology and Risk Factors
- impaired lung defenses
  - poor cough/gag reflex (e.g. illness, drug-induced)
  - impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  - immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
- increased risk of aspiration
- impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia, mechanical obstruction)
- no organ sm identified in 75% of hospitalized cases, and >90% of ambulatory cases

Table 8. Common Organisms in Pneumonia

<table>
<thead>
<tr>
<th>Community-Acquired</th>
<th>Nosocomial</th>
<th>Aspiration</th>
<th>Immunocompromised Patients</th>
<th>Alcoholic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Enteric GNB (e.g. E. coli)</td>
<td>Oral anaerobes (e.g. Bacteroides)</td>
<td>Pneumocystis jiroveci</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>Pseudomonas aeruginosa</td>
<td>Enteric GNB (e.g. E. coli)</td>
<td>Fungi (e.g. Cryptococcus)</td>
<td>Enteric GNB</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>S. aureus (including MRSA)</td>
<td>S. aureus</td>
<td>Nocardia</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>GAS</td>
<td>Gastric contents (chemical pneumonitis)</td>
<td>CMV</td>
<td>Oral anaerobes (aspiration)</td>
</tr>
<tr>
<td>Atypical Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legionella pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See Pediatrics, P91, Table for Common Causes and Treatment of Pneumonia at Different Ages

Clinical Presentation
- cough (± sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
- elderly often present atypically; altered LOC sometimes the only sign
- evidence of consolidation (dullness to percussion, bronchial breath sounds, crackles)
- features of parapneumonic effusion (decreased air entry, dullness to percussion)
- complications: ARDS, lung abscess, parapneumonic effusion/empyema, pleuritis ± hemorrhage

Investigations
- pulse oximetry to assess severity of respiratory distress
- CBC and differential, electrolytes, urea, Cr, ABG (if respiratory distress), troponin/CK, LFTs, urinalysis
- sputum Gram stain/C&S, blood C&S, ± serology/viral detection, ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
- CXR±CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
- bronchoscopy ± washings for:
  - (1) severely ill patients refractory to treatment and (2) immunocompromised patients

Treatment
- ABC, O2, IV fluids, consider salbutamol (nebulized or MDI)
- determine prognosis and need for hospitalization and antibiotics

Criteria for Hospitalization

Table 9. CURB 65 Score – Pneumonia Clinical Prediction Tool

<table>
<thead>
<tr>
<th>Component</th>
<th>Measurement(s)</th>
<th>Points</th>
<th>Total Score</th>
<th>Mortality</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>Altered mental status</td>
<td>1</td>
<td>0-1</td>
<td>&lt;5%</td>
<td>Can treat as outpatient</td>
</tr>
<tr>
<td>Urea/BUN</td>
<td>Urea &gt;7 mmol/L or BUN &gt;20 mg/dL</td>
<td>1</td>
<td>2-3</td>
<td>5 15%</td>
<td>Consider hospitalization</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>&gt;30 breaths/min</td>
<td>1</td>
<td>4-5</td>
<td>15-30%</td>
<td>Consider ICU</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Systolic &lt;90 or diastolic &lt;60 mmHg</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65 or older</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A CRB-65 score may be applied in the community as its criteria depend on clinical assessment alone.
Table 10. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007

<table>
<thead>
<tr>
<th>Setting</th>
<th>Circumstances</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>Previously well</td>
<td>Macrolide¹ OR Doxycycline</td>
</tr>
<tr>
<td></td>
<td>No antibiotic use in last 3 mo</td>
<td>Respiratory fluoroquinolone² OR β-lactam + Macrolide³</td>
</tr>
<tr>
<td></td>
<td>Comorbidities²</td>
<td>Respiratory fluoroquinolone² OR β-lactam + Macrolide³</td>
</tr>
<tr>
<td></td>
<td>Antibiotic use in last 3 mo (use different class)</td>
<td>Respiratory fluoroquinolone²</td>
</tr>
<tr>
<td>Inpatient</td>
<td>Ward</td>
<td>Respiratory fluoroquinolone²</td>
</tr>
<tr>
<td></td>
<td>ICU</td>
<td>β-lactam⁴ + (Macrolide¹ OR Respiratory fluoroquinolone²)</td>
</tr>
</tbody>
</table>

1. Macrolide: azithromycin, clarithromycin, erythromycin
2. Comorbidities: chronic heart, lung, liver, or renal disease; DM; alcoholism; malignancy; asplenia; immunocompromised
3. β-lactams: cefotaxime, ceftriaxone, ampicillin-sulbactam
4. Fluoroquinolone: moxifloxacin, gemifloxin, levofloxacin

Table 11. IDSA/ATS Hospital-Acquired (HAP) and Ventilator-Associated (VAP) Pneumonia Clinical Practice Guidelines 2016

<table>
<thead>
<tr>
<th>Setting</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically suspected HAP (non-VAP) with no increase in likelihood of MRS</td>
<td>One of: Piperacillin-tazobactam OR ceftazidime OR levofloxacin OR imipenem or meropenem</td>
</tr>
<tr>
<td></td>
<td>Clinically suspected HAP (non-VAP) with increasing likelihood of MRS</td>
</tr>
<tr>
<td>Clinically suspected HAP (non-VAP) with high risk of mortality or recipient of IV Abx in last 90 d</td>
<td>Two of the following (avoid 2 β-lactams): Piperacillin-tazobactam OR ceftazidime OR levofloxacin OR imipenem or meropenem OR aztreonam* OR amikacin or gentamicin or tobramycin PLUS either MRS or MSA coverage: MRS: vancomycin or linezoid OR MSA: piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem</td>
</tr>
<tr>
<td>Clinically suspected VAP in units where empiric MRS coverage and double antipseudomonal/gram-negative coverage are appropriate</td>
<td>One of: β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) OR antipseudomonal cephalosporin (ceftazidime) OR antipseudomonal carbapenem (imipenem or meropenem) OR monobactam (aztreonam)* PLUS one of: Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside (amikacin, gentamicin, or tobramycin) OR polymyxins (colistin or polymyxin B) PLUS one of: Vancomycin or linezolid for MRS coverage</td>
</tr>
</tbody>
</table>

*Not available in Canada

| Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult community-acquired pneumonia. Results: The presence of fever or immunosuppression had a positive likelihood ratio (LR) of 2, while a history of diabetes had an LR of 3; however, these traits are not confirmatory. The presence of an abnormality in any vital sign, including tachycardia, tachypnea, or fever had a +LR ranging from 2-4, which was not significantly affected by different cut-points. The absence of vital sign abnormality had a -LR ranging from 0.5-0.8. The combination of respiratory rate <30/min, heart rate <100/min, and temperature <37.8°C had a -LR of 0.18. Findings on chest exam raised the likelihood of diagnosis, but were uncommonly seen in studies. For example, presence of asymmetric breath sounds essentially confirmed the diagnosis, but was only present in 4% of patients. In patients with a clinical diagnosis, but normal radiographs, only ~10% will develop radiographic findings in 72 h. |

**Prevention**

- Public Health Agency of Canada recommends the following:
  - Vaccine for influenza A and B annually for all ages ≥ 6 mo
  - Pneumococcal polysaccharide vaccine (Pneumovax®) for all adults >65 yr and in younger patients 24 mo of age and older at high risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia, congenital or acquired immunodeficiency)
  - Pneumococcal conjugate vaccine (Prevnar-13®) for all children ≤5 yr, and for children and adolescents at high risk for invasive pneumococcal disease who are 5-17 yr and who have not previously received Prevnar-13 (CDC recommends giving Prevnar-13 to all adults at high risk for invasive pneumococcal disease)
Influenza

Definitions and Etiology
- influenza viruses A and B
- influenza A further divided into subtypes based on envelope glycoproteins
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: influenza A (H1N1), influenza A (H3N2) and influenza B
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift: abrupt, major changes due to mixing of two different viral strains from different hosts
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

Table 12 Difference Between Influenza Strains

<table>
<thead>
<tr>
<th></th>
<th>Influenza A</th>
<th>Influenza B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host(s)</td>
<td>Humans, birds, mammals</td>
<td>Humans only</td>
</tr>
<tr>
<td>Antigenic drift</td>
<td>Yes, new strains</td>
<td>Yes, new strains</td>
</tr>
<tr>
<td>Antigenic shift</td>
<td>Yes, new subtypes</td>
<td>No</td>
</tr>
<tr>
<td>Epidemics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pandemics</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Clinical Presentation
- incubation period 1-4 d and symptoms typically resolve in 7-10 days
- acute onset of systemic (fever, chills, myalgias, arthralgias, H/A, fatigue) and respiratory symptoms (cough, dyspnea, pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, Guillain-Barré syndrome)
- severe disease more likely in the elderly, children, pregnant women, patients with immunocompromise, asthma, COPD, CVD, diabetes and obesity

Investigations
- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for RT-PCR (gold standard), or rapid antigen detection (DFA, direct fluorescent antigen) detection
- serology: rarely used for clinical management

Treatment and Prevention
- primarily supportive unless severe infection or high-risk of complications
- neuraminidase inhibitors: zanamivir (Relenza®) and oseltamivir (Tamiflu®) for treatment and prophylaxis against types A and B
  - decreases duration (by ~1 d) and severity of symptoms if given within 48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- vaccine for influenza A and B viruses is recommended annually for all ages ≥ 6 mo
  - vaccine is reformulated each year to reflect circulating influenza A and B strains

Beware! Do Not Confuse H. influenzae with Influenza Virus
H. influenzae: a bacterium (Types A, B, C, D, E; F, refer to capsule)
Influenza: a virus (Types A and B refer to strain)
Skin and Soft Tissue Infections

Cellulitis

Definition
• acute infection of the skin principally involving the dermis and subcutaneous tissue

Etiology
• common causative agents: S. aureus, β-hemolytic streptococci
• immunocompromised patients or water exposure: may also include GN rods and fungi
• risk factors
  ■ trauma with direct inoculation, recent surgery
  ■ peripheral vascular disease, lymphedema DM, cracked skin in feet/toes (tinea pedis)

Clinical Presentation
• pain, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
• can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

Investigations
• CBC and differential, blood C&S if febrile
• skin swab ONLY if open wound with pus

Treatment
• antibiotics: cephalexin (broader coverage if risk factors for GN rods)
• if extensive erythema or systemic symptoms, consider cefazolin IV
• if MRSA is suspected, alternative therapy should be prescribed (see A Simplified Look at Antibiotics, ID47)
• limb rest and elevation may help reduce swelling

Necrotizing Fasciitis

Definition
• life- and limb-threatening infection of the deep fascia characterized by rapid spread

Etiology
two main forms
• Type I: polymicrobial infection – aerobes and anaerobes (e.g. S. aureus, Bacteroides, Enterobacteriaceae)
• Type II: monomicrobial infection with GAS, and less commonly S. aureus

Clinical Presentation
• pain out of proportion to clinical findings and beyond border of erythema
• edema, ± crepitus (subcutaneous gas from anaerobes), ± fever
• infection spreads rapidly
• patients may rapidly become very sick (tachycardia, hypotension, lightheadedness)
• late findings
  ■ skin turns dusky blue and black (secondary to thrombosis and necrosis)
  ■ induration, formation of hemorrhagic bullae

Investigations
• clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
• blood and tissue C&S
• serum CK (elevated CK usually means myonecrosis – a late sign)
• plain film x-ray (soft tissue gas may be visualized)
• surgical exploration for debridement of infected tissue

Treatment
• resuscitation with IV fluids
• emergency surgical debridement to confirm diagnosis and remove necrotic tissue (may require amputation)
• IV antibiotics
  ■ unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin if MRSA is considered
  ■ Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  ■ Type II (monomicrobial): cefazolin (or cloxacillin) + clindamycin IV; with confirmed GAS infection, penicillin G + clindamycin IV
  ■ with Type II, evaluate for streptococcal toxic shock syndrome and the need for IV Ig
Gastrointestinal Infections

Acute Diarrhea

- see Gastroenterology, G15 and Pediatrics, P34

Epidemiology
- one of the top five leading causes of death worldwide, according to the World Health Organization
- significant morbidity in developed countries (over 900,000 hospitalizations in the United States each year)

Definition
- passage of ≥3 loose or liquid stools/d OR >200 g stool/d for >2 d but ≤14 d

Approach to Acute Diarrhea
- rationale
  - the vast majority of acute diarrhea is caused by infection
  - in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
  - investigations are costly and are necessary only in certain circumstances
- therefore the evaluation of acute diarrhea involves
  - identifying characteristics of the illness or patient that warrant further investigation
  - assessing volume status to determine appropriate method of rehydration

Physical Exam
- volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
- abdominal exam: pain, guarding, peritoneal signs

Treatment
- rehydration is mainstay of treatment
  - oral rehydration therapy
  - IV rehydration if oral intake insufficient to replace fluid loss
  - antidiarrheal agents reduce duration of diarrhea: loperamide, bismuth salicylate
    - delays excretion of causative pathogens
  - contraindications: diarrhea with fever, bloody stool or diarrhea caused by C. difficile
- antibiotic therapy is rarely indicated because:
  - most acute diarrheal illness is viral and self-limited
  - antibiotics can eradicate normal gut flora, predisposing patient to C. difficile infection
  - antibiotics prolong the shedding of Salmonella and other causes of bacterial diarrhea
  - in EHEC infection, antibiotics may increase the risk of HUS

Initial Assessment

Any of:
- fever
- blood in stool
- severe abdominal pain ± peritoneal signs
- profuse diarrhea with signs of hypovolemia
- hospitalized or recent use of antibiotics
- age ≥65 yr with comorbidities
- immunocompromised (chemotherapy, HIV)
- diarrhea >7 d in duration
- exposure to suspicious foods or untreated water
- sexual contacts: MSM

Investigations

Routine Tests:
- Stool C&S for EHEC, stool for Shiga toxin
- Stool C&S for Campylobacter, Salmonella, and Shigella

Special Tests
- Stool C&S for EHEC, stool for Shiga toxin A and B
- Stool O&P for Giardia, Cryptosporidium, E. histolytica

Indication

Blood in stool

Recent use of antibiotics or hospitalized

Age ≥65 yr with comorbidities

Immunocompromised

Diarrhea >7 d

Exposure to untreated water

HIV

MSM

Indications for Antimicrobial Therapy

Absolute Indications:
- infection with S. typhi, Shigella, C. difficile, Cryptosporidium, E. histolytica
- immunocompromised patients

Relative Indications:
- infection with V. cholerae, non-typhoid Salmonella, Campylobacter, Yersinia, Giardia, ETEC
- decision to treat is determined by severity of illness (see Tables 13 and 14 for information on common pathogens)

Causes of Acute Bloody Diarrhea

CHES
- Campylobacter
- Hemorrhagic E. coli (e.g., O157:H7)
- Entamoeba histolytica
- Salmonella
- Shigella

Treat Symptoms

Rehydration

Antidiarrheal agents

bismuth salicylate

loperamide

Illness persists

Illness resolves

Figure 7. Approach to acute diarrhea
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. cereus – Type A (emetic)</td>
<td>Rice dishes</td>
<td>1-6 h</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>&lt;12 h</td>
</tr>
<tr>
<td>B. cereus – Type B (diarrheal)</td>
<td>Meats, vegetables, dried beans, cereals</td>
<td>8-16 h</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>&lt;24 h</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Uncooked meat, especially poultry</td>
<td>2-10 d</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>&lt;1 wk</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antimicrobials)</td>
<td>Unclear</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>Variable</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>Contaminated food, especially meat and poultry</td>
<td>8-12 h</td>
<td>±</td>
<td>–</td>
<td>+</td>
<td>&lt;24 h</td>
</tr>
<tr>
<td>E. coli (EIEC)</td>
<td>Contaminated food/water</td>
<td>1-3 d</td>
<td>+</td>
<td>±</td>
<td>–</td>
<td>7-10 d</td>
</tr>
<tr>
<td>E. coli (ETEC)</td>
<td>Contaminated food/water</td>
<td>1-3 d</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>3 d</td>
</tr>
<tr>
<td>Enterohemorrhagic E. coli (EHEC)/STEC i.e. O157:H7</td>
<td>Contamination of hamburger, raw milk, drinking, and recreational water</td>
<td>3-8 d</td>
<td>–</td>
<td>+</td>
<td>±</td>
<td>5-10 d</td>
</tr>
<tr>
<td>Salmonella Typhi</td>
<td>Fecal-oral Contaminated food/water, travel to endemic area</td>
<td>10-14 d</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>&lt;5-7 d</td>
</tr>
<tr>
<td>Non-typhoidal Salmonellosis S. Typhimurium, S. Enteritidis</td>
<td>Contaminated animal food products, especially eggs, poultry, meat, milk</td>
<td>12-72 h</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>3-7 d</td>
</tr>
<tr>
<td>Shigella dysenteriae</td>
<td>Fecal-oral, Contaminated food/water</td>
<td>1-4 d</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>&lt;1 wk</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)</td>
<td>2-4 h</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>1-2 d</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>Contaminated food/water, especially shellfish</td>
<td>1-3 d</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3-7 d</td>
</tr>
<tr>
<td>Yersinia</td>
<td>Contaminated food Unpasteurized milk</td>
<td>5 d</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>Up to 3 wk</td>
</tr>
</tbody>
</table>
Traveller’s Diarrhea

- see Acute Diarrhea, ID11

Epidemiology
- most common illness to affect travellers
- up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

Etiology
- bacterial (80-90%): E. coli most common (ETEC), Campylobacter, Shigella, Salmonella, Vibrio (non-cholera); wide regional variation (e.g. Campylobacter more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): Giardia, Entamoeba histolytica, Cryptosporidium, and Cyclospora for ~10% in long-term travellers
- pathogen-negative traveller’s diarrhea common despite exhaustive microbiological workup

Treatment
- rehydration is the mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss, use oral rehydration solutions (1 package in 1 L boiled or treated water)
  - treat symptoms: antidiarrheal agents (e.g. bismuth salicylate, loperamide)
  - empiric antibiotics in moderate or severe illness: ciprofloxacin or azithromycin or rifaximin
  - note: there is increasing fluoroquinolone resistance in causative agents, especially in South and Southeast Asia

Prevention
- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
  - bismuth salicylate (Pepto-Bismol®): 60% effective (2 tablets qid according to CDC website)
  - CDC Guidelines: antibiotic prophylaxis not recommended
  - increased risk of infection with resistant organisms
  - high risk groups (e.g. immunocompromised) likely to be infected with pathogen not covered by standard antimicrobial agents

Table 14. Parasites in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium</td>
<td>Fecal-oral</td>
<td>7 d</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>Paromomycin + nitazoxanide Immune reconstitution if immunosuppressed</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Worldwide endemic areas: Fecal-oral</td>
<td>2-4 wk</td>
<td>±</td>
<td>+</td>
<td>–</td>
<td>Metronidazole + iodoquinol or paromomycin if symptomatic infection Only iodoquinol or paromomycin for asymptomatic cyst passage If untreated, potential for liver abscess Sigmoidoscopy shows flat ulcers with yellow exudates</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Fecal-oral</td>
<td>1-4 wk</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Metronidazole or nitazoxanide Treatment of asymptomatic carriers NOT recommended Higher risk in: day care children, intake of untreated water (“beaver fever”), MSM, immunodeficiency (decreased IgA) May need duodenal biopsy</td>
</tr>
</tbody>
</table>

Table 15. Viruses in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>Fecal-oral</td>
<td>24 h</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>None Noroviruses includes Norwalk virus</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Fecal-oral</td>
<td>2-4 d</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>3-8 d None Can cause severe dehydration Virtually all children are infected by 3 yr of age Oral vaccine given at 2 and 4 mo of age</td>
</tr>
</tbody>
</table>

Bismuth salicylate (Pepto-Bismol®) can cause patients to have black stools, which may be mistaken for melena
Chronic Diarrhea

• Dukoral®: oral vaccine that offers protection against V. cholerae (efficacy ~80%) and ETEC (efficacy ~50-67%)
  • PHAC recommends that it may be considered for the following situations (not recommended for routine use in travellers):
    - short-term travellers >2 yr old who are high-risk (e.g. chronic illness) for whom there is an increased risk of serious consequences for traveller’s diarrhea (e.g. chronic renal failure, CHF, type 1 DM, inflammatory bowel disease)
    - immunosuppressed
    - history of repeat traveller’s diarrhea
    - increased risk of acquiring traveller’s diarrhea (gastric hypochlorhydria or young children >2 yr),
    - travellers to cholera endemic countries at increased risk of exposure
  • two vaccines against Salmonella typhi are available and their effectiveness is estimated to be between 50-70%

Chronic Diarrhea

• see Gastroenterology, G16

Peptic Ulcer Disease (H. pylori)

• see Gastroenterology, G11

Bone and Joint Infections

Septic Arthritis

Routes of Infection
  • hematogenous
    - contiguous osteomyelitis common in children
  • direct inoculation via skin/trauma
  • iatrogenic (surgery, arthroscopy, arthrocentesis)

Etiology
  • gonococcal
    - N. gonorrhoeae: previously accounted for 75% of septic arthritis in young sexually active adults
  • non-gonococcal
    - S. aureus: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
    - Streptococcus species (Group A and B)
    - Gram-negatives: affect neonates, elderly, IV drug users, immunocompromised
    - S. pneumoniae: affects children
    - Kingella kingae: affects children aged <4 yr of age
    - Haemophilus influenzae type B (Hib) now rare due to Hib vaccine: consider in unvaccinated children
    - Salmonella spp.: characteristic of sickle cell disease
    - coagulase-negative Staphylococcus species: prosthetic joints
  • if culture negative: partially-treated infection (prior to oral antibiotics), reactive arthritis, rheumatic fever, less common bacterial causes such as Borrelia spp. (Lyme disease) or Tropheryma whipplei (Whipple’s disease), and non-infectious causes

Risk Factors
  • gonococcal
    - age (<40 yr), multiple partners, unprotected intercourse, MSM
  • non-gonococcal
    - most affected children are previously healthy with no risk factors: occasionally preceding history of minor trauma
    - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
    - prosthetic joints/recent joint surgery
    - underlying joint disease (rheumatoid arthritis, osteoarthritis)
    - immunocompromise (DM, chronic kidney disease, alcoholism, cirrhosis)
    - loss of skin integrity (cutaneous ulcer, skin infection)
    - age >80 yr

Clinical Presentation of Gonococcal Arthritis
  • two forms (although often overlap)
    - bacteremic form
    - systemic symptoms: fever, malaise, chills
    - gonococcal triad: migratory polyarthritis, tenosynovitis, dermatitis (pustular skin lesions)
    - septic arthritis form
    - local symptoms in involved joint: swelling, warmth, pain, inability to bear weight, marked decrease in range of motion)
Clinical Presentation of Non-Gonococcal Arthritis

- acute onset of pain, swelling, warmth, decreased range of motion ± fever and chills; in children, refusal to weight bear
- most often in large weight-bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)

Investigations

- consider rheumatologic causes for monoarthritis (see Rheumatology, RH3)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal, and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBCs (>15,000/mm³); likelihood of infection increases with increasing WBCs, PMNs >90%, culture positive
  - growth of N. gonorrhoea from synovial fluid is successful in <50% of cases
  - ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment

Treatment

- medical
  - empiric IV antibiotics: specific choice depends on clinical scenario; for most adults, vancomycin + ceftriaxone is reasonable; for fully vaccinated children, cefazolin or cefoxitin IV unless MRSA is a consideration – delay may result in joint destruction
  - Gram stain and cultures guide subsequent treatment
  - gonococcal: ceftriaxone + azithromycin, for concurrent treatment of C. trachomatis
  - non-gonococcal: antibiotics against Streptococcus spp. (2-3 wk IV/PO), S. aureus (4 wk IV minimum), or GNB (4 wk)
  - surgical drainage if (see Orthopedics, OR10)
    - persistent positive joint cultures on repeat arthrocentesis
    - hip joint involvement
    - prosthetic joint
    - daily joint aspirations until culture sterile; no need to give intra-articular antibiotics
    - physiotherapy

Prognosis

- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: in children, generally good outcome if treated promptly; in adults, up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections

Etiology

- neuropathy, peripheral vascular disease, and hyperglycemia contribute to foot ulcers that heal poorly, and are predisposed to infection
- organisms in mild infection: S. aureus, Streptococcus spp.
- organisms in moderate/severe infection: polymicrobial with aerobes (S. aureus, Streptococcus, Enterococcus, GNB) and anaerobes (Peptostreptococcus, Bacteroides, Clostridium)

Clinical Presentation

- not all ulcers are infected
- consider infection if: probe to bone (see below), ulcer present >30 d, recurrent ulcers, trauma, PVD, prior amputation - loss of protective sensation, renal disease, history of walking barefoot
- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) OR the presence of pus
- ± crepitis, osteomyelitis, systemic toxicity
- visible bone or probe to bone → osteomyelitis
- infection severity
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint) or erythema >2 cm
  - severe = infection in a patient with systemic toxicity (fever, tachypnea, leukocytosis, tachycardia, hypotension)

Investigations

- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infection)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages) or MRI if high clinical suspicion
  - if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity

Treatment

- evaluate for early surgical debridement ± revascularization or amputation
- eliminate/reduce pressure and provide regular local wound care
- mild: cephalixin or clindamycin

---

Does this Patient with Diabetes have Osteomyelitis of the Lower Extremity? JAMA 2008;299:806-813 Study: Systematic literature review. 21 studies. Population: 1,027 adult patients with DM being investigated for osteomyelitis. Intervention: Various aspects of history, physical exam, laboratory tests, and diagnostic imaging studies versus bone biopsy. Primary Outcome: Diagnostic utility. Results: No studies examined any part of history taking. Temperature, ulcer characteristics (erythema, swelling, purulence), elevated WBC, skin swabs, and soft tissue cultures were not useful. Nuclear imaging has poor specificity for osteomyelitis (62%-88.5%), and MRIs have greater accuracy in detecting osteomyelitis.

<table>
<thead>
<tr>
<th>Finding</th>
<th>(+)LR</th>
<th>(–)LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visualization of bone</td>
<td>9.2</td>
<td>0.70</td>
</tr>
<tr>
<td>Ulcer area &gt;2 cm²</td>
<td>7.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Probe-to-bone</td>
<td>6.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Clinical judgment</td>
<td>5.5</td>
<td>0.54</td>
</tr>
<tr>
<td>ESR &gt;70 mm/h</td>
<td>11</td>
<td>NS*</td>
</tr>
<tr>
<td>Plain radiographs</td>
<td>2.3</td>
<td>0.63</td>
</tr>
<tr>
<td>MRI</td>
<td>3.8</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*NS = not significant
• moderate: clindamycin + ciprofloxacin or moxifloxacin PO, ceftriaxone or ertapenem IV ± MRSA coverage
• severe: piperacillin/tazobactam or meropenem IV ± vancomycin if MRSA known or suspected
• encourage glycemic control

Osteomyelitis

• see Orthopedics, OR9

Cardiac Infections

Infective Endocarditis

Definition
• infection of cardiac endothelium, most commonly the valves
• classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
• leaflet vegetations are made of platelet-fibrin thrombi, WBCs, and bacteria

Risk Factors and Etiology
• predisposing conditions
  • high risk: prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 mo, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  • moderate risk: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  • low/no risk: secundum ASD or surgically repaired ASD < VSD, PDA, MV prolapse, ischemic heart disease, previous CABBG
• opportunity for bacteremia: IVDU, indwelling venous catheter, hemodialysis, poor dentition, DM, HIV
• frequency of valve involvement MV >> AV > TV > PV
  • but in 50% of IVDU related IE the tricuspid valve is involved

Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors

<table>
<thead>
<tr>
<th>Native Valve</th>
<th>Intravenous Drug Users (IVDU)</th>
<th>Prosthetic Valve (recent surgery &lt;2 mo)</th>
<th>Prosthetic Valve (remote surgery &gt;2 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus (36%)</td>
<td>S. aureus (68%)</td>
<td>S. aureus (36%)</td>
<td>Streptococcus (20%)</td>
</tr>
<tr>
<td>S. epidermidis (28%)</td>
<td>Enterococcus (13%)</td>
<td>S. epidermidis (17%)</td>
<td>S. aureus (20%)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>GNB</td>
<td>Other</td>
<td>GNB</td>
</tr>
<tr>
<td>GNB</td>
<td>Candida</td>
<td>Other</td>
<td>Other</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

Organisms in bold are the most common isolates
1. Streptococcus includes mainly viridans group streptococci
2. Other includes less common organisms such as:
  • Streptococcus galalactiae (previously known as S. bovis; usually associated with underlying GI malignancy, cirrhosis)
  • Culture-negative organisms including nutritionally-deficient streptococci; HACEK, Bartonella, Coxiella, Chlamydia, Legionella, Brucella
  • Candida
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = Pseudomonas, saliva = oral flora, toilet water = GI flora)

Clinical Presentation
• systemic
  • fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia
• cardiac
  • dyspnea, chest pain, clubbing (subacute)
  • regurgitant murmur (new onset or increased intensity)
  • signs of CHF (secondary to acute MR, AR)
• embolic/vascular
  • petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  • Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  • focal neurological signs (CNS emboli), H/A (mycotic aneurysm)
  • splenomegaly (subacute)
  • microscopic hematuria, flank pain (renal emboli) ± active sediment
• immune complex
  • Osler’s nodes (painful, raised, red/brown, 3-15 mm on digits)
  • glomerulonephritis
  • arthritis
  • Roth’s spots (retinal hemorrhage with pale centre)

Diagnosis
• Modified Duke Criteria
  • definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  • possible diagnosis if: 1 major + 1 minor, OR 3 minor
Table 17. Modified Duke Criteria

**Major Criteria (2)**

1. Positive blood cultures for IE
   - Typical microorganisms for IE from 2 separate blood cultures (Streptococcus viridans, HACEK group, Staphylococcus gallolyticus (previously known as S. bovis), Staphylococcus aureus, community-acquired enterococci) OR Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart OR
   - All of 3 or a majority of 4 or more separate blood cultures with first and last drawn >1 h apart OR
   - Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer >1:800

2. Evidence of endocardial involvement
   - Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve) OR
   - New valvular regurgitation (insufficient if increase or change in preexisting murmur)

**Minor Criteria (5)**

1. Predisposing condition (abnormal heart valve, IVDU)
2. Fever (38.0°C/100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler’s nodes, Roth’s spots
5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE

**Investigations**

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of endovascular infection (such as IE)
- repeat blood cultures (at least 2 sets) after 48-72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), ESR (increased), RF (+), BUN/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- echo findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

**Treatment**

- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment
  - empiric antibiotic therapy if patient is unstable; administer ONLY after blood cultures have been taken
    - first line empiric treatment for native valve: vancomycin + gentamicin OR ceftriaxone
    - first line empiric treatment for prosthetic valve: vancomycin + gentamicin + cefepime + rifampin
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism, and sensitivities
  - monitor for complications of IE (e.g. CHF, conduction block, new emboli) and complications of antibiotics (e.g. interstitial nephritis)
  - prophylaxis only for high risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure, or musculoskeletal tissue
    - dental/respiratory: amoxicillin single dose 30-60 min prior; clindamycin if penicillin-allergic
    - skin/soft tissue: cephalexin single dose 30-60 min prior; clindamycin if penicillin-allergic
      (modify based on etiology of skin/soft tissue infection)
  - surgical
    - most common indication is refractory CHF
    - other indications include: valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, Staphylococci on a prosthetic valve

**Prognosis**

- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess, embolization, persistent bacteremia, altered mental status
- mortality: prosthetic valve IE (25-50%), non-IVDU S. aureus IE (30-45%) IVDU S. aureus or streptococcal IE (10-15%)
CNS Infections

Meningitis

- see Pediatrics, P54

**Definition**
- inflammation of the meninges

**Etiology**

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0-4 wk</td>
<td>Age 1-3 mo</td>
<td>Age &gt;3 mo</td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>GBS</td>
<td>S. pneumoniae</td>
<td>HSV-1, 2</td>
</tr>
<tr>
<td>E. coli</td>
<td>E. coli</td>
<td>N. meningitidis</td>
<td>VZV</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>S. pneumoniae</td>
<td>L. monocytogenes (age &gt;50 and comorbidities)</td>
<td>Enteroviruses</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>N. meningitidis</td>
<td></td>
<td>Pareaoviruses</td>
</tr>
<tr>
<td>H. influenzae</td>
<td></td>
<td></td>
<td>West Nile</td>
</tr>
</tbody>
</table>

**Risk Factors**
- lack of immunization against H. influenzae type b, S. pneumoniae, and N. meningitidis in children
- most cases of bacterial meningitis are due to hematogenous spread from a mucosal surface (nasopharynx)
- direct extension from a parameningeval focus (otitis media, sinusitis) less common
- penetrating head trauma
- anatomical meningeal defects – CSF leaks
- previous neurosurgical procedures, shunts
- immunodeficiency (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
- contact with colonized or infected persons

**Clinical Presentation**
- neonates and children: fever, lethargy, irritability, vomiting, poor feeding
- older children and adults: fever, H/A, neck stiffness, confusion, lethargy, altered level of consciousness, seizures focal neurological signs, N/V, photophobia, papilledema
- petechial rash in meningococcal meningitis, seen more frequently on trunk or lower extremities

**Investigations**
- blood work: CBC and differential, electrolytes (for SIADH), blood C&S
  - CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
  - AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
  - PCR for HSV, VZV, enteroviruses; in infants <6 mo, parechoviruses
  - WNV serology in blood and CSF during summer and early fall if viral cause suspected
- imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

**Treatment**
- bacterial meningitis is a medical emergency: do not delay antibiotics for CT or LP
  - empiric antibiotic therapy
    - age ≤28 days: ampicillin + cefotaxime
    - age 29 days-3 mo: cefotaxime + vancomycin
    - age >3 mo: ceftriaxone + vancomycin
    - add ampicillin IV if risk factors for infection with L. monocytogenes present: age >50, alcoholism, immunocompromised
    - steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics
    - continue in those patients with proven pneumococcal meningitis
    - not recommended for patients with suspected bacterial meningitis in some resource-limited countries
    - not recommended for neonatal meningitis

**Table 18. Common Organisms in Meningitis**

**Table 19. Typical CSF Profiles for Meningitis**

**CSF Analysis**
- Glucose (mmol/L)
  - Decreased
  - Normal
- Protein (g/L)
  - Markedly Increased
  - Increased
- WBC
  - 500-10,000/μL
  - 10-500/μL
- Predominant WBC
  - Neutrophils
  - Lymphocytes

**Results**

| Study | Sensitive Clinical Exams: Data were heterogeneous, and lacked standardization of clinical exams. No single item on clinical history or physical exam was sufficient to rule out meningitis, including Kernig’s and Brudzinski’s signs, or the absence of the classic triad of fever, neck stiffness, and altered mental status (AUC=0.85). Jolt accentuation had a sensitivity of 87%.
| Study | Conclusions: Data were heterogeneous, and lacked standardization of clinical exams. No single item on clinical history or physical exam was sufficient to rule out meningitis, including Kernig’s and Brudzinski’s signs, or the absence of the classic triad of fever, neck stiffness, and altered mental status. Jolt accentuation has high sensitivity, but further research is needed. LP may be performed safely without CT head in patients without altered LOC, no recent seizure, no history of CNS disease, not immunocompromised, and <60 yr.

Brudzinski’s Sign
- Passive neck flexion causes involuntary flexion of hips and knees

Kernig’s Sign
- Resistance to knee extension when hip is flexed to 90°

Jolt Accentuation of H/A
- Headache worsens when head turned horizontally at 2-3 rotations; more sensitive than Brudzinski’s and Kernig’s

CSF Gram Stain Findings
- S. pneumoniae – GP diplococci
- N. meningitidis – GN diplococci
- H. influenzae – Pleomorphic GN cocccobacilli
- L. monocytogenes – GP rods

Does this Adult Patient Have Acute Meningitis? From The Rational Clinical Examination
- JAMA 2009: http://www.jamaevidence.com/content/109/2/295
- Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult meningitis.
- Results: In retrospective studies, sensitivity for headache was 69%, and 52% for nausea and vomiting. Sensitivity for physical exam findings is similarly low (fever: 87%, neck stiffness: 80%, altered mental status: 69%). Sensitivity for the combination of the classic triad of fever, neck stiffness, and altered mental status was 45%.
- In prospective studies, sensitivity of H/A was 92% while sensitivity of N/V could not be pooled, and ranged from 32-70%. Brudzinski’s and Kernig’s signs had a sensitivity of 5% and Kernig’s sign only 5-9%. Jolt accentuation had a sensitivity of 87%.
- Conclusions: Data were heterogeneous, and lacked standardization of clinical exams. No single item on clinical history or physical exam was sufficient to rule out meningitis, including Kernig’s and Brudzinski’s signs, or the absence of the classic triad of fever, neck stiffness, and altered mental status. Jolt accentuation has high sensitivity, but further research is needed. LP may be performed safely without CT head in patients without altered LOC, no recent seizure, no history of CNS disease, not immunocompromised, and <60 yr.
Prevention
- see Pediatrics, P54
- immunization
  - child: immunization against *H. influenzae* type B (Pentacel®), *S. pneumoniae* (Synflorix®, Prevenar-13®), *N. meningitidis* (Menjugate®, Menactra®, Nimenrix®, Menveo®, Bexzero®)
  - adults: immunization against *N. meningitidis* in selected circumstances (outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with *H. influenzae* type B should be treated with rifampin if they live with an inadequately immunized (<4 yr) or immunocompromised child (<18 yr); ciprofloxacin, rifampin, or ceftriaxone if close or household contact of a patient with *N. meningitidis*; meningococcal vaccines are also recommended for post-exposure prophylaxis for close contacts and in outbreak control

Prognosis
- complications
  - H/A, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness, death
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

**Encephalitis**

Definition
- inflammation of the brain parenchyma

Etiology
- identified in only 40-70% of cases
  - when cause is identified, the most common etiology is viral: HSV, VZV, EBV, CMV, enteroviruses, parechoviruses, West Nile and other arboviruses, influenza and other respiratory viruses, HIV, mumps, measles, rubies, polio
  - bacteria: *L. monocytogenes*, *mycobacteria*, spirochetes (Lyme, syphilis), *Mycoplasma pneumoniae*
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. acute disseminated encephalomyelitis [ADEM])
  - auto-antibody mediated encephalitis
  - anti-N-methyl-D-aspartate (NMDA) receptor encephalitis most common
  - in adults, most autoantibody-mediated encephalitis cases are associated with malignancy

Pathophysiology
- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response
- viruses may reach the CNS via peripheral nerves (e.g. rubies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
  - associated with HSV-1, but can also be caused by HSV-2
- influenza and other respiratory viruses are associated with acute necrotizing encephalopathy (ANE); likely mediated by pathogen-initiated immune response

Clinical Presentation
- constitutional: fever, chills, malaise, N/V
- meningeal involvement (meningoencephalitis): H/A, nuchal rigidity
- parenchymal involvement: seizures, altered mental status focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioural disturbance
  - usually rapidly progressive over several days and may result in coma or death
  - common sequelae: memory and behavioural disturbances

Investigations
- CSF: opening pressure, cell count and differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses/parechoviruses, *M. pneumoniae*, and selectively for other less common etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. EBV, West Nile virus, rubies, *Bartonella henselae*)
- imaging/neurologic studies: CT, MRI, EEG to define anatomical sites affected
- invasive testing: brain tissue biopsy may be required for culture histological examination, and immunocytotoxicity (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges
**CNS Infections**

**Treatment**
- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out

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**Generalized Tetanus**

- see Pediatrics, P4

**Etiology and Pathophysiology**
- caused by *Clostridium tetani*: motile, spore forming, anaerobic GP bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wounds, burns, nonsterile surgeries or deliveries)
- upon inoculation, spores transform into *C. tetani* bacilli that produce tetanus toxin
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

**Clinical Presentation**
- generalized tetanus
  - initially present with painful spasms of masseters (trismus or "lockjaw")
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
- autonomic hyperactivity
  - diaphoresis, tachycardia, HTN, fever as illness progresses

**Investigations**
- primarily a clinical diagnosis, often although not always with a history of a traumatic wound and lack of immunization
- culture wounds, CK may be elevated

**Treatment**
- stop toxin production
  - wound debridement to clear necrotic tissue and spores
  - antimicrobial therapy: IV metronidazole; IV penicillin G is an effective alternative
  - neutralize unbound toxin with tetanus immune globulin (TIG)
  - supportive therapy: intubation, spasmyloytic medications (benzodiazepines), quiet environment, cooling blanket
  - control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate

**Prevention**
- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see Pediatrics, P4 and Emergency Medicine, ER17)

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**Rabies**

**Definition**
- acute progressive encephalitis caused by RNA virus (genus *Lyssavirus* of the Rhabdoviridae family)

**Etiology and Pathophysiology**
- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoon, skunk, bat, fox, cat, and dog; monkeys also a risk in the developing world
  - transmission: breach of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
  - almost all cases due to bites
  - virus travels via retrograde axonal transport from PNS to CNS
  - virus multiplies rapidly in brain, then spreads to other organs, including salivary glands
  - development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
  - infected animal can transmit rabies virus as soon as it shows signs of disease

**Clinical Presentation**
- five stages of disease
  - 1. incubation period
    - 1-3 mo on average (can range from days to years)
2. prodrome (<1 wk)
   - influenza-like illness: low-grade fever, malaise, anorexia, N/V, H/A, sore throat
   - pain, pruritus, and paresthesia may occur at wound site
   - once prodromal symptoms develop, there is rapid, irreversible progression to death
     progression from prodrome to coma and death may occur without an intervening acute
     neurologic syndrome

3. acute neurologic syndrome: 2 types (<1 wk)
   a. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia
      hypersalivation, fever, seizures
      - painful pharyngeal spasms on encountering gust of air or swallowing water cause aerophobia
      and hydrophobia, respectively
   b. paralytic: quadriplegia, loss of anal sphincter tone, fever

4. coma
   - complete flaccid paralysis, respiratory and cardiovascular failure

5. death (within days to weeks of initial symptoms)

Investigations
- purpose of diagnosis by investigations is to limit patient contact with others and to identify others
  exposed to the infectious source
- ante-mortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, serum, CSF
- post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in
  neurons)

Treatment
- post-exposure prophylaxis depends on regional prevalence (contact Public Health) and circumstances
  surrounding injury
- 3 general principles
  - wound care: clean wound promptly and thoroughly with soap and running water
  - passive immunization: HRIG infiltrated into wound site, with any remaining volume administered
    IM in anatomical site distant from vaccine administration
  - active immunization: inactivated human diploid cell rabies virus vaccine (series of 4 shots post-
    exposure if not pre-immunized)
- treatment is supportive once victim manifests signs and symptoms of disease

Prevention
- pre-exposure vaccination
  - recommended for high risk persons: laboratory staff working with rabies, veterinarians, animal and
    wildlife control workers, long-term travellers to endemic areas
  - eliminates need for HRIG following an exposure, and reduces number of HDCV PEP shots from 4 to 2

Systemic Infections

Sepsis and Septic Shock

- see Respilology, R34

Definitions
- systemic inflammatory response syndrome (SIRS): 2 or more of
  1. temperature <36°C/96.8°F or >38°C/100.4°F
  2. heart rate >90 beats/min
  3. respiratory rate >20 breaths/min or PaCO2 <32 mmHg
  4. WBC <4 x 10^9/L or >12 x 10^9/L or >10% bands
- sepsis: SIRS + proven or provable infection
- severe sepsis: sepsis + signs of end-organ dysfunction and hypoperfusion
- septic shock: severe sepsis + hypotension (<90 mmHg sBP), despite adequate fluid resuscitation

Pathophysiology
- causative agents are identified in only 50-70% of cases
- when organisms are identified, GP and GN organisms are the cause in 90% of cases
- primary bloodstream infection or secondary bacteraemia → local immune response → immune
  cells release pro-inflammatory cytokines → immune response spreads beyond local environment →
  unregulated, exaggerated systemic immune response → vasodilation and hypotension → involvement
  of tissues remote from the site of injury/infection resulting in multiple major organ dysfunction →
  periodic immunoparalysis

Clinical Presentation
- history: fever, chills, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: abnormal vitals (fever, tachypnea, tachycardia, hypotension), local signs of infection
**Systemic Infections**

**Investigations**
- CBC and differential, electrolytes, BUN, creatinine, liver enzymes, ABG, lactate, INR, PTT, FDP, blood C&S x2, urinalysis, urine C&S and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus of infection)

**Treatment (see Respirology, R34)**
- respiratory support: O2 ± intubation
- cardiovascular support: IV fluids, ± norepinephrine + ICU
- IV antibiotics (empiric, depends on suspected source)
  - start with broad spectrum antibiotics (piperacillin/tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology of infection, and local microbial susceptibilities (± aminoglycoside for drug-resistant GNs or vancomycin for MRSA)
  - narrow once susceptibilities are known
- hydrocortisone IV in patients with septic shock unresponsive to fluid resuscitation and vasopressors

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**Leprosy (Hansen’s Disease)**

**Etiology**
- *Mycobacterium leprae*: obligate intracellular bacteria, slow growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

**Clinical Presentation**
- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  i. paucibacillary “tuberculoid” leprosy (intact cell-mediated immune response)
    - ≤5 hypohesitic lesions, usually hypopigmented, well-defined, dry
    - early nerve involvement, enlarged peripheral nerves, neuropathic pain
  ii. multibacillary “lepromatous” leprosy (weak cell-mediated immune response)
    - ≥6 lesions, symmetrical distribution
    - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
    - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  iii. borderline leprosy
    - lesions and progression lies between tuberculoid and lepromatous forms

**Investigations**
- skin biopsy down to fat or slit skin smears for AFB staining, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

**Treatment (WHO Treatment Regimens)**
- paucibacillary: dapsone daily + rifampin monthly x 6 mo
- single skin lesion paucibacillary: single dose of rifampin, ofloxacin, and minocycline
- multibacillary: dapsone + rifampin monthly + clofazimine monthly x 12 mo AND low dose clofazimine once daily x 12 mo
- treatment of leprosy can cause an immune reaction to killed or dying bacteria (e.g. erythema nodosum leprosum and reversal reaction): symptomatic management with NSAIDs if mild, prednisone with 6-12 wk taper if severe; thalidomide for erythema nodosum leprosum

**Prognosis**
- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum leprosum, social stigmatization due to clofazimine hyperpigmentation
- long post-treatment follow-up warranted to monitor for relapse and immune reactions
Lyme Disease

Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (N. America) *B. garinii, B. afzelii* (Europe and Asia)
- transmitted by *Ixodes* tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- in Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick and Nova Scotia, as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white-tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment

Clinical Presentation
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, H/A, myalgias
  - erythema migrans: expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) on thigh/groin/axilla
- stage 2 (early disseminated stage): weeks post-infection
  - CNS: aseptic meningitis, CN palsies (CN VII palsy), peripheral neuritis
  - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronica atrophicans (due to *B. afzelii*)
  - neurologic: encephalopathy, meningitis, neuropathy

Investigations
- serology: ELISA, Western blot

Prevention
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks and prompt removal of tick
- doxycycline prophylaxis within 72 h of removal of an engorged, *Ixodes scapularis* tick in hyperendemic area (local rate of infection of ticks ≥20%) for patients >8 yr who are not pregnant or lactating

Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone

Toxic Shock Syndrome

Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF)
- course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- Staphylococcal TSS involves the production of superantigen TSST-1 (toxic shock syndrome toxin 1)
- Streptococcal TSS involves the production of superantigens SPEA, SPEB, SPEC

Risk Factors
- Staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or Cesarean or other surgical infections)
- Streptococcal: minor trauma, surgical procedures, preceding viral illness (e.g. chickenpox), use of NSAIDs

Clinical Presentation and Investigations
- acute onset
- Staphylococcal TSS
  - T >38.9°C
  - sBP <90 mmHg
  - diffuse erythroderma with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
• Streptococcal TSS
  • SBP <90 mmHg
  • isolation of GAS from a normally sterile site (e.g. blood, pleural, tissue biopsy, or surgical wound)
  • ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment, erythematous macular rash that may desquamate

**Treatment**
- supportive: fluid resuscitation
- Staphylococcal: for methicillin-susceptible *S. aureus*: clindamycin + cloxacillin (IV); for MRSA: clindamycin + vancomycin x 10-14 d
- Streptococcal: IV penicillin and clindamycin and ± IVIg

### Cat Scratch Disease

**Etiology**
- *Bartonella henselae*: intracellular bacteria
- cat-to-human transmission via cat scratch/bite

**Clinical Presentation**
- skin lesion appears 3-10 d post-inoculation
- may be followed by fever, tender regional lymphadenopathy
- in some patients, organism may disseminate causing fever of unknown origin, hepatosplenomegaly, retinitis, encephalopathy
- usually self-limited

**Investigations**
- serology, PCR, lymph node biopsy

**Treatment**
- the disease may be self-limited but treatment is recommended by the Infectious Disease Society of America with a 5 d course of azithromycin for immunocompetent patients with mild to moderate illness
- needle aspiration of painful suppurative lymph nodes may hasten the relief of symptoms
- combination therapy consisting of doxycycline or azithromycin plus rifampin often used for disseminated disease (neuroretinitis, hepatosplenomegaly involvement)

### Rocky Mountain Spotted Fever

**Etiology**
- *Rickettsia rickettsii*: obligate intracellular GN organism
- reservoir hosts: rodents, dogs
- vectors: *Dermacentor* ticks
- organisms cause inflammation of endothelial lining of small blood vessels, leading to small hemorrhages and thrombi
- can cause widespread vasculitis leading to H/A, and CNS changes; can progress to death if treatment is delayed

**Clinical Presentation**
- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, H/A, myalgia, N/V, anorexia
- macular rash appearing on day 2-4 of fever
  - begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  - occasionally “spotless” (10% of patients)

**Investigations**
- skin biopsy and serology (indirect fluorescent antibody test)

**Treatment**
- doxycycline, usually 5-7 d (treat for 3 d after defervescence)

### West Nile Virus

**Epidemiology**
- virus has been detected throughout the United States and much of southern Canada
- overall case-fatality rates in severe cases is ~10%

**Transmission**
- primarily from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation
Clinical Presentation
- Most are asymptomatic.
- Most symptomatic cases are mild (West Nile fever): acute onset of H/A, back pain, myalgia, anorexia, maculopapular rash involving chest, back, arms.
- Severe complications: encephalitis, meningoencephalitis, and acute flaccid paralysis (especially in those >60 yr).

Investigations
- IgM antibody in serum or CSF (cross-reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo.
- Viral isolation by PCR from CSF tissue, blood, and fluids (all have low sensitivity).
- CSF: elevated lymphocytes and protein if CNS involvement.

Treatment and Prevention
- Treatment: supportive.
- Prevention: mosquito repellent (DEET), drain stagnant water, community mosquito control programs.

Syphilis

Etiology
- Treponema pallidum: thick motile spirochetes historically detectable by dark-field microscopy.
- Transmitted sexually, vertically, or parenterally (rare).

Clinical Presentation
- see Dermatology, D31 and Gynecology, GY30.
- Multi-stage disease:
  1. Primary syphilis (3-90 d post infection)
     - Painless chancre at inoculation site (any mucosal surface).
     - Regional lymphadenopathy.
     - Acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment.
  2. Secondary syphilis = systemic infection (2-8 wk following chancre)
     - Maculopapular rash involving palms and soles.
     - Generalized lymphadenopathy, low-grade fever, malaise, H/A, aseptic meningitis, ocular/otic syphilis.
     - Condylomata lata: painless, wart-like lesion on palate, vulva, or scrotum (highly infectious).
  3. Late syphilis
     - Asymptomatic infection that follows untreated primary/secondary syphilis.
     - Early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection).
     - Increased transmission risk with early latent; longer treatment duration required for late latent.
  4. Tertiary syphilis (1-30 yr post-infection)
     - Gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain.
     - Aortic aneurysm and aortic insufficiency.
     - Neurosyphilis: dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis.
  5. Congenital syphilis
     - Causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness.
     - Most infected newborns are asymptomatic.
     - Clinical manifestation in early infancy include rhinitis (snuffles), lymphadenopathy, hepatosplenomegaly, pseudoparalysis (bone pain associated with osteitis) and rash (usually maculopapular and involving palms and soles).
     - Late onset manifestations (>2 yr of age) include saddle nose, saber shins, Glutton joints, Hutchinson's teeth, mulberry molars, rhagades, CN VIII deafness, interstitial keratitis, juvenile paresis.

Investigations
- Screening tests: CMIA, CLIA, EIA (treponemal), RPR, or VDRL (non-treponemal).
- Confirmatory tests: TPPA, FTA-ABS, MHA-TP, TPI, dark field microscopy with silver stain (rarely).
- LP for neurosyphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms, or with HIV and late latent/unknown duration syphilis; consider in others.
- For congenital syphilis, LP is essential; long bone x-rays may also be helpful.

Treatment
- For 1st, 2nd, early latent: benzathine penicillin G 2.4 million units IM x 1.
- For 3rd, late latent: benzathine penicillin G 2.4 million units IM weekly x 3.
- If allergic to penicillin: doxycycline 100 mg PO bid x 14 d.
- Neurosyphilis: aqueous Penicillin G 18-24 million units/d IV x 14 d.
- For congenital syphilis, penicillin G IV x 10 d.
- See Family Medicine, FM42 for generalized STI workup.
Tuberculosis

Etiology, Epidemiology, and Natural History

- 1/3 of the world’s population is infected with TB
- contracted by aerosolized inhalation of Mycobacterium tuberculosis, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive, and replicate in macrophages
- inhalation and deposition in the lung can lead to one of the following outcomes
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 95% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 1-2 yr of initial infection) at a pulmonary or extrapulmonary site

Risk Factors

- social and environmental factors
  - travel or birth in a country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  - Aboriginal (particularly Inuit), crowded living conditions, low SES/homeless, IVDU
  - personal or occupational contact
- host factors
  - immunocompromise/immunosuppressed (especially HIV, including extremes of age)
  - silicosis
  - chronic renal failure requiring dialysis
  - malignancy and chemotherapy
  - substance abuse (e.g. drug use, alcoholism, smoking)

Clinical Presentation

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitut oral symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms
  1. pulmonary TB
    - chronic productive cough ± hemoptysis
    - CXR consolidation or cavitation, lymphadenopathy
    - non-resolving pneumonia despite standard antimicrobial therapy
  2. miliary TB
    - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
    - CXR: multiple small 2-4 mm millet seed-like lesions throughout lung
  3. extrapulmonary TB
    - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott’s disease), adrenal (causing Addison’s disease), renal, ovarian

Investigations

- screening for latent TB
  - PPD/Mantoux skin tests
    - both tests diagnose prior TB exposure; neither can diagnose or exclude active disease
IFN-γ release assay (IGRA)
- in patients previously infected with TB, T-cells produce increased amounts of IFN-γ when re-exposed to TB antigen
- detects antigen not present in the BCG vaccine or in most types of non-tuberculous-Mycobacteria (NTM), therefore fewer false positives
- Canadian and American guidelines treat IGRA as equivalent to the TB skin test and preferable in patients with a history of BCG vaccination or who may not return for a skin test reading

Diagnostic tests/investigations for active pulmonary TB
- three sputum specimens (either spontaneous or induced) should be collected for acid-fast bacilli smear and culture; the three specimens can be collected on the same day, a minimum of 1 hour apart
- BAL
- CXR
  - nodular or alveolar infiltrates with cavitation (middle/lower lobe if primary, apical if secondary)
  - pleural effusion (usually unilateral and exudative) may occur independently of other radiograph abnormalities
  - hilar/mediastinal adenopathy (especially in children)
  - tuberculoma (semi-calcified well-defined solitary coin lesion 0.5-4 cm that may be mistaken for lung CA)
  - miliary TB (see clinical features)
  - evidence of past disease: calcified hilar and mediastinal nodes, calcified pulmonary focus, pleural thickening with calcification, apical scarring

Prevention
- primary prevention
  - airborne isolation for active pulmonary disease
  - BCG vaccine
    - ~80% effective against pediatric miliary and meningeal TB
    - effectiveness in adults debated (anywhere from 0-80%)
    - recommended in high-incidence communities in Canada for infants in whom there is no evidence of HIV infection or immunodeficiency; widely used in other countries
- secondary prevention (defer in pregnancy unless mother is high risk)
  - likely INH-sensitive: isoniazid (INH) + pyridoxine (vit B6 to help prevent INH-associated neuropathy) x 9 mo
  - likely INH-resistant: rifampin x 4 mo

Treatment of Active Infection
- pulmonary TB: INH + rifampin + pyrazinamide + ethambutol + pyridoxine x 2 mo (initiation phase), then INH + rifampin + pyridoxine x 4 mo in fully susceptible TB (continuation phase), total 6 mo
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
  - MDR = resistance to INH and rifampin ± others
  - XDR = resistance to INH + rifampin + fluoroquinolone + ≥1 of injectable, second-line agents
    - very difficult to treat, global public health threat, 5 documented cases in Canada from 1997-2008
  - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area

HIV and AIDS

Epidemiology

Canadian Situation (Public Health Agency of Canada, 2013)
- estimated 71,300 Canadians living with HIV infection at the end of 2011, 25% unaware of HIV positive status
- 2,090 new infections were reported in 2013: MSM account for 49.3% of cases, IVDU 12.8%

Global Situation (WHO and UNAIDS Core Epidemiology Slides, July 2014)
- estimated 35 million people living with HIV/AIDS in 2013
- estimated 2.1 million newly infected in 2013
- estimated 1.5 million AIDS-related deaths in 2013

HIV-1 is the predominant type in North America and most of the world
HIV-2 is found mainly in West Africa
Both lead to AIDS but HIV-2 is generally less virulent
Etiology

- HIV is a retrovirus that causes progressive immune system dysfunction which predisposes patients to various opportunistic infections and malignancies.
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17) and capsid (p24) enclosing 2 single-stranded copies of RNA plus enzymes in its core.
- Virion glycoproteins bind CD4 and CCR5/CXCR4 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells.
- RNA converted to dsDNA by viral reverse transcriptase; dsDNA is integrated into host genome by viral integrase.
- Virus DNA transcribed and translated using host cell machinery, post-translational modifications include proteolytic activity of virally encoded protease enzymes.
- New virions bud out of host cell, incorporating host cell membrane; additional maturation steps are required before virions are considered infectious.
- Exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, and increased cell turnover.

Modes of Transmission

Table 20. Modes of Transmission in Adolescents and Adults by Site and Medium

<table>
<thead>
<tr>
<th>HIV Invasion Site</th>
<th>Sub-Location</th>
<th>Transmission Medium</th>
<th>Transmission Probability per Exposure Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital tract</td>
<td>Vagina, ectocervix, endocervix</td>
<td>Semen</td>
<td>1 in 200 to 1 in 2,000</td>
</tr>
<tr>
<td>Male genital tract</td>
<td>Inner foreskin, penile urethra</td>
<td>Cervicovaginal and rectal secretions and desquamations</td>
<td>1 in 700 to 1 in 3,000</td>
</tr>
<tr>
<td>Intestinal tract</td>
<td>Rectum, upper GI tract</td>
<td>Semen</td>
<td>1 in 20 to 1 in 300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semen</td>
<td>1 in 2,500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal blood/genital secretions (intrapartum)</td>
<td>1 in 5 to 1 in 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breastmilk</td>
<td>1 in 5 to 1 in 10</td>
</tr>
<tr>
<td>Placenta</td>
<td>Chorionic villi</td>
<td>Maternal blood (intrapartum)</td>
<td>1 in 10 to 1 in 20</td>
</tr>
<tr>
<td>Blood stream</td>
<td></td>
<td>Contaminated blood products</td>
<td>95 in 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sha p/needlestick injuries</td>
<td>1 in 150</td>
</tr>
</tbody>
</table>

Adapted with permission from Macmillan Publishers Ltd. Nat Rev Immunology 2008;8:447-457.

NOTE: these estimates are for “all comers” i.e. they estimate transmission risk for anyone with HIV infection and do not take into account treatment status of the HIV+ person (in contrast to results of PARTNER study).

Natural History

![Figure 9. HIV viral particle](image)

- **Acute Infection** Retroviral Syndrome
  - 40-90% experience an acute “flu-like” illness (may include fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, H/A, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
  - hematologic disturbances (lymphopenia, thrombocytopenia)
  - 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
  - associated with a high level of plasma viremia and therefore high risk of transmission
Asymptomatic (Latent) Stage
- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count in adults: 500-1,100 cells/mm³
- CD4 count drops 60-100 cells/mm³ per year
- by 10 yr post-infection, 50% have AIDS, 30% demonstrate milder symptoms, and <20% are asymptomatic if left untreated

Definition of AIDS
- HIV-positive AND one or more of the clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. PJP (previously PCP), esophageal candidiasis, CMV, MAC, TB, toxoplasmosis), malignancy (Kaposi's sarcoma, invasive cervical cancer), wasting syndrome
- OR CD4 <200 (or <15%); this is largely historical since ART can reverse CD4 count decline

Table 21. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)

<table>
<thead>
<tr>
<th>CD4 Counts</th>
<th>Possible Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 cells/mm³</td>
<td>Often asymptomatic Constitutional symptoms: fever, night sweats, fatigue, weight loss</td>
</tr>
<tr>
<td></td>
<td>Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi's sarcoma (KS)</td>
</tr>
<tr>
<td></td>
<td>Recurrent bacterial infections, especially pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pulmonary and extrapulmonary tuberculosis</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>Pneumocystis jiroveci pneumonia (formerly PCP)</td>
</tr>
<tr>
<td></td>
<td>KS</td>
</tr>
<tr>
<td></td>
<td>Oral thrush</td>
</tr>
<tr>
<td></td>
<td>Local and/or disseminated fungal infections: Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum</td>
</tr>
<tr>
<td>&lt;100 cells/mm³</td>
<td>Progressive multifocal leukoencephalopathy (PML) – JCV virus</td>
</tr>
<tr>
<td></td>
<td>CNS toxoplasmosis</td>
</tr>
<tr>
<td>&lt;50 cells/mm³</td>
<td>CMV infection: retinitis, colitis, cholangiopathy, CNS disease</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium avium complex (MAC)</td>
</tr>
<tr>
<td></td>
<td>Bacillary angiomatosis (disseminated Bartonella)</td>
</tr>
<tr>
<td></td>
<td>Pr mary central nervous system lymphoma (PCNSL)</td>
</tr>
</tbody>
</table>

Laboratory Diagnosis
- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo (therefore 3 mo window period)
- initial screening test (3rd generation antibody test): enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%
- increasingly, combination p24 antigen/HIV antibody tests (4th generation) used for screening; improved sensitivity in early or acute infection and sensitivity/specificity approach 100% for chronic infection
- confirmatory test: if positive screen, Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160); specificity >99.99%
- rapid (point of care) antibody tests: higher false positives, therefore need to confirm positive results with traditional serology
- p24 antigen: detection by ELISA may be positive during “window period”

Management of the HIV Positive Patient
- verify positive HIV test
- complete baseline history and physical exam, then follow-up every 3-6 mo
- laboratory evaluation
  - routine CD4 count to measure status of the immune system
  - routine HIV-RNA levels (viral load)
  - also important indicator of effect of ART
  - baseline HIV resistance testing to guide ARV therapy
  - HLA-B*5701 genetic test to screen for abacavir hypersensitivity if considering abacavir in treatment regimen
  - CCR5 tropism testing if considering CCR5 antagonist in treatment regimen
  - baseline tuberculosis skin test (PPD): induration greater than 5 mm is positive
  - baseline serologies (hepatitis A, B, and C, syphilis, toxoplasmosis, CMV, VZV)
  - routine biochemistry and hematology, CXR, urinalysis
  - annual fasting lipid profile and fasting glucose (due to ART side effects)
- education
  - regular follow-up on CD4 counts and viral loads (q3-6mo) as well as strict adherence to ART improves prognosis
  - prevention of further transmission through safer sex and clean needles for IVDU
  - HIV superinfection (transmission of different HIV strains from another HIV+ person) does rarely occur so barrier protection during sex is still recommended
  - discuss importance of disclosing HIV status to partners including risk of criminal prosecution of non disclosure in jurisdictions where applicable
  - connect to relevant community groups and resources
• health care maintenance
  • assessment of psychosocial concerns and referral to psychiatry or social work if appropriate
  • vaccines influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative)
  • annual screening (PAP smear, STIs)
  • management of comorbid conditions and provision of general primary care

### Table 22. Prophylaxis Against Opportunistic Infections in HIV-infected Patients

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication for Prophylaxis</th>
<th>Prophylactic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis jiroveci</em></td>
<td>CD4 count &lt;200 cells/mm³ or history of oral candidiasis</td>
<td>TMP-SMX 1 SS or DS OD</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>IgG antibody to <em>Toxoplasma</em> and CD4 count &lt;100 cells/mm³</td>
<td>TMP-SMX 1 DS OD</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>PPD reaction &gt;5 mm or contact with case of active TB</td>
<td>INH + pyridoxine dly x 9 mo</td>
</tr>
<tr>
<td><em>Mycobacterium avium complex</em></td>
<td>CD4 count &lt;50 cells/mm³</td>
<td>Azithromycin 1,200 mg q1wk</td>
</tr>
</tbody>
</table>

SS = single strength; DS = double strength


### Anti-Retroviral Treatment

#### Overall Treatment Principles
- recommended that all HIV+ patients initiate combination ART to restore and preserve immune function, reduce morbidity, prolong survival and prevent transmission
- patients starting ART should be committed to treatment and understand the importance of adherence; poor compliance can lead to viral resistance; may defer treatment on the basis of clinical and psychosocial factors on case by case basis
- consider results of baseline resistance testing and complete ART history before (re-) initiating ART
- goal: keep viral load below limit of detection i.e. <40 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo, and restore immunological function
- strong evidence against intermittent ART or ‘drug holidays’
- ART leads to 96% reduction in risk of transmitting HIV to sexual partners

#### ART Recommendations for Treatment of Naïve Patients
- 2 NRTIs + 1 INSTI/PI (boosted with ritonavir or cobicistat)

#### Treatment Failure
- defined primarily by viral load (persistently >200 copies/mL)
- ensure that viral load >40 is not just a transient v remia or ‘blip’; confirm medication adherence, assess drug interactions, perform resistance testing

### Anti-Retroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals

**Cochrane DB Syst Rev 2012 Jul 11;7:CD007189.**

**Purpose:** To evaluate the efficacy of oral anti-retroviral prophylactic therapy in preventing HIV infection.

**Study:** Systematic review of 12 randomized controlled trials with 6 trials forming the core analysis.

**Population:** 9849 HIV-uninfected patients at high risk of contracting HIV including men who have sex with men, serodiscordant couples and others.

**Outcome:** New infection with HIV.

**Results:** Daily oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) reduced the risk of HIV acquisition compared to placebo (RR 0.49; 95% CI 0.28-0.85). TDF alone also showed significant risk reduction in trials with fewer patients (RR 0.33; 95% CI 0.20-0.55). There was no significant increase in adverse events in any of the treatment groups. Sexual practices and adherence did not differ between treatment and placebo arms.

**Conclusions:** Pre-exposure prophylaxis with TDF with or without FTC effectively reduces the risk of HIV acquisition in high risk, HIV uninfected patients without causing significant adverse effects.
### Table 23. Anti-Retroviral Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors (NRTIs)</td>
<td>zidovudine (AZT) lamivudine (3TC) stavudine (d4T) didanosine (ddI) abacavir (ABC) emtricitabine (FTC) tenofovir disoproxil fumarate (TDF) Combination Tablets: AZT/3TC (Combivir®) AZT/3TC/ABC (Trizivir®) ABC/3TC (Kivexa®) TDF/FTC (Truvada®)</td>
<td>Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth</td>
<td>Lactic acidosis Lipodystrophy Rash N/V/diarrhea Bone marrow suppression (AZT) Peripheral neuropathy (ddI, d4T) Drug-induced hypersensitivity (ABC) Pancreatitis (ddI/d4T) Myopathy (AZT)</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</td>
<td>efavirenz (EFZ) nevirapine (NVP) delavirdine (DLV) etravirine (ETR) rilpivirine (RPV)</td>
<td>Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication</td>
<td>Rash, Stevens-Johnson syndrome CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz) Hepatotoxicity (nevirapine – avoid in females with CD4 &gt;250, men with CD4 &gt;400) CYP3A4 interactions</td>
</tr>
<tr>
<td>Protease inhibitors (PIs)*</td>
<td>ritonavir (RTV) saquinavir (SDV) amprenavir (APV) nefavir (NFV) indinavir (IDV) atazanavir (ATV) fosamprenavir (FPV) lopinavir/ritonavir (Kaletra®) tipranavir (TPV) darunavir (DRV)</td>
<td>Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins</td>
<td>Lipodystrophy, metabolic syndrome N/V/diarrhea Hepatitis (indinavir) Rash (APV) Hyperbilirubinemia (atazanavir, indinavir) CYP3A4 interactions Hyperlipidemia</td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>enfuvirtide (T-20)</td>
<td>Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection</td>
<td>Injection site reactions, rash, infection, diarrhea, nausea, fatigue</td>
</tr>
<tr>
<td>CCR5 antagonist</td>
<td>maraviroc</td>
<td>Inhibit viral entry by blocking host CCR5 co-receptor</td>
<td>Fever, cough, dizziness</td>
</tr>
<tr>
<td>Integrase strand transfer inhibitors (INSTIs)</td>
<td>raltegravir elvitegravir dolutegravir bictegravir</td>
<td>Inhibits integration of HIV DNA into the human genome thus preventing HIV replication</td>
<td></td>
</tr>
</tbody>
</table>

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations.

### Single Tablet ART Regimens
- reduces pill burden and increases adherence
- generally better tolerated

### Table 24. Single Tablet ART Regimens

<table>
<thead>
<tr>
<th>Name</th>
<th>Contents</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla®</td>
<td>efavirenz/tenofovir/emtricitabine</td>
<td>psychiatric events, vivid dreams</td>
</tr>
<tr>
<td>Complera®</td>
<td>rilpivirine/emtricitabine/tenofovir</td>
<td>good side effect profile</td>
</tr>
<tr>
<td>Odefsey®</td>
<td>rilpivirine/emtricitabine/tenofovir alafenamide</td>
<td>good side effect profile</td>
</tr>
<tr>
<td>Stibild®</td>
<td>elvitegravir/cobicistat/emtricitabine/tenofovir</td>
<td>good side effect profile</td>
</tr>
<tr>
<td>Triumeq®</td>
<td>dolutegravir/abacavir/tenofovir</td>
<td>good side effect profile; use only in HLAB*5701 negative patients</td>
</tr>
<tr>
<td>Genvoya®</td>
<td>tenofovir/emtricitabine/elvitegravir/cobicistat</td>
<td>good side effect profile</td>
</tr>
</tbody>
</table>
Prevention of HIV Infection
- education, including harm-reduction
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm reduction for IVDU: avoid sharing needles
- prevention of vertical HIV infection: treatment with ART should be initiated prior to pregnancy or as early as possible during pregnancy. The risk of vertical HIV transmission can be reduced to < 1% if maternal ART is started in a timely manner and the maternal viral load is undetectable prior to delivery.
- universal blood and body precautions for health care workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV
- ART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation

Figure 11. Mechanism of HIV replications
Types of Testing

1. Nomina /Name-Based HIV Testing
   - person ordering the test knows the identity of the person being tested for HIV
   - HIV test is ordered using the name of the person being tested
   - person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
   - test result is recorded in the health care record of the person being tested

2. Non-Nominal/Non-Identifying HIV Testing
   - similar to nominal/name-based testing on all points except:
   - HIV test is ordered using a code or the initials of the person being tested

3. Anonymous Testing
   - available at specialized clinics
   - person ordering the HIV test does not know the identity of the person being tested
   - HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
   - test results are not recorded on the health care record of the person being tested
   - patient identification and notification of Public Health required to gain access to ART

HIV Pre- and Post-Test Counselling

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV+ patients should be connected with local support services

Fungal Infections

Skin and Subcutaneous Infections

Superficial Fungal Infections

- see Dermatology, D25

Dermatophytes

- see Dermatology, D26

Subcutaneous Fungal Infection

Etiology
- subcutaneous inoculation by fungi that naturally reside in the soil, including *Sporothrix schenckii*, which usually occurs in gardeners injured by a rose thorn or splinter

Clinical Presentation
- causes subcutaneous nodules at the point of entry, may develop into an ulcer
- fungi may migrate up lymphatic vessels creating nodules along the way – “nodular lymphangitis”

Treatment
- oral azole (e.g. itraconazole)
- IV amphotericin B for severe or disseminated infection

Endemic Mycoses

Etiology
- fungal infection that occurs through the inhalation of spores (from soil, bird droppings, vegetation) or inoculation injury
- thermally dimorphic organisms: mould in cold temperature (e.g. soil) and yeast at higher temperature (e.g. tissue)
- in North America, the three major endemic mycoses are: histoplasmosis, blastomycosis, and coccidioidomycosis
Clinical Presentation
- may be asymptomatic
- all can cause pneumonia and may disseminate hematogenously
- may reactivate or disseminate during immunocompromised states

Treatment
- common to all endemic mycoses
  - oral azole (e.g. itraconazole for mild-moderate local infection)
  - IV amphotericin B for systemic infection

Table 25. Endemic Mycoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endemic Region</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasma capsulatum</td>
<td>Ohio and Mississippi River valleys in central USA, Ontario, Quebec; widespread</td>
<td>Asymptomatic (in most people)</td>
<td>Fungal culture, fungal stain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary pulmonary</td>
<td>Antigen detection (urine and serum)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fever, cough, chest pain, H/A, myalgia, anorexia</td>
<td>Serology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CXR (chronic): pulmonary infiltrates, cavitary disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated (rare)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occurs primarily in immunocompromised patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(lymphadenitis), skin, liver, adrenals, CNS</td>
<td></td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>States east of Mississippi River, Northern Ontario and along the Great Lakes</td>
<td>May be asymptomatic</td>
<td>Sputum smear and culture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary: acute or chronic pneumonia</td>
<td>Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fever, cough, chest pain, chills, night sweats, weight loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CXR (acute): lobal or segmental pneumonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CXR (chronic): lobal infiltrates, fibronodular interstitial disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spread to skin (vernaceous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), GU tract (prostatitis, epididymitis)</td>
<td></td>
</tr>
<tr>
<td>Coccioides immitis</td>
<td>Deserts in southwest USA, northwest Mexico</td>
<td>Primary</td>
<td>Sputum culture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• “Valley fever”: subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for weeks to months</td>
<td>Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can develop hypersensitivity with arthralgias, erythema nodosum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Common opportunistic infection in patients with HIV</td>
<td></td>
</tr>
</tbody>
</table>

Opportunistic Fungi

Pneumocystis jiroveci (formerly P. carinii)
Pneumonia: PJP or PCP

Etiology
- respiratory exposure to a unicellular fungi (previously classified as a protozoa)
- rarely transmitted from person to person
- without prophylaxis, HIV patients with a CD4 count <200 cells/mm³ have an 80% lifetime risk of PJP

Clinical Presentation
- symptoms of pneumonia: fever, nonproductive cough, progressive dyspnea
- classic CXR
- most clinical disease is due to reactivation of latent infection or reinfection by a different genotype in immunocompromised patients (steroid use, HIV)

Investigations
- demonstration of organism in induced sputum, bronchoalveolar lavage, or endotracheal aspirate (if intubated)

Treatment and Prevention
- oxygen to keep SaO₂ >90%
- antimicrobial options
  - TMP/SMX (PO or IV)
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV)
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia (pO₂ <70 mmHg or A-a gradient O₂ >35 mmHg)
- prophylactic TMP/SMX for those at high risk of infection (HIV patients when CD4 <200 cells/mm³ or non HIV immunocompromised patients under specific conditions)
**Cryptococcus spp.**

**Etiology**
- inhalation of airborne encapsulated yeast from soil contaminated with pigeon droppings (C. neoformans) or certain tree species such as Eucalyptus or Douglas fir (C. gattii)
- C. neoformans tends to affect immunocompromised hosts vs. C. gattii which tends to affect immunocompetent hosts

**Clinical Presentation**
- asymptomatic
- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of Molluscum contagiosum
  - other: bone, lymph nodes, bone marrow, soft tissues, eyes

**Investigations**
- serum cryptococcal antigen
- CSF for meningitis: India-ink stain, cryptococcal antigen test, culture to confirm

**Treatment**
- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance

---

**Candida albicans**

**Etiology**
- overgrowth of C. albicans (normally found as part of the microbiome of the skin, mouth, vagina and GI tract)
- risk factors for overgrowth:
  - immunocompromised state (DM, corticosteroids)
  - ICU patients (broad-spectrum antibiotic use, central venous catheters, TPN)
  - obesity → maceration and moisture in intertriginous areas, pannus, under breasts

**Clinical Presentation**
- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY26), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease

**Treatment**
- thrush: nystatin suspension or pastilles for mild disease, fluconazole for severe disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles
Aspergillus spp.

Etiology
- infection with Aspergillus fungi (A. fumi, A. flavus) which is found ubiquitously in the air and the environment
  - Aspergillus produces a toxin called aflatoxin that contaminates nuts, grains, and rice

Clinical Presentation
- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a preexisting lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia or transplantation
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, cavitation; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules with surrounding ground glass ("halo" sign)
- mycotoxicosis
  - aflatoxin produced by A. flavus (nuts, grains, rice)
  - results in liver hemorrhage, necrosis, and hepatocellular carcinoma formation

Treatment Options
- for invasive aspergillosis: voriconazole or amphotericin B
- surgical resection for aspergilloma
- corticosteroids ± itraconazole for Allergic Bronchopulmonary Aspergillosis

Protozoa – Intestinal/Genitourinary Infections

Entamoeba histolytica (Amoebiasis)

Etiology
- infection with E. histolytica occurs when the cysts are transmitted via the oral-fecal route in areas of poor sanitation that have been contaminated by other infected humans
- seen in migrants, travellers, institutionalized individuals, Aboriginal Canadians, MSM

Clinical Presentation
1. asymptomatic carriers
2. amoebic dysentery
   - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction and ulceration of large intestine
3. amoebic abscesses (liver abscesses, see General Surgery, GS43)
   - most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
   - can also occur in lungs and brain

Investigations
- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- E. histolytica indistinguishable microscopically from the non-pathogen E. dispar (distinguish by specific stool antigen detection)

Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst shedding: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)
Giardia lamblia

**Etiology**
- infect on with *G. lamblia* occurs via the fecal-oral route with the ingestion of cysts from water/food contaminated by infected humans and other mammals (especially in the Rockies)
- risk factors: travel, camping, institutions, day care centres, MSM

**Clinical Presentation**
- giardiasis ("beaver fever")
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats the small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucous in stool

**Investigations**
- multiple stool samples (daily x 3 d) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

**Treatment and Prevention**
- metronidazole; nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

Trichomonas vaginalis

**Etiology**
- infection with *T. vaginalis* occurs via sexual contact

**Clinical Presentation**
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- *Trichomonas vaginalis* (see Gynecology, GY27)
  - vaginal discharge (profuse, malodourous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

**Investigations**
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

**Treatment**
- metronidazole for patient and partner(s)

Cryptosporidium spp.

**Etiology**
- infection with *Cryptosporidium* spp. via the fecal-oral route occurs with the ingestion of cysts from water contaminated by infected humans and other animals (including cows)
- risk factors: summer and fall, young children (day care), MSM, contact with farm animals, immunodeficiency

**Clinical Presentation**
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with N/V, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)

**Investigations**
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody

**Treatment and Prevention**
- supportive care
- in HIV+ patients, (re)initiate ART and try to increase their CD4 count to >100; if fails, try nitazoxanide
- good personal hygiene, water filtration
**Blood and Tissue Infections**

**Plasmodium spp. (Malaria)**

**Etiology**
- Transmission of *Plasmodium* spp. (P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi) primarily occurs during the blood meal of a night-biting female *Anopheles* mosquito
- Sporozoites injected during the blood meal then infect human liver cells, where they multiply and are released as merozoites; merozoites infect RBCs and cause disease
- Infection with malaria parasites can also occur via vertical transmission (rare) or blood transfusion
- Occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

**Clinical Presentation**
- Flu-like prodrome
- Paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of RBCs) (lasts several hours)
  - P. vivax and P. ovale: chills and fever x48 h but can be variable
  - P. malariae: chills and fever x72 h but can be variable
  - P. falciparum: less predictable fever interval, can be highly variable
- Abdominal pain, diarrhea, myalgia, H/A, and cough
- Hepatosplenomegaly and thrombocytopenia without leukocytosis
- >90% of patients infected with *P. falciparum* are ill within 30 d
- Relapsing malarial attacks may occur after many months due to the reactivation (entering the erythrocytic cycle) of dormant liver hypnozoites of either *P. ovale* or *P. vivax*
- Complications:
  - P. falciparum (most common and most lethal): CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute kidney injury, ARDS, primarily responsible for fatal disease
  - P. knowlesi, and rarely *P. vivax*, can be fatal

**Investigations**
- Microscopy: blood smear q12-24h (x3) to rule out infection
- Thick smear (Giemsa stain) for presence of organisms
- Thin smear (Giemsa stain) for species identification and quantification of parasites
- Rapid antigen detection tests

**Treatment and Prevention**
- *P. vivax, P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: atovaquone/proguanil + primaquine or quinine and doxycycline + primaquine
- *P. malariae, P. knowlesi*: chloroquine
- *P. falciparum*: most areas of the world show chloroquine resistance – check local resistance patterns
  - Artemisinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - Atovaquone/proguanil combination (Malarone®)
  - Quinine + doxycycline or clindamycin
- Mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- Prevention with antimalarial prophylaxis, covering exposed skin, bed nets, insect repellent

**Trypanosoma cruzi**

**Etiology**
- Found in Mexico, South America, and Central America
- Transmission by Reduviid insect vector (“Kissing Bug”), which defecates on skin and tryptomastigotes in the stoe are rubbed into bite site by host
- Also transmitted via placental transfer, organ donation, blood transfusion, and ingestion of contaminated food containing Reduviid insects (especially cane juice)

**Clinical Presentation**
- American trypanosomiasis (Chagas disease)
  - Acute: usually asymptomatic, local swelling at site of inoculation (“Romana’s sign”; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly, and hepatosplenomegaly
  - Chronic indeterminate phase: asymptomatic but increasing levels of antibody in blood, most infected persons (60-70%) remain in this phase, and do not go on to manifest a determinate form of Chagas disease
  - Chronic determinate: leads to chronic dilated cardiomyopathy, esophagomegaly, and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

**Figure 13. Life cycle of Plasmodium spp.**

**Drugs for Preventing Malaria in Travellers**

**Cochrane DB Syst Rev 2009;CD006491**

**Study:** Cochrane Systematic Review: 8 RCTs.

**Population:** 4,240 non-immune adults and children traveling to regions with *P. falciparum* resistance to chloroquine.

**Intervention:** Atovaquone-proguanil, doxycycline, mefloquine, chloroquine-proguanil, or primaquine used for malaria prophylaxis.

**Outcome:** Efficacy, safety, and tolerability.

**Results:** Atovaquone-proguanil and doxycycline had similar adverse events. Atovaquone-proguanil had fewer overall (RR 0.72), GI (RR 0.54), and neuropsychiatric events (RR 0.49) than mefloquine. Doxycycline also had fewer neuropsychiatric events than mefloquine (RR 0.84).

**Conclusion:** Atovaquone-proguanil or doxycycline as prophylaxis against malaria is best tolerated in terms of adverse effects and mefloquine is associated with adverse neuropsychiatric outcomes.
Investigations
• wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

Treatment and Prevention
• acute: nifurtimox or benznidazole
• indeterminate: increasing trend to treat as acute infection for children and adults under age 50 years
• chronic indeterminate: symptomatic therapy, surgery as necessary including heart transplant, esophagectomy, and colectomy; there may be a benefit to antiparasitic treatment
• insect control, bed nets

**Toxoplasma gondii**

Etiology
• infection with *T. gondii* occurs through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), vertical transmission, organ transplantation, gardening without gloves (cat oocyst exposure), whole blood transfusions

Clinical Presentation
• congenital
  ■ result of acute primary infection of mother during pregnancy (see Obstetrics, OB29, TORCH infection)
  ■ stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  ■ initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult
  ■ blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
  ■ usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  ■ infection remains latent for life unless reactivation due to immunosuppression
• immunocompromised (most commonly AIDS with CD4 <200)
  ■ encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (H/A and focal neurological signs)
  ■ lymph node, liver, and spleen enlargement and pneumonitis
  ■ chorioretinitis

Investigations
• serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
• immunocompromised patients: consider CT scan (ring enhancing lesion in cortex or deep nuclei) and ophthalmologic examination
• negative serology in many AIDS patients (false negative due to decreased lymphocyte population)

Treatment and Prevention
• no treatment if: immunocompetent, not pregnant, no severe organ damage
• pregnancy: spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folinic acid), avoid undercooked meat and refrain from emptying cat litter boxes
• HIV: pyrimethamine + sulfadiazine (see Prophylaxis, ID30)
• eye disease, meningitis: corticosteroids
• proper hand hygiene, cook meat thoroughly to proper temperature
### Helminths

#### Roundworms – Nematodes

<table>
<thead>
<tr>
<th>Nematode</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascaris lumbricoides</td>
<td>Tropics</td>
<td>Human feces, ingestion of contaminated food or water containing eggs</td>
<td>Abdominal pain and intestinal obstruction from high worm burden</td>
<td>Mebendazole OR albendazole OR pyrantel pamoate</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>Tropics</td>
<td>Ingestion of eggs in soil</td>
<td>Diarrhea (± mucous, blood), abdominal pain, rectal prolapse, stunted growth</td>
<td>Mebendazole OR albendazole</td>
</tr>
<tr>
<td>Onchocerca volvulus</td>
<td>Africa, Latin America</td>
<td>Blackfly bite</td>
<td>Damage to lymphatics resulting in lymphadenopathy, lymphedema, and elephantiasis</td>
<td>Diethylcarbamazine + doxycycline</td>
</tr>
<tr>
<td>Wuchereria bancrofti</td>
<td>Tropics</td>
<td>Mosquito bite</td>
<td>Tropical pulmonary eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Loa Loa</td>
<td>Central Africa</td>
<td>Deer fly bite</td>
<td>Subcutaneous migration of worm, hyperresponsiveness in travellers</td>
<td>Diethylcarbamazine</td>
</tr>
<tr>
<td>Enterobius vermicularis</td>
<td>Worldwide</td>
<td>Human host: fecal-oral self-inoculation andomite person-to-person transfer</td>
<td>Asymptomatic carriers or severe nocturnal perianal itching (pruritus ani)</td>
<td>Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out)</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>Subtropical, tropical, and temperate (including southern US)</td>
<td>Fecal contamination of soil: transmission via unbroken skin, walking barefoot</td>
<td>One of few worms able to multiply in human host Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löffler’s syndrome) Abdominal pain, diarrhea, pruritis ani, larva current (itchy rash) Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; imm noablative therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection</td>
<td>Ivermectin (OR Albendazole)</td>
</tr>
</tbody>
</table>

**Figure 15. Life cycle of Enterobius**

1. Embryonated eggs ingested by humans  
2. Larvae hatch in small intestine  
3. Females migrate out anus at night  

**Figure 16. Life cycle of Strongyloides**

1. Step on stool containing larvae  
2. Larvae migrate to lungs via bloods ream  
3. Larvae crawl up trachea and down to GI tract (cough/swallow)  
4. Adult worms in intestine  
5. Eggs produced in bowel  
6. Larvae  
7. Bowel movement containing larvae
Flatworms

Cestodes/Trematodes

Table 27. Cestodes/Trematodes (Flatworms)

<table>
<thead>
<tr>
<th>CESTODES</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taenia solium</td>
<td>Developing countries</td>
<td>Undercooked pork (larvae), human feces (eggs)</td>
<td>Taeniasis: mild abdominal symptoms</td>
<td>Corticosteroids + albendazole for cysticercosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cysticercosis: mass lesions in CNS, eyes, skin, seizures</td>
<td>Antiepileptics if seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Praziquantel for adult tapeworm in gut (taeniasis)</td>
</tr>
<tr>
<td>Taenia saginata</td>
<td>Developing countries</td>
<td>Undercooked beef (larvae)</td>
<td>Mild GI symptoms</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>Diphyllobothrium latum</td>
<td>Europe, North America, Asia</td>
<td>Raw fish</td>
<td>B12 deficiency leading to macrocytic anemia and posterior column deficits</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>Echinococcus granulosus</td>
<td>Rural areas, Sheep-raising countries</td>
<td>Dog feces (eggs)</td>
<td>Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture)</td>
<td>Albendazole ± praziquantel alone Surgery + perioperative albendazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of anaphylaxis if cystic fluid released during surgical evacuation</td>
<td>Percutaneous aspiration + perioperative albendazole</td>
</tr>
</tbody>
</table>

TREMATODES

| Clonorchis sinensis | Japan, Taiwan, China, SE Asia | Raw fish | Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma | Praziquantel |
| Schistosoma spp. | Africa, SE Asia, focal in Western Hemisphere | Fresh water exposure | Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, SCC of the bladder) | Praziquantel |

Schistosoma spp.

Etiology
- Infection with Schistosoma spp. (S. mansoni, S. hematobium, S. japonicum) occurs following penetration of unbroken skin by their larvae (cercariae) which are found in infested fresh water
- Adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- Eggs must reach fresh water to hatch where they infect an intermediate host (snails) which then release cercariae into the water
- Schistosomes cannot multiply in or pass between humans
- More common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa

Clinical Presentation
- Most asymptomatic; symptoms seen in travellers (nonimmune)
- Swimmer’s itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- Acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - Fever, hives, H/A, weight loss, cough, abdominal pain, chronic diarrhea, high-grade eosinophilia
- Chronic schistosomiasis (can persist for years):
  - S. mansoni, S. japonicum
    - Worms in mesenteric vein, eggs in portal tracts of liver and bowel
    - Heavy infections: intestinal polyps, portal and pulmonary HTN, splenomegaly (2+ to portal HTN), hepatomegaly
  - S. hematobium
    - Worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
    - Hematuria and obstructive uropathy; associated with squamous cell bladder cancer
    - Neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
    - Pulmonary complications: granulomatous pulmonary endarteritis, pulmonary HTN, cor pulmonale; especially in patients with hepatosplenic involvement

Investigations
- Serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia)
- S. mansoni, S. japonicum: eggs in stool, liver U/S shows fibrosis, rectal biopsy
- S. hematobium: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

Figure 17. Life cycle of Schistosoma
Treatment and Prevention
- praziquantel
- add glucocorticoid if acute schistosomiasis or neurologic complications develop
- proper disposal of human fecal waste, molluscicide (pesticide against molluscs), avoidance of infested fresh water while traveling

Ectoparasites
- scabies, lice
- see Dermatology, D26

Travel Medicine

General Travel Precautions
- vector-borne: long sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings, and bed nets, and skin repellents (such as DEET) applied to exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (Lake Malawi), fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller’s diarrhea (bismuth salicylate), standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio, influenza)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury
- vector-borne: long sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings, and skin repellents (such as DEET) applied to exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (Lake Malawi), fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller’s diarrhea (bismuth salicylate), standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio, influenza)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera

Infectious Diseases to Consider
- vector borne: malaria, dengue fever, Chikungunya, yellow fever, spotted fever rickettsioses, West Nile virus, typhoid fever
- sexually transmitted: HIV, HBV, acute HSV, syphilis usual STIs
- zoonotic: rabies, hantavirus, tularemia, Q fever, leptospirosis, brucellosis
- airborne: TB
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amoebiasis, dysentery, traveller’s diarrhea, cholera, Campylobacter spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

Fever in the Returned Traveller

Etiology
- commonly identified causes of fever in returning traveller
  - parasitic: malaria (20-30%), schistosomiasis, hookworms
  - viral: non specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: from Salmonella (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller’s diarrhea (10-20%), RTI (10-15%), UTI/STI (2-3%)
  - febrile illness in travellers can be caused by routine infections that are common in non-travellers (e.g. URTI, UTI)
  - less commonly, fever can be due to non-infectious causes (e.g. DVT, PE)

History
- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
- persons visiting friends and family more likely to be exposed to local population and pathogens
  - style of travel: lodgings, camping, adventure travelling
  - local population: sick contacts
  - transportation: use of animals

Important Exposures

Insect Bites
- Mosquito: Plasmodium spp. (Malaria), Anopheles spp., Aedes aegypti
- Tick: Borrelia burgdorferi (Lyme Disease), Ixodes scapularis (Rocky Mountain Spotted Fever)
- Fly: Tsetse fly (sleeping sickness)
- Flea: Yersinia (Plague), Bartonella bacilliformis

Mammal Bites
- Dog/Cat: Rabies, Pasteurella, anaerobes, Streptococcus, S. aureus
- Human: Streptococcus, S. aureus, oral anaerobes, Eikenella

Oral Exposures
- Unpasteurized Milk: Brucella spp., non-tuberculous Mycobacteria, Salmonella, E. coli, Listeria
- Undercooked Meat/Fish: Enteric bacteria, helminths, protozoa
- Water: Hepatitis A/E, Norovirus, cholera, Salmonella, Shigella, Giardia, poliovirus, Cryptosporidium, Cyclospora

Environmental Exposures
- Fresh Water: Lactoporella spp., schistosomiasis, Acanthamoeba, Naegleria fowleri
- Soil: Helminths, Taenaria sp., Strongyloides, Necator americanus, Ascaris lumbricoides, Capillaria hepatica

Adapted with permission from Lancet 2003;361:1459-69
• exposure history
  ■ street foods, untreated water: increased risk of traveller’s diarrhea, enteric fever
  ■ uncooked meat/unpasteurized dairy: increased risk of parasitic infection
  ■ body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  ■ increased risk of HBV, HCV, HIV, GC, C. trachomatis, syphilis
  ■ animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies

• fever pattern

• incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  ■ <21 d: consider malaria, typhoid fever, dengue fever, chikungunya, rickettsioses; exclude HBV, TB
  ■ >21 d: consider malaria, TB, typhoid fever; exclude dengue fever, chikungunya, traveller’s diarrhea, rickettsioses

• body systems affected: GI, respiratory, CNS, skin

Investigations

• all travellers with fever should undergo the following tests
  ■ blood work: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  ■ urine: urinalysis, urine C&S if dysuria or other localizing signs

• special tests based on symptoms, exposure history, and geography
  ■ stool: C&S, O&P
  ■ CXR
  ■ dengue serology for IgM

Table 28. Fever in the Returned Traveller

<table>
<thead>
<tr>
<th>Illness</th>
<th>Geography/Timing</th>
<th>Pathogen</th>
<th>Incubation Period</th>
<th>Clinical Manifestations</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Africa, India, C. and S. America, SE Asia</td>
<td>Plasmodium falciparum, Plasmodium vivax</td>
<td>7-30 d to mo or yrs</td>
<td>Fever and flu-like illness, (shaking chills, H/A, muscle aches, and fatigue)</td>
<td>Blood smear (thick and thin) x3</td>
<td>Artesunate (for severe disease) + malarone, doxycycline, or clindamycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P. malariae, P. ovale, P. knowlesi</td>
<td></td>
<td>N/V and diarrhea</td>
<td>Rapid Diagnostic Test (with smear or PCR confirmation)</td>
<td>Quinine sulfate + doxycycline or clindamycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anemia and jaundice</td>
<td>Antigen detection PCR (mostly a research tool)</td>
<td>Chloroquine + primaquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasmodium falciparum (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue</td>
<td>South East Asia, Caribbean, Usually urban, day-biting mosquitoes</td>
<td>Dengue viruses</td>
<td>3 d to 2 wk</td>
<td>Sudden onset of fever, H/A, retro-orbital pain, myalgias, and arthralgias</td>
<td>Anti-dengue IgM positivity</td>
<td>Symptom relief: Acetaminophen (avoid using NSAIDs because of anticoagulant properties)</td>
</tr>
<tr>
<td>Typhoid (enteric fever)</td>
<td>Global but mostly Indian subcontinent, Usually rural, night-biting mosquitoes</td>
<td>Salmonella typhi, Salmonella paratyphi</td>
<td>3 to 60 d</td>
<td>Sustained fever 39°-40°C (103°-104°F) Abdominal pain, H/A, loss of appetite, cough, constipation</td>
<td>Stool, urine, or blood sample positive for S. typhi or S. paratyphi</td>
<td>Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone, or macrolide</td>
</tr>
<tr>
<td>Tick Typhus</td>
<td>Mediterranean, South Africa</td>
<td>Rickettsia</td>
<td>1 to 2 wk</td>
<td>Fever, H/A, fatigue, muscle aches, occasionally rash Eschar at site of tick bite Elevated liver enzymes</td>
<td>Serology Presence of classic tick eschar</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>TB</td>
<td>Global</td>
<td>M. tuberculosis</td>
<td>Variable</td>
<td>Fever, cough, hemoptysis</td>
<td>CXR</td>
<td>Ethambutol, isoniazid, pyrazinamide, rifampin, +/− pyridoxine (vit. B6)</td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>Caribbean, C. and S. America</td>
<td>EBV or CMV</td>
<td>30 to 50 d</td>
<td>Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly</td>
<td>Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test</td>
<td>Acetaminophen or NSAIDs, fluids</td>
</tr>
<tr>
<td>Zika Virus Disease</td>
<td>Africa, SE Asia, S. America, spreading</td>
<td>Zika virus</td>
<td>Unknown, likely 3 to 12 d</td>
<td>Headache, malaise, muscle/joint pain, mild fever, rash, conjunctivitis</td>
<td>RT-PCR Serology</td>
<td>Rest, fluids, analgesics/ antipyretics (avoid NSAIDs until Dengue ruled out), condom use, avoid pregnancy</td>
</tr>
</tbody>
</table>

Fever in traveller from malaria endemic area is malaria until proven otherwise
Fever of Unknown Origin

Table 29. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C/101°F on several occasions

<table>
<thead>
<tr>
<th>Classical FUO</th>
<th>Nosocomial FUO</th>
<th>Neutropenic FUO</th>
<th>HIV-associated FUO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &gt;3 wk</td>
<td>Hospitalized patient</td>
<td>Neutrophil count &lt;500/mL or is expected to fall to that level in 1-2 d</td>
<td>HIV infections Duration &gt;4 wk for outpatients &gt;3 d for hospitalized patients</td>
</tr>
<tr>
<td>Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
</tr>
</tbody>
</table>

Etiology of Classic FUO
- infectious causes (~30%)
  - TB: extra pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvis, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - uncommon: viral (CMV, EBV), bacterial (brucellosis, bartonellosis), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin's) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - solid tumours: RCC (most common), also breast, liver (hepatoma), colon, pancreas, or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still's disease
- miscellaneous (~20%)
  - drugs, factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- unknown in 30-50% despite detailed workup

Approach to Classic FUO
- careful history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - blood work: CBC and differential, electrolytes, BUN, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis (SPEP), blood smear
  - cultures: blood (x2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
  - serology: HIV monospot, CMV IgM
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established
- if no diagnosis with the above, consider empiric therapy vs. watchful waiting
  - without intervention: patients that remain undiagnosed despite extensive workup have good prognosis
- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent
- type of immunodeficiency predicts probable spectrum of agents

Causes of Nosocomial FUO
B, C, D, E
- Bacterial and fungal infections of respiratory tract and surgical sites
- Catheters (intravascular and urinary)
- Drugs (intravascular and urinary)
- Emboli

Drugs that may Cause Fever
- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimicrobials)
- Anti-hypertensives (hydralazine, methyldopa)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arythmics (quinine, procainamide)
- Anti-inflammatory (NSAIDs)
- Anti-thrombotics (ASA)
- Anti-histamines
- Anti-thyroid
Infections in the Immunocompromised Host

Factors that Compromise the Immune System

- general: age (very young or elderly), malnutrition
- immune disease: HIV/AIDS, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

Table 30. Types of Immunodeficiency

<table>
<thead>
<tr>
<th>Type</th>
<th>Conditions</th>
<th>Vulnerable To</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-Mediated Immunity</td>
<td>HIV, Hodgkin’s, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome</td>
<td>Latent viruses, Fungi, Parasites</td>
</tr>
<tr>
<td>Humoral Immunity</td>
<td>CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome</td>
<td>Encapsulated organisms (S. pneumoniae, H. influenzae, N. meningitidis, Salmonella typhi, GBS)</td>
</tr>
<tr>
<td>Neutrophil Function</td>
<td>Myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease</td>
<td>Catalase-producing organisms (Staphylococcus, Serratia, Nocardia, Aspergillus)</td>
</tr>
</tbody>
</table>

Febrile Neutropenia

Definition
- fever (≥38.3°C/101°F or ≥38.0°C/100.4°F for ≥1 h) and one of
  - ANC <0.5 OR
  - ANC <1.0 but trending down to 0.5

Pathophysiology
- decreased neutrophil production
  - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - iatrogenic: cancer chemotherapy, radiation, drugs
  - deficiencies: vitamin B12, folate
- increased peripheral neutrophil destruction
  - autoimmune: Felty’s syndrome, SLE, antineutrophil antibodies
  - splenic sequestration

Epidemiology/Etiology
- most common life-threatening complication of cancer therapy
- causative organism identified only 1/3 of the time
- GN (especially Pseudomonas) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially Candida, Aspergillus)

Investigations
- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region
- blood C&S (≥2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and nasopharyngeal swab for respiratory viruses
- CBC and differential, Cr, BUN, electrolytes, AST/ALT, total bilirubin

Treatment
- most hospitals have their own specific protocol; one example see Figure 18
Infections in the Immunocompromised Host

Figure 18. Example of treatment protocol for febrile neutropenia

Infections in Solid Organ Transplant Recipients

- Infection is a leading cause of early morbidity/mortality in transplant recipients
- Infection depends on degree of immunosuppression
- Common infections <1 mo post-transplant
  - Bacterial infection of wound/lines/lungs, herpetic stomatitis
- Common infections >1 mo post-transplant
  - Viral (especially CMV, EBV, VZV)
  - Fungal (especially Aspergillus, Cryptococcus, P. jiroveci)
  - Protozoan (especially Toxoplasma)
  - Unusual bacterial/mycobacterial infections (especially TB, Nocardia, Listeria)

Prophylactic Vaccinations Given Before Transplant

- To all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B vaccines
- If low titre or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 wk later)

Immune Reconstitution Syndrome

Definition

- A harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

Etiology

- Paradoxical worsening of a successfully or partially treated opportunistic infection
- New onset response to a previously unidentified opportunistic infection
- The majority of cases are in HIV/AIDS or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation
- Can occur in response to multiple infections
  - Mycobacteria (tuberculosis, avium complex)
  - Cryptococcus
  - Pneumocystis
  - Toxoplasma
  - HBV and HCV
  - Herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Molluscum contagiosum
- Clinical features are dependent on the type and location of the pre-existing infection
- Thought to be worse with a quick increase in CD4 count and with lower pre-treatment CD4 count
- Non HIV conditions with documented IRS: solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy
Epidemiology
• in HIV patients starting ART, IRS reported to affect ~10%

Investigations
• IRS is a diagnosis of exclusion
• rule out drug reaction, patient non-adherence, drug resistance

Treatment
• continue HAART therapy in HIV patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
• treat underlying infection; initiate treatment for some infections prior to HAART initiation
• consider starting corticosteroids/NSAIDs to decrease inflammatory response

A Simplified Look at Antibiotics
• general overview see Table 31 for more details

1. Penicillins

2. Cephalosporins (PO/IV)
• 1st generation: cephalexin/cefazolin (mostly GP, some GN)
• 2nd generation: cefuroxime/cefprozil (some GP and some GN, *anaerobes)
• 3rd generation: cefixime/ceftaxime, ceftriaxone (good Streptococcal coverage, mostly GN), and ceftazidime (no GP, mostly GN, Pseudomonas)
• 4th generation: --/cefepime (most GP, most GN, Pseudomonas)

3. Aminoglycosides (GN aerobic bacilli)
• gentamicin
• tobramycin
• amikacin

4. Macrolides (GP, Haemophilus, and atypical bacteria [Legionella, Chlamydia, Mycoplasma])
• erythromycin
• clarithromycin
• azithromycin

5. Fluoroquinolones (GN – although resistance becoming a huge problem)
• ciprofloxacin (+ Pseudomonas)
• norfloxacin (for UTI only)
• respiratory fluoroquinolones (some GP, GN, “atypicals”, Legionella, Mycoplasma, Chlamydia, Mycobacteria)
  ◦ levofloxacin, ofloxacin
  ◦ moxifloxacin (+ anaerobes)

6. Carbapenems (broad coverage: GP, GN, and anaerobes)
• imipenem (+ Pseudomonas)
• meropenem (+ Pseudomonas)
• ertapenem
Antimicrobials

7. Others
- doxycycline/tetracycline (GP, syphilis, Chlamyphila, Rickettsia, Mycoplasma)
- tigecycline (for resistant GP infections, GN, anaerobes, Chlamyphila, Rickettsia, Mycoplasma)
- vancomycin (all GP and C. difficile – the oral form for)
- linezolid (for resistant GP infections)
- daptomycin (for resistant GP infections)
- clindamycin (most GP, GN anaerobes)
- TMP/SMX (most S. aureus including: MRSA, GN aerobes, Pneumocystis)
- nitrofurantoin (GN bacilli, S. saprophyticus, Enterococcus)
- metronidazole (anaerobes including: C. difficile, Trichomonas, Entamoeba)
- treatment for C. difficile: metronidazole OR oral vancomycin; consider both in serious infection

Antimicrobials

Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S
    - if causative organism identified, use antibiotic to which organism is sensitive
    - if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)

Reasons for Combination Therapy
- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. Enterococcus spp. causing endocarditis)
- To prevent emergence of resistance

Figure 20. Mechanism of action of antibiotics

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### Table 31. Antibiotics

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL WALL INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Penicillins</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Benzyl penicillin, penicillin G IV/IM, penicillin V PO</td>
<td>GP except Staphylococcus, Enterococcus, N. meningitidis, oral anaerobes</td>
<td>Bactericidal: ( \beta )-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan</td>
<td>Immediate allergy (IgE): anaphylaxis Urticaria Late-onset allergy (IgE): urticaria, rash, serum sickness Interstitial nephritis Dose related toxicity: seizures Diarrhea</td>
<td>Mild to moderately severe infections caused by susceptible organisms including acinetobacter, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis</td>
<td>Hyposensitivity to penicillin or ( \beta )-lactam antibiotics</td>
</tr>
<tr>
<td>Aminopenicillin, ampicillin IV, amoxicillin PO (Amoxicillin(^\text{®}))</td>
<td>Same as penicillin AND Enterococcus Listeria selectively H. influenzae, E. coli, K. pneumoniae</td>
<td>See above</td>
<td>See above</td>
<td>Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (AOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for H. pylori treatment, Lyme disease, pneumococcal pneumonia, UTI (amoxicillin and ampicillin) for most enterococci and susceptible gram-negative pathogens</td>
<td>Hyposensitivity to penicillin or ( \beta )-lactam antibiotics</td>
</tr>
<tr>
<td>Isoxazolyl penicillin, cloxacillin, nafcillin, oxacillin</td>
<td>Methicillin-sensitive Staphylococcus aureus; streptococci</td>
<td>See above</td>
<td>See above</td>
<td>Bacterial infections caused by staphylococci and streptococci including skin and soft-tissue infections</td>
<td>Hyposensitivity to cloxacillin or any penicillin</td>
</tr>
<tr>
<td>( \beta )-lactam/( \beta )-lactamase inhibitor combinations</td>
<td>Same as penicillin AND Staphylococcus H. influenzae Enterococcus Anaerobes (oral and gut)</td>
<td>( \beta )-lactamases produced by certain bacteria inactivate ( \beta )-lactams Lactamase inhibitors ( \beta )-lactams prevent the process, preserving antibacterial effect of ( \beta )-lactams</td>
<td>See above</td>
<td>Various ( \beta )-lactamase producing bacteria, Clavulin(^\text{®}) sensitive bacteria including RTI, sinusitis, ADM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections</td>
<td>Hyposensitivity to penicillin or cephalosporin History of Clavulin(^\text{®}) associated jaundice or hepatic dysfunction</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO 1° cephalxin (Keflex(^\text{®}))</td>
<td>IV cefazolin (Ancef(^\text{®}))</td>
<td>GP Good with the exception of Enterococcus and MRSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( 2^\circ ) cefuroxime (Ceftin(^\text{®})), cefpazil (Cefotil(^\text{®}))</td>
<td>cefuroxime (Zinacef(^\text{®})), cefotixin(^\text{®})</td>
<td>Weaker activity than 1°</td>
<td>More coverage than 1° (( \text{not all isolates} ))</td>
<td>See above</td>
<td></td>
</tr>
<tr>
<td>( 3^\circ ) cefixime (Suprax(^\text{®}))</td>
<td>cefixime (Rocephin(^\text{®})), cefotaxime (Claforan(^\text{®})), cefazidime(^\text{®}) (Fortaz(^\text{®}))</td>
<td>S. aureus + streptococcal coverage (cefotaxime and cefixime) especially S. pneumoniae</td>
<td>Broad coverage (( \text{not all isolates} ))</td>
<td>See above</td>
<td></td>
</tr>
<tr>
<td>4° cefepime (Maxipen(^\text{®}))</td>
<td>Broad spectrum</td>
<td>Broad coverage including Pseudomonas</td>
<td>See above</td>
<td>Empiric therapy for febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td><strong>Class and Drugs</strong></td>
<td><strong>Coverage</strong></td>
<td><strong>Mechanism of Action</strong></td>
<td><strong>Adverse Effects</strong></td>
<td><strong>Indications</strong></td>
<td><strong>Contraindications</strong></td>
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<tr>
<td><strong>CELL WALL INHIBITORS</strong></td>
<td></td>
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<tr>
<td><strong>Carbapenems</strong></td>
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</tr>
<tr>
<td>imipenem (Primaxin™)</td>
<td>GP except MRSA GN including <em>Pseudomonas</em> + <em>Enterobacter</em> ESBLS, anaerobes</td>
<td>β-lactam inhibits PBP and prevents cross-linking of peptidoglycan</td>
<td>Penicillin allergy cross-reactivity Seizures</td>
<td>Treatment of infections caused by GN producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms</td>
<td>Hypersensitivity to imipenem</td>
</tr>
<tr>
<td>meropenem (Merrem™)</td>
<td>See above; does not cover <em>Enterococcus</em></td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Hypersensitivity to β-lactams</td>
</tr>
<tr>
<td>ertapenem (Invanz®)</td>
<td>GP except <em>Enterococcus</em>, MRSA GN including <em>Enterobacter</em> (but not <em>Pseudomonas</em>), anaerobes</td>
<td>See above</td>
<td>See above</td>
<td>See above; once-daily administration makes it convenient for outpatient IV therapy</td>
<td>Hypersensitivity to β-lactams</td>
</tr>
<tr>
<td><strong>Glycopeptides</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td>GP including MRSA, not VRE <em>C. difficile</em> if PO</td>
<td>Glycopeptide sterically inhibits cell wall synthesis</td>
<td>Red Man Syndrome Nephrotoxicity Ototoxicity Thrombocytopenia</td>
<td>Severe or life-threatening GP infections patients with β-lactam allergy May only be taken orally for severe <em>C. difficile</em> infection</td>
<td>Hypersensitivity to vancomycin</td>
</tr>
<tr>
<td><strong>PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Macrolides</strong></td>
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</tr>
<tr>
<td>erythromycin (Erybid®, Eryc®)</td>
<td>GP except <em>Enterococcus</em> GN: <em>Legionella</em>, <em>B. pertussis</em> “Atypicals”: <em>Chlamydophila</em>, <em>Mycoplasma</em></td>
<td>Binds to 50S ribosomal subunit inhibiting protein synthesis</td>
<td>GI upset Acute cholestatic hepatitis Prolonged QT</td>
<td>Susceptible RTI, pertussis, diphtheria, <em>Legionnaires’</em> disease, skin and soft tissue infections</td>
<td>Hypersensitivity to erythromycin Concurrent therapy with astemizole, terfenadine</td>
</tr>
<tr>
<td>clarithromycin (Biaxin®)</td>
<td>See above, some mycobacteria</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for <em>H. pylori</em> treatment</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td>azithromycin (Zithromax®)</td>
<td>See above, some mycobacteria</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, <em>Campylobacter</em> infections if treatment indicated, chlamydia</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td><strong>Lincosamides</strong></td>
<td></td>
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</tr>
<tr>
<td>clindamycin (Dalacin®)</td>
<td>GP except Enterococcus, most community-acquired MRSA Anaerobes</td>
<td>Inhibits peptide bond formation at 50S ribosome</td>
<td>Pseudomembranous colitis GI upset</td>
<td>Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections</td>
<td>Hypersensitivity to clindamycin Infants &lt;30 d</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>GP GN Anaerobes</td>
<td>Inhibits peptidyl transferase action of tRNA at 50S ribosome</td>
<td>Aplastic anemia Grey Baby Syndrome</td>
<td>Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β lactams</td>
<td>Hypersensitivity to chloramphenicol</td>
</tr>
<tr>
<td>linezolid (Zyvoxam®)</td>
<td>GP including VRE + MRSA</td>
<td>Binds 50S ribosome and prevents functional 70S initiation complex</td>
<td>HTN (acts as MAOII) Risks with prolonged use: myelosuppression optic neuropathy, peripheral neuropathy</td>
<td>Vancomycin-resistant <em>Enterococcus faecium</em> infections including intra-abdominal, skin and skin structure, and urinary tract infections, MRSA infections as outpatient therapy</td>
<td>Hypersensitivity to linezolid</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
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</tr>
<tr>
<td>gentamicin</td>
<td>GN (includes Pseudomonas)</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>Nephrotoxicity (reversible)</td>
<td>GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections</td>
<td>Pre-existing hearing loss and renal dysfunction</td>
</tr>
<tr>
<td>tobramycin</td>
<td></td>
<td></td>
<td>Vestibular and ototoxicity (irreversible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amikacin (Amikin®)</td>
<td></td>
<td></td>
<td>Vestibular toxicity is the most important aminoglycoside toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>tetracycline (Apo-Tetra®, Nu-TetraT®)</td>
<td>GP, Anaerobes, &quot;Atypicals&quot;: Chlamyphila, Mycoplasma, Rickettsia, Borrelia burgdorferi, Treponema</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>GI upset</td>
<td>Rickettsial infections, Chlamyphila, Malaria prophylaxis (doxycycline), PID (step-down), malaria prophylaxis (doxycycline)</td>
<td>Severe renal or hepatic dysfunction Pregnant or lactation Children under 8 yr</td>
</tr>
<tr>
<td>minocycline (MinocinT®)</td>
<td></td>
<td></td>
<td>Allergy, Seizures, Prolonged QT, Dysgycemia (levofloxacin, moxifloxacin), Tendonitis, Tendon rupture</td>
<td></td>
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<tr>
<td>doxycycline (Doxycin®)</td>
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<tr>
<td>tigecycline (Tygacil®)</td>
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<tr>
<td><strong>TOPOISOMERASE INHIBITORS</strong></td>
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<tr>
<td>Fluoroquinolones (FQs)</td>
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</tr>
<tr>
<td>ciprofloxacin (Cipro®)</td>
<td>Poor GP activity GN (includes Pseudomonas)</td>
<td>Inhibits DNA gyrase</td>
<td>H/A, dizziness, Allergy, Seizures, Prolonged QT, Dysglycemia (levofloxacin, moxifloxacin), Tendonitis, Tendon rupture</td>
<td>Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or ciprofloxacin in combination with amoxicillin-clavulanate low management of “low-risk” febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>norfloxacin (Apo-Norflox®)</td>
<td></td>
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<tr>
<td>ofloxacin (Floxin®)</td>
<td>Respiratory FQs: levofloxacin (Levaquin®), moxifloxacin (Avelox®)</td>
<td></td>
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</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>GP cocc</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatic dysfunction, P450 enzyme induction Orange tears/saliva/urine</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with N. meningitidis or Hib meningitis</td>
<td>Jaundice Not to be used as monotherapy (except for prophylaxis)</td>
</tr>
<tr>
<td>Metronidazole (Flagyl®)</td>
<td>Anaerobes Protozoa</td>
<td>Forms toxic metabolites in bacterial cell which damage microbial DNA</td>
<td>Disulfiram-type reaction with EtOH Seizures Peripheral neuropathy</td>
<td>Protozoal infections (trichomoniasis, amoebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>GP, including MRSA and VRE</td>
<td>Hypothesized to bind to cell wall and form channels leading to intracellular K⁺ depletion</td>
<td>Skeletal muscle injury at high doses (elevated CPK) Peripheral neuropathy</td>
<td>Bacteremia, endocarditis, skin and soft tissue, and other infections due to resistant GP infections including MRSA and VRE</td>
<td>Known hypersensitivity</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-METABOLITE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-Sulfamethoxazole (TMP/SMX) (Septra®, Bactrim®)</td>
<td>GP, especially S. aureus (including most MRSA) GN: enteric Nocardia Other: Pneumocystis Toxoplasmosis</td>
<td>Inhibits folic acid pathway (TMP inhibits DHFR and SMX competes with PABA)</td>
<td>Hepatitis Stevens-Johnson syndrome Bone marrow suppression Hyperkalemia Drug toxicity (increases free levels of many drugs, including glyburide, warfarin)</td>
<td>Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of P. jiroveci pneumonia</td>
<td>Hypersensitivity to TMP-SMX, sulfadiazine</td>
</tr>
<tr>
<td>nitrofurantoin (MacroBID®, Macrodantin®)</td>
<td>Enterococcus, S. saprophyticus GN (coliroms)</td>
<td>Reactive metabolites inhibit ribosomal protein synthesis</td>
<td>Cholestasis, hepatitis Hemolysis if G6PD deficiency Interstitial lung disease with chronic use</td>
<td>Lower UTI; not pyelonephritis or bacteremia</td>
<td>Hypersensitivity to nitrofurantoin Anuria, oliguria, or significant renal impairment Pregnant patients during labour and delivery or when labour imminent Infants &lt;1 mo of age</td>
</tr>
<tr>
<td><strong>ANTI-MYCOBACTERIALS</strong></td>
<td></td>
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</tr>
<tr>
<td>isoniazid (INH)</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Hepatotoxicity Hepatitis Drug-induced SLE Peripheral neuropathy</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB</td>
<td>Drug-induced hepatitis or acute liver disease</td>
</tr>
<tr>
<td>rifampin (RIF)</td>
<td>Mycobacteria</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatotoxicity P450 enzyme inducer Orange tears, saliva, urine</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections</td>
<td>Jaundice Not to be used monotherapy (except for prophylaxis)</td>
</tr>
<tr>
<td>ethambutol</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Loss of central and colour vision</td>
<td>Part of multidrug treatment for active TB and other mycobacterial infections</td>
<td>Renal failure</td>
</tr>
<tr>
<td>pyrazinamide (PZA)</td>
<td>Mycobacteria</td>
<td>Unknown</td>
<td>Hepatotoxicity Gout Gastric irritation</td>
<td>Part of multidrug treatment for active TB</td>
<td>Severe hepatic damage or acute liver disease Patients with acute gout</td>
</tr>
<tr>
<td><strong>SULFONES</strong></td>
<td></td>
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<tr>
<td>dapsone sulfone</td>
<td>M. leprae, P. jiroveci, Toxoplasma</td>
<td>Inhibit folic acid synthesis by competition with PABA</td>
<td>Rash Drug fever Agranulocytosis</td>
<td>Part of multidrug treatment for M. leprae, part of treatment for P. jiroveci pneumonia (with TMP), P. jiroveci pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine</td>
<td></td>
</tr>
</tbody>
</table>

### Table 32. Antibiotics for Selected Bacteria

<table>
<thead>
<tr>
<th>Pseudomonas</th>
<th>S. aureus</th>
<th>Enterococcus</th>
<th>H. influenzae</th>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
<td>metronidazole</td>
</tr>
<tr>
<td>gentamicin, tobramycin</td>
<td></td>
<td></td>
<td></td>
<td>clindamycin</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td></td>
<td></td>
<td></td>
<td>amoxicillin-clavulanate</td>
</tr>
<tr>
<td>cefazolin</td>
<td></td>
<td></td>
<td></td>
<td>amoxicillin-clavulanate</td>
</tr>
<tr>
<td>cefpime</td>
<td></td>
<td></td>
<td></td>
<td>ampicillin</td>
</tr>
<tr>
<td>meropenem</td>
<td></td>
<td></td>
<td></td>
<td>amoxicillin-clavulanate</td>
</tr>
<tr>
<td>imipenem</td>
<td></td>
<td></td>
<td></td>
<td>ampicillin-clavulanate</td>
</tr>
</tbody>
</table>

**Rifampin**
- Good adjunct for treating prosthetic device infection (bacterial biofilm)
- Always used in combination with other antibiotics to reduce emergence of resistance
## Antivirals

### Table 33 Antivirals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-HERPESVIRUS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>acyclovir</td>
<td>HSV-1,2 VZV</td>
<td>Guanosine analog inhibits viral DNA polymerase</td>
<td>PO well-tolerated IV: nephrotoxicity, CNS</td>
<td>Hypersensitivity to acyclovir or valacyclovir</td>
</tr>
<tr>
<td>valacyclovir (Valtrex®) (prodrug of acyclovir)</td>
<td>HSV-1,2 VZV</td>
<td>See above</td>
<td>H/A, nausea</td>
<td></td>
</tr>
<tr>
<td>famciclovir (Famvir®) penciclovir</td>
<td>HSV-1,2 VZV</td>
<td>See above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ganciclovir (Cytovene®) valganciclovir (prodrug of ganciclovir)</td>
<td>CMV HSV-1,2, VZV, HHV-6, EBV</td>
<td>See above</td>
<td>Heme: neutropenia, thrombocytopenia, anemia</td>
<td>Hypersensitivity to ganciclovir or valganciclovir Possible cross-hypersensitivity between acyclovir and valacyclovir</td>
</tr>
<tr>
<td>foscarnet</td>
<td>CMV Acyclovir-resistant HSV, VZV</td>
<td>Pyrophosphate analog inhibits viral DNA polymerase</td>
<td>Nephrotoxicity Anemia Electrolyte disturbance</td>
<td>Hypersensitivity to foscarnet</td>
</tr>
</tbody>
</table>

| **OTHER ANTIVIRALS** | | | | |
| (pegylated) interferon-α-2a or 2b | Chronic hepatitis B or C HPV | Inhibits viral protein synthesis | “Flu-like” syndrome Depression Bone marrow suppression | Hypersensitivity to any interferon Cannot use in combination with ribavirin if renal impairment |
| ribavirin (Virazole®) | Chronic hepatitis C RSV Lassa fever | Guanosine analog with multiple postulated mechanisms of action | Hemolytic anemia Rash, conjunctivitis Highly teratogenic | Pregnancy, women who may become pregnant or their partners Renal impairment |
| Cidofovir | Adenovirus CMV retinitis Foscarnet-resistant HSV | Deoxycytidine analogue inhibits DNA synthesis | Nephrotoxicity (proximal tubule dysfunction) | Renal failure; probenecid can reduce renal toxicity |
| lamivudine (Epivir®) | Chronic hepatitis B HIV | See HIV and AIDS, ID27 | See HIV and AIDS, ID27 | See HIV and AIDS, ID27 |
| Tenofovir | Chronic hepatitis B HIV | See HIV and AIDS, ID27 | See HIV and AIDS, ID27 | See HIV and AIDS, ID27 |
| Neuraminidase inhibitors: zanamivir (Relenza®) oseltamivir (Tamiflu®) | Influenza A and B: treatment and prophylaxis | Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation | Gl: N/V, diarhoea Bronchospasm in zanamivir | Hypersensitivity to the neuraminidase inhibitors |

## Antifungals

### Table 34 Antifungals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>POLYENES</strong></td>
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</tr>
<tr>
<td>amphotericin B</td>
<td>Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis Pulmonary: Aspergillosis CNS: Cryptococcus</td>
<td>A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death</td>
<td>Nephrotoxicity Hypo/hyperkalemia Infusion reactions: chills, fevers, H/A Peripheral phlebitis</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>nystatin (oral, topical)</td>
<td>Candidiasis: mucocutaneous, GI, oral (thrush), vaginal</td>
<td>See above</td>
<td>Not absorbed from the GI tract</td>
<td>Gl: N/V, diarhoea Highly toxic if given IV</td>
</tr>
<tr>
<td><strong>IMIDAZOLES</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>clotrimazole (Canesten®)</td>
<td>Oral and vulvovaginal candidiasis Dermatomycoses</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Pruritis, skin irritation</td>
<td></td>
</tr>
<tr>
<td>miconazole (Monistat®, Micozole®)</td>
<td>Vulvovaginal candidiasis Dermatomycoses</td>
<td></td>
<td>Vaginal burning N/V</td>
<td></td>
</tr>
<tr>
<td>ketoconazole (Nizoral®)</td>
<td>Dermatomycoses Seborrhic dermatitis</td>
<td></td>
<td>Pruritis, skin irritation GI nonspecific Results in decreased androgen and testosterone synthesis</td>
<td>Cross sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant</td>
</tr>
</tbody>
</table>
### Antifungals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
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<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRIAZOLEs</strong></td>
<td></td>
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</tr>
<tr>
<td>fluconazole (Diflucan®)</td>
<td>Candida infections (mucosal and invasive)</td>
<td>Cryptococcal meningitis (step-down therapy)</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Elevated liver enzymes GI nonspecific</td>
</tr>
<tr>
<td>itraconazole (Sporanox®)</td>
<td>Sporotrichosis Onychomycoses</td>
<td>Endemic mycoses: Histoplasmosis Blastomycosis Coccioidiomycosis</td>
<td>Fluconazole, Itraconazole, Ketoconazole</td>
<td>Elevated liver enzymes Rash GI nonspecific HTN Hypokalemia Peripheral edema</td>
</tr>
<tr>
<td>voriconazole (Vfend®)</td>
<td>Aspergillosis</td>
<td>Candidiasis</td>
<td>Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma with long-term use in immunosuppressed patients</td>
<td>Prolonged QT Pneumonia Neurologic toxicity</td>
</tr>
<tr>
<td>posaconazole (Posanol®, Noxafil®)</td>
<td>Candidiasis</td>
<td>Aspergillosis</td>
<td>Elevated liver enzymes H/A</td>
<td>Prolonged QT</td>
</tr>
<tr>
<td><strong>ALLYLAMINES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>terbinafine (Lamisil®)</td>
<td>Dermatomycoses Onychomycoses</td>
<td>Inhibits enzyme needed for ergosterol synthesis</td>
<td>Rash, local irritation GI nonspecific transaminitis</td>
<td>Active liver disease</td>
</tr>
<tr>
<td><strong>ECHINOCANDINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>caspofungin</td>
<td>Refractory aspergillosis, candidemia (azole-resistant)</td>
<td>Inhibits 1-3 β-D-glucan synthesis (needed for fungal cell wall)</td>
<td>Hepatotoxicity Infusion and injection site reactions</td>
<td></td>
</tr>
<tr>
<td>micafungin</td>
<td></td>
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<tr>
<td>anidulafungin</td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 21. Mechanism of action of antifungals**
# Table 35 Antiparasitics

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIMALARIALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chloroquine</td>
<td>Malaria: treatment of erythrocytic phase of all five species of Plasmodium that infect humans Note: High resistance of P. falciparum and P. vivax in certain geographic areas</td>
<td>Inhibits parasite heme polymerase</td>
<td>CNS: blurred vision, retinopathy, dizziness Nonspecific GI (rare with prophylaxis)</td>
<td>Hypersensitivity to chloroquine or other 4-aminoquinoline Retinal or visual field changes due to 4-aminoquinoline</td>
</tr>
<tr>
<td>quinine</td>
<td>Malaria: treatment of all five species of Plasmodium that infect humans, including chloroquine-resistant P. falciparum</td>
<td>Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (N/V, diarrhea), CNS (H/A, fever)</td>
<td>Hypersensitivity to quinine, may have cross-sensitivity with quinidine Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use</td>
<td></td>
</tr>
<tr>
<td>mefloquine (Lariam®)</td>
<td>Malaria: prophylaxis</td>
<td>Interferes with mitochondrial electron transport and dihydrofolate reductase</td>
<td>N/V, anorexia, diarrhea, abdominal pain (take with food)</td>
<td>History of seizures, psychosis, severe anxiety or depression</td>
</tr>
<tr>
<td>primaquine</td>
<td>Malaria: treatment and prophylaxis of P. falciparum</td>
<td>Interferes with mitochondrial function</td>
<td>Hemolytic anemia in G6PD deficient GI upset (take with food)</td>
<td>GI nonspecific G6PD deficiency Concurrent or recent use of quinacrine Pregnancy</td>
</tr>
<tr>
<td>atovaquone/proguanil (Malarone®)</td>
<td>Malaria: treatment and prophylaxis of all Plasmodium spp. P. falciparum</td>
<td>Inhibits mitochondrial electron transport and dihydrofolate reductase</td>
<td>N/V, anorexia, diarrhea, abdominal pain (take with food)</td>
<td>Hypersensitivity to atovaquone or proguanil Severe renal impairment</td>
</tr>
<tr>
<td>artemisinin derivatives (artemether, artemunate, etc.) Note: marketed primarily in endemic countries</td>
<td>Malaria: treatment of all Plasmodium spp. Severe malaria (IV artesunate) Typically used in combination with a longer-acting agent from above</td>
<td>Binds iron, leading to formation of free radicals that damage parasite proteins</td>
<td>Transient neurologic deficits (dizziness, balance disturbance) Transient neutropenia (at high doses of oral artemate) Transient neutropenia (at high doses of oral artesunate) Delayed hemolysis</td>
<td>Hypersensitivity to artemisinins</td>
</tr>
<tr>
<td><strong>OTHER ANTI-PROTOZOAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iodoquinol (Dioquin®)</td>
<td>Amoebiasis: E. histolytica, Dientamoeba fragilis, Balantidium coli, Blastocystis hominis</td>
<td>Contact amoebicide that acts in intestinal lumen by uncertain mechanism</td>
<td>GI: N/V, diarrhea, abdominal pain CNS: H/A, seizures, encephalitis Hypersensitivity to any 8-hydroxy-quinoline or iodine Patients with hepatic damage or optic neuropathy Pregnancy</td>
<td></td>
</tr>
<tr>
<td>metronidazole</td>
<td>Amoebiasis, T. vaginalis, giardiasis, D. fragilis</td>
<td>See Antibiotics, ID49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitazoxanide</td>
<td>Cryptosporidium, giardiasis, cyclosporiasis</td>
<td>Interferes with parasite anaerobic metabolism</td>
<td>N/V, diarrhea, abdominal pain, H/A</td>
<td>Hypersensitivity to nitazoxanide</td>
</tr>
<tr>
<td><strong>ANTI-HELMINTHICS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>praziquantel</td>
<td>Schistosomiasis and other flukes Tapeworms</td>
<td>Increases Ca^{2+} permeability of helminth cell membrane, causing paralysis and detachment</td>
<td>N/V, fever, dizziness</td>
<td>Ocular cysticercosis</td>
</tr>
<tr>
<td>albendazole</td>
<td>Intestinal roundworms Neurocysticercosis Echinococcus Hydatid disease</td>
<td>Inhibits glucose uptake into susceptible parasites Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis</td>
<td>Pregnancy Ocular cysticercosis or intraventricular cysticercosis</td>
<td></td>
</tr>
<tr>
<td>mebendazole (Vermox®)</td>
<td>Intestinal roundworms: pinworm, whipworm, hookworm, roundworm (e.g. Ascaris)</td>
<td>Inhibits microtubule formation and glucose uptake</td>
<td>Nonspecific GI</td>
<td>Pregnancy, infants</td>
</tr>
<tr>
<td>ivermectin</td>
<td>Strongyloidiasis Onchocerciasis Scabies</td>
<td>Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis</td>
<td>Nausea, bloating, diarrhea, myalgias, lightheadedness, H/A</td>
<td>Hypersensitivity to ivermectin Pregnancy</td>
</tr>
<tr>
<td>diethylcarbamazine</td>
<td>Wuchereria bancrofti Loa loa</td>
<td>Anemia, N/V, H/A, drowsiness, encephalitis, retinal hemorrhage Mazzotti reaction if infected with onchocerciasis</td>
<td>Pregnancy Onchocerciasis</td>
<td></td>
</tr>
</tbody>
</table>
Quick Reference: Common Infections and Their Antibiotic Management

see Family Medicine, FM49

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Neurological Infections

Respiratory Infections

Cardiac Infections

Gastrointestinal Infections

Bone and Joint Infections

Systemic Infections

HIV and AIDS
Hedlin F, Mcbrath MJ. Setting the stage: host invasion by HIV. Nat Rev Immunol 2008;8:447-457.
Okanwo CI, Uhman OA, Okonmah CAN. Antiretroviral pre-exposure prophylaxis (PREP) for preventing HIV in high-risk individuals. Cochrane Database of Syst Rev 2012; 7:CD007189.

Fungal Infections

Parasitic Infections
Infections in the Immunocompromised Host

Fever of Unknown Origin
Spira AM. Assessment of travellers who return home ill. Lancet 2003;361:1459-1469

Nosocomial Infections

Travel Medicine

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Antivirals
Acronyms ........................................... 2

Introduction to Genetics ................................. 2
  Background
  Pedigrees
  Genetic Testing and Counselling

Dysmorphisms .......................................... 4
  Congenital Anomalies
  Approach to the Dysmorphic Child

Syndromes and Diseases ................................. 5
  Large Genomic Changes
  Single Gene Disorders
  Metabolic Diseases

References ................................................. 9
### Introduction to Genetics

#### Terms

- **Penetrance**: extent that a gene is observably expressed in an individual that carries it
- **Expressivity**: extent of gene expression
- **Genetic heterogeneity**: genetic disorder can arise from different allele/locus mutations
- **Phenotypic heterogeneity**: mutations in the same gene resulting in multiple diverse clinical manifestations and degree of severity
- **Imprinting**: epigenetic process that involves methylation or acetylation of DNA, affecting gene expression
- **Uniparental disomy**: two full or partial copies of a chromosome from one parent and no chromosome from the other parent

#### Mendelian Inheritance

- disorders caused by mutation of one or both copies (alleles) of a gene, inherited in one of two patterns
  - autosomal: when disorder is caused by genes on one of 22 pairs of autosomes (chromosomes 1-22)
  - X-linked: when disease is caused by a gene on the X chromosome

#### Triplet Repeat Expansions

- disorder in which trinucleotide repeats in certain genes exceed the normal number and result in altered gene expression or production of an abnormal protein (e.g. Fragile X syndrome, Huntington’s disease)

#### Imprinting Disorders

- imprinted genes are expressed entirely from either the maternal or paternal allele, depending on the gene (parent-of-origin gene expression)
- occur when a mutation disrupts the normally expressed allele of imprinted gene (e.g. Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome) or through uniparental disomy of the normally silenced allele

#### Mitochondrial Disorders

- disorders caused by mutations of the DNA present in mitochondria or nuclear genes whose protein products are important for mitochondrial function
- inheritance pattern of mitochondrial DNA mutations: mother passes on the defect to all her children; father cannot pass on defect since embryo only receives mitochondria from the mother (in the egg)

#### Copy Number Variation

- difference in the amount of genetic material
  - decrease: deletion of a chromosomal region, leaving only one copy of the genetic material in that region (e.g. 22q11.2 deletion syndrome due to deletion on chromosome 22)
  - increase: duplication of a chromosomal region, resulting in more than two copies of the genetic material in that region (e.g. Potocki-Lupski syndrome due to duplication of chromosome 17p11.2)
- CNVs can be part of normal range of genetic variation
Pedigrees

- diagrams that show the pattern/distribution of phenotypes for a genetic disorder within a family, often across multiple generations

<table>
<thead>
<tr>
<th>Male, unaffected</th>
<th>Female, unaffected</th>
<th>Gender Unknown, unaffected</th>
<th>Deceased</th>
<th>Affected Individual</th>
<th>Affected Individual ≥2 conditions</th>
<th>Carrier not likely to manifest disease</th>
<th>Carrier unaffected at this time but could manifest disease later</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

Figure 1. Common pedigree symbols

Genetic Testing and Counselling

- microarray analysis
  - array comparative genomic hybridization (CGH): a collection of DNA probes attached to a solid surface to which test DNA hybridizes in order to determine copy number of DNA regions
  - microarray analysis can identify small deletions or duplications of genetic material anywhere in the genome
  - commonly indicated when there is developmental delay OR two or more congenital anomalies
- FISH (fluorescence in situ hybridization): a DNA probe used to identify a gain or loss of chromosomal material
- karyotype: microscopic analysis of chromosomes with a special stain that shows large changes in the number or structure of chromosomes; can detect large CNVs
- Sanger sequencing: the ‘gold-standard’ method for identification of single nucleotide variants in short DNA sequences (e.g. the exons of the gene(s) known to cause suspected syndrome)
- next-generation sequencing: high throughput method to sequence exomes or whole-genomes; useful when genetic syndrome is suspected, but diagnosis is unclear: increasingly used for multi-gene test panels
- prenatal screening
  - offer optional prenatal screening before diagnostic testing
  - first trimester screening (FTS)
    - biochemistry (β-hCG, PAPP-A)
    - US estimate of gestational age and measurement of nuchal translucency
    - screen for trisomy 21 and 18
    - done between 11 and 14 wk, sensitivity=80-85%
  - integrated prenatal screening (IPS)
    - ONTD, trisomy 21 and 18
    - use results from FTS and combine with additional biomarkers completed between 15-21 weeks (inhibin A, unconjugated estradiol, AFP, 2nd trimester β-hCG)
    - improved sensitivity, reduced false positive rate compared to FTS
  - fetal anatomy scan
    - US at 18-20 wk
- newborn screening
  - detect potentially fatal, treatable disorders before symptoms begin to allow for early therapy
  - performed on all newborns in Canada
  - heel puncture to collect blood
  - screens for CF, congenital hypothyroidism, congenital adrenal hyperplasia, SCID, hemoglobinopathies, metabolic diseases, etc.

Whole-Genome Sequencing Expands Diagnostic Utility and Improves Clinical Management in Paediatric Medicine

Genomic Med 2016;1:15012

While the standard of care for neurodevelopmental and congenital malformations is chromosome microarray analysis for copy number variations, whole exome sequencing allows the identification of sequence-level mutations across all known coding genes. Whole genome sequencing has been previously associated with a diagnostic yield of ~25% for neurological disorders or congenital anomalies. A recent study published in Genomic Medicine has demonstrated that whole genome sequencing exceeds other technologies in detecting genetic variants with a 34% diagnostic yield, a four-fold increase in molecular diagnosis relative to chromosome microarray analysis and a two-fold increase relative to all genetic testing protocols. These results suggest that whole genome sequencing may be used as a first-tier molecular test in individuals with development delays and congenital abnormalities, with a higher diagnostic yield than conventional genetic testing and decreased time to genetic diagnosis.
### Dysmorphisms

#### Congenital Anomalies

**Minor and Major Anomalies**
- minor anomaly: an unusual anatomic feature that is of no serious medical or cosmetic consequence to the patient
- major anomaly: anomaly that creates significant medical, surgical, or cosmetic problems for the patient

**Mechanism for Anomalies**
- malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
- disruption: results from the extrinsic breakdown of, or interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
- deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter deformation sequence)
- dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g. bone dysplasia)

**Multiple Anomalies**
- association: non-random occurrence of multiple independent anomalies that appear together more than would be predicted by chance but are not known to have a single etiology (e.g. VACTERL)
- sequence: related anomalies that come from a single initial major anomaly or precipitating factor that changes the development of other surrounding or related tissues or structures (e.g. Potter sequence or Pierre-Robin sequence)
- syndrome: a pattern of anomalies that occur together and are known or thought to have a single cause (e.g. Down syndrome)

### Approach to the Dysmorphic Child

- congenital abnormalities are the most common cause of infant death in developed countries

**General Approach to the Dysmorphic Child**
- Are the anomalies major or minor?
- What is the mechanism underlying the anomaly?
- Do the anomalies fit as part of an association, sequence, or syndrome?

**History**
- prenatal/obstetrical history (see Obstetrics, OB4) with particular attention to potential teratogenic exposures, development history (see Pediatrics, P22), and past medical history
- complete 3 generation family pedigree: health history, consanguinity, stillbirths, neonatal deaths, specific illnesses, intellectual disability, multiple miscarriages, ethnicity

**Physical Exam**

**Figure 2. Physical exam of the dysmorphic child**
Investigations
- screening for TORCH infections
- serial photographs if child is older
- x-rays for bony abnormalities
- cytogenetic studies
  - karyotype if recognized aneuploidy syndrome
  - chromosomal microarray analysis (array comparative genomic hybridization) if development delay OR two or more congenital anomalies
  - FISH if aneuploidy syndrome (e.g. trisomy 13, 18 or 21) suspected
- biochemistry: various biochemical profiles, specific enzyme assays
- single gene testing, multi-gene panel testing

Management
- prenatal counselling and assessing risk of recurrence
- referral for specialized pediatric or genetic care for symptomatic management
- specific treatments are available for certain metabolic disorders and genetic syndromes
  - metabolic disorders: enzyme replacement therapy, substrate reduction therapy, etc. (e.g. low-protein diet in PKU patients)
  - genetic syndromes: e.g. mTOR inhibitors in tuberous sclerosis

### Syndromes and Diseases

#### Large Genomic Changes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>Down syndrome</td>
<td>Edwards’ syndrome</td>
<td>Patau syndrome</td>
</tr>
<tr>
<td>Incidence</td>
<td>1:600-800 births</td>
<td>1:6,000 live births</td>
<td>1:10,000 live births</td>
</tr>
<tr>
<td>Most common abnormality of autosomal chromosomes</td>
<td>Rises with advanced maternal age from 1:1,500 at age 20 to 1:20 by age 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranium/Brain</td>
<td>Mild microcephaly, flat occiput, 3rd fontanelle, brachycephaly</td>
<td>Microcephaly, prominent occiput</td>
<td>Microcephaly, sloping forehead, occipital scalp defect, holoprosencephaly</td>
</tr>
<tr>
<td>Eyes</td>
<td>Upslanting palpebral fissures, inner epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus</td>
<td>Microphthalmia, hypotelorism, iris coloboma, retinal anomalies</td>
<td>Microphthalmia, corneal abnormalities</td>
</tr>
<tr>
<td>Ears</td>
<td>Low-set, small, overfolded upper helix, frequent AOM, hearing loss</td>
<td>Low-set, malformed</td>
<td>Low-set, malformed</td>
</tr>
<tr>
<td>Facial Features</td>
<td>Protruding tongue, large cheeks, low flat nasal bridge, small nose</td>
<td>Cleft lip/palate, Small mouth, micrognathia</td>
<td>60-80% cleft lip and palate</td>
</tr>
<tr>
<td>Skeletal/MSK</td>
<td>Short stature, Excess nuchal skin, Joint hyperflexibility (80%) including dysplastic hips, vertebral anomalies, atlantoaxial instability</td>
<td>Short stature, Clenched fist with overlapping digits, hypoplastic nails, clinodactyly, polydactyly</td>
<td>Severe growth retardation, Polydactyly, clenched hand</td>
</tr>
<tr>
<td>Cardiac Defect</td>
<td>50%, particularly atrioventricular septal defect</td>
<td>60% (VSD, PDA, ASD)</td>
<td>80% (VSD, PDA, ASD)</td>
</tr>
<tr>
<td>GI</td>
<td>Duodenal/oesophageal/anal atresia, TEF, Hirschsprung’s disease, chronic constipation</td>
<td>Hernia, TEF</td>
<td>Polycystic kidneys, cryptorchidism</td>
</tr>
<tr>
<td>GU</td>
<td>Cryptorchidism, rarely fertile</td>
<td>Polycystic kidneys, cryptorchidism</td>
<td>Hypertension</td>
</tr>
<tr>
<td>CNS</td>
<td>Hypotonia at birth, Low IQ, developmental delay, hearing problems, Onset of Alzheimer’s disease in 40s</td>
<td>Hypertonia</td>
<td>Hypo- or hypertonia, Seizures, deafness, Severe developmental delay</td>
</tr>
<tr>
<td>Other Features</td>
<td>Transverse palmar crease, clinodactyly, and absent middle phalanx of the 5th finger, 1% lifetime risk of leukemia, Polycythemia, Hypothyroidism</td>
<td>SGA, Rocker-bottom feet</td>
<td>Single umbilical artery, Midline anomalies: scalp, pituitary, palate, heart, umbilicus, anus, Rocker-bottom feet</td>
</tr>
<tr>
<td>Prognosis/Management</td>
<td>Prognosis: long term management per AAP Guidelines (Health Supervision of Children with Down syndrome), recommend chromosomal analysis, CBC, Echo, yearly thyroid test, atlanto-occipital x-ray at 2 yr, sleep study, hearing test, and ophthalmology assessment</td>
<td>13% 1-year survival, 10% ten-year survival, Profound intellectual disability in survivors</td>
<td>20% 1-year survival, 13% ten-year survival, Profound intellectual disability in survivors</td>
</tr>
</tbody>
</table>

Check the umbilical cord for 2 arteries and 1 vein. The presence of a single umbilical artery may be associated with other congenital anomalies.
### Table 2. Common Genetic Disorders Involving the Sex Chromosomes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Fragile X Syndrome</th>
<th>Klinefelter Syndrome</th>
<th>Turner Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>X-linked</td>
<td>47,XXY (most common)</td>
<td>45,X (most common)</td>
</tr>
<tr>
<td></td>
<td>Genetic anticipation</td>
<td>48,XXYY, 49,XXXXY</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>1:3,600 males, 1:6,000 females</td>
<td>1:1,000 live male births, increased risk with advanced maternal age</td>
<td>1:4,000 live female births, risk not increased with advanced maternal age</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Overgrowth: prominent jaw, forehead, and nasal bridge with long and thin face; large protuberant ears; macroorchidism; hyperextensibility; and high arched palate</td>
<td>Tall, slim, underweight; No features prepuberty</td>
<td>Short stature, short webbed neck, low posterior hair line, wide carrying angle</td>
</tr>
<tr>
<td></td>
<td>Complications: seizures, scoliosis, mitral valve prolapse</td>
<td>Postpuberty: male may suffer from developmental delay, long limbs, gynecomastia, lack of facial hair</td>
<td>Broad chest, widely spaced nipples</td>
</tr>
<tr>
<td>IQ and Behaviour</td>
<td>Mild to moderate intellectual disability, 20% of affected males have normal IQ</td>
<td>Mild intellectual disability</td>
<td>Mild intellectual disability to normal intelligence</td>
</tr>
<tr>
<td>Gonad and Reproductive Function</td>
<td>Male carriers may demonstrate tremor/ataxia syndrome in later life</td>
<td>Infertility due to hypogonadism/hyposperma</td>
<td>Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics</td>
</tr>
<tr>
<td>Diagnosis/Prognosis/Management</td>
<td>Molecular testing of FMR1 gene: overamplification of the trinucleotide repeat, length of segment is proportional to severity of clinical phenotype</td>
<td>Increased risk of germ cell tumours and breast cancer</td>
<td>Normal life expectancy if no complications</td>
</tr>
<tr>
<td></td>
<td>(genetic anticipation)</td>
<td>Management: testosterone in adolescence</td>
<td>Increased risk of X-linked diseases</td>
</tr>
</tbody>
</table>

### Table 3. Other Genetic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>22q11.2 Deletion Syndrome</th>
<th>Prader-Willi Syndrome</th>
<th>Angelman Syndrome</th>
<th>Noonan Syndrome</th>
<th>CHARGE Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>Microdeletions of chromosome region 22q11.2</td>
<td>Lack of expression of genes on paternal chromosome 15q11-13 due to deletion, maternal uniparental disomy of chromosome 15, or imprinting defect</td>
<td>Lack of expression of genes on maternal chromosome 15q11-13 due to deletion or inactivation or paternal uniparental disomy</td>
<td>Autosomal dominant with variable expression</td>
<td>2/3 of children with CHARGE have been found to have a CHD7 mutation on chromosome 8</td>
</tr>
<tr>
<td>Incidence</td>
<td>1:4000; Second most common genetic diagnosis (next to Down syndrome)</td>
<td>1:15,000</td>
<td>1:10,000</td>
<td>1:2,000 male and female live births</td>
<td>1 10,000</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>“CATCH 22”</td>
<td>“H-O”: Hypotonia and weakness, Hypogonadism, Obsessive Hyperphagia, Obesity</td>
<td>Ataxia with severe intellectual disability, seizures, tremulousness, hypotonia</td>
<td>Short stature, webbed neck, triangular facies, hypertelorism, low set ears, epicanthal folds, ptosis, pectus excavatum</td>
<td>“CHARGE”</td>
</tr>
<tr>
<td></td>
<td>Cyanotic CHD</td>
<td>Short stature, almond-shaped eyes, small hands and feet with tapering of fingers</td>
<td>Midface hypoplasia, fair hair, uncontrollable laughter</td>
<td>Right sided CHD, pulmonary stenosis</td>
<td>Congenital Heart disease</td>
</tr>
</tbody>
</table>
|          | Anomalies: craniofacial anomalies, micrognathia and low set ears | Developmental delay (variable) | | Increased risk of hematological cancers, moderate intellectual disability, delayed puberty | |}

**MG6 Medical Genetics**

**Syndromes and Diseases**

**Toronto Notes 2018**
Table 4. Familial Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Fraumeni Syndrome</td>
<td>TP53</td>
<td>Breast, osteosarcoma, leukemia, soft tissue carcinoma, and numerous other cancers</td>
</tr>
<tr>
<td>Lynch Syndrome (HNPCC)</td>
<td>MSH2, MLH1, MSH6, PMS2, EPCAM</td>
<td>Colorectal, endometrial, ovarian, renal, pancreatic, liver/biliary duct, stomach, brain, breast</td>
</tr>
<tr>
<td>FAP</td>
<td>APC</td>
<td>Colorectal, small intestine/stomach tumours</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome</td>
<td>BRCA1, BRCA2</td>
<td>Female: breast, ovarian, pancreatic \ Male: prostate, breast, pancreatic</td>
</tr>
<tr>
<td>Von Hippel-Lindau Syndrome</td>
<td>VHL</td>
<td>Kidney + tumours (e.g. pheochromocytoma)</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>PTEN</td>
<td>Breast, thyroid, endometrial</td>
</tr>
<tr>
<td>NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>NF1</td>
<td>Astrocytoma, optic glioma, neurofibroma, leukemia</td>
</tr>
<tr>
<td>Type 2</td>
<td>NF2</td>
<td>Vestibular schwannoma, meningioma, ependymoma, astrocytoma</td>
</tr>
</tbody>
</table>

Single Gene Disorders

**CYSTIC FIBROSIS**
- see Respirology, R12 and Pediatrics, P82

**SICKLE CELL DISEASE**
- see Hematology, H20

**DUCHENNE MUSCULAR DYSTROPHY**

**Epidemiology**
- 1:4,000 males

**Etiology**
- one type of muscular dystrophy characterized by progressive skeletal and cardiac muscle degeneration
- X-linked recessive: 1/3 spontaneous mutations, 2/3 inherited mutations
- missing structural protein (dystrophin) → muscle fibre fragility → fibre breakdown → necrosis and regeneration

**Clinical Presentation**
- proximal muscle weakness by age 3, positive Gower's sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy

**Diagnosis**
- molecular genetic studies of dystrophin gene (DMD) (first line)
- family history (pedigree analysis)
- increased CK (50-100x normal) and lactate dehydrogenase
- elevated transaminases
- muscle biopsy, EMG

**Management**
- supportive (e.g. physiotherapy, wheelchairs, braces, prevent obesity
- cardiac health monitoring and early intervention
- bone health monitoring and intervention (vitamin D, bisphosphonates)
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

**Complications**
- patient usually wheelchair-bound by 12 yr of age
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or CHF in 2nd-3rd decade
Metabolic Diseases

- inherited disorders of metabolism; often autosomal recessive
- infants and older children may present with FTT or developmental delay
- organellar diseases can present with dysmorphism
  universal newborn screening in Ontario includes metabolic disorders

<table>
<thead>
<tr>
<th>Table 5. Metabolic Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic and Amino Acid Disorders</strong></td>
</tr>
<tr>
<td>PKU</td>
</tr>
<tr>
<td>Tyrosinemia</td>
</tr>
<tr>
<td>Homocystinuria</td>
</tr>
<tr>
<td>MSUD</td>
</tr>
<tr>
<td>Alkaptonuria</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Clinical Manifestations</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Laboratory Findings</td>
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<td></td>
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<tr>
<td>Physical Exam</td>
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</tbody>
</table>

Initial Investigations

- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, ABCs (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects, and GSDs)
- lactate, ammonium (hyperammonemia with urea cycle defects), plasma Ca²⁺ and Mg²⁺
- routine urinalysis: ketonuria must be investigated
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, plasma amino acid screen, urine organic acids, CSF glycine, free fatty acids (3-β-hydroxybutyrate ratio >4 in fatty acid oxidation defect)
- storage diseases: urine mucopolysaccharide and oligosaccharide screen

Treatment

- varies according to inborn error of metabolism
- dietary restrictions, supplementation, enzyme replacement therapy, gene therapy, liver transplant, stem cell transplant
PHENYLKETONURIA

Epidemiology
• 1:10,000; autosomal recessive disease

Etiology
• deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to build up of toxic metabolites
• mothers who have PKU may have infants with congenital abnormalities

Clinical Presentation
• baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors, and mental retardation
• hypopigmentation due to low tyrosine (fair hair, blue eyes)

Management
• PKU screening at birth
• dietary restriction of phenylalanine starting within the first 10 d of life
• duration of dietary restriction controversial – lifelong or until end of puberty; should be resumed during pregnancy to maintain normal phenylalanine levels
• large neutral amino acid (tyrosine) replacement, BH4 enzyme treatment, phenylalanine lyase treatment are other options

GALACTOSEMIA

Epidemiology
• 1:60,000; autosomal recessive disease

Etiology
• most commonly due to deficiency of galactose-1-phosphate uridyltransferase leading to an inability to process lactose/galactose

Clinical Presentation
• signs of liver and renal failure, jaundice, FTT, and cataracts with ingestion of lactose/galactose

Management
• elimination of galactose from the diet (e.g. dairy, breast milk)
• most infants are fed a soy-based diet

Complications
• increased risk of sepsis, especially E. coli
• if the diagnosis is not made at birth, liver and brain damage may become irreversible

References
Blake RD, Prasad C. CHARGE syndrome, o phenotype. J Rare Diseases 2006;1.
Medical Imaging

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Acronyms ........................................ 2

Imaging Modalities ......................... 2
X-Ray Imaging
Ultrasound
Magnetic Resonance Imaging
Positron Emission Tomography Scans
Contrast Enhancement

Chest Imaging ................................. 4
Chest X-Ray
Computed Tomography Chest
Lung Abnormalities
Pulmonary Vascular Abnormalities
Pleural Abnormalities
Mediastinal Abnormalities
Tubes, Lines, and Catheters

Abdominal Imaging ......................... 10
Abdominal X-Ray
Approach to Abdominal X-Ray
Abdominal Computed Tomography
Approach to Abdominal Computed Tomography
Contrast Studies
Specific Visceral Organ Imaging
“itis” Imaging
Angiography of Gastrointestinal Tract

Genitourinary System and Adrenal .... 16
Urological Imaging
Gynecological Imaging
Adrenal Mass

Neuroradiology ............................... 18
Modalities
Approach to CT Head
Selected Pathology

Musculoskeletal System ................. 21
Modalities
Approach to Bone X-Rays
Trauma
Arthritis
Bone Tumour
Infection
Metabolic Bone Disease

Nuclear Medicine ............................ 25
Brain
Thyroid
Respiratory
Cardiac
Abdomen and Genitourinary System
Bone

Interventional Radiology ............... 28
Vascular Procedures
Nonvascular Interventions

Breast Imaging .............................. 30
Modalities
Breast Interventional Procedures
Breast Findings

References .................................... 32
**Acronyms**

### DSA, DEXA, CXR, CVP, CVD, CTA, CSF, CNS, BOOP, AV, ARDS
- DSA: Digital Subtraction Angiography
- DEXA: Dual-energy x-ray absorptiometry
- CXR: Chest x-ray
- CVP: Central Venous Pressure
- CVD: Collagen Venous Pressure
- CTA: Computed Tomographic Angiogram
- CSF: Cerebrospinal Fluid
- CNS: Central Nervous System
- BOOP: Bronchitis Obliterans
- AV: Arteriovenous
- ARDS: Acute Respiratory Distress Syndrome

### X-Ray Imaging

#### X-rays
- x-rays, or Roentgen rays, are a form of electromagnetic energy of short wavelength
- as x-ray photons traverse matter, they can be absorbed (a process known as "attenuation") and/or scattered
- the density of a structure determines its ability to attenuate or "weaken" the x-ray beam
  - air < fat < water < bone < metal
- structures that have high at euation (e.g. bone) appear white on the resulting images

#### Plain Films
- x-rays pass through the patient and interact with a detection device to produce a 2-dimensional projection image
- structures closer to the film appear sharper and less magnified
- contraindications: pregnancy (relative)
- advantages: inexpensive, non-invasive, readily available, reproducible, fast
- disadvantages: radiation exposure, generally poor at distinguishing soft tissues

#### Fluoroscopy
- continuous x-rays used for guiding angiographic and interventional procedures, in contrast examinations of the GI tract, and in the OR for certain surgical procedures (e.g. orthopedic, urological)
- on the fluoroscopic image, black and white are reversed so that bone and contrast agents appear dark and radiolucent structures appear light
- advantages: allows for real-time visualization of structures
- disadvantages: increased radiation dose; however, the use of pulsed fluoroscopy has reduced fluoroscopy time by 76% and radiation dose by 64% as compared with continuous fluoroscopy

#### Computed Tomography
- x-ray beam opposite a detector moves in a continuous 360º arc as patient is advanced through the imaging system
- subsequent computer assisted reconstruction of anatomical structures from the axial plane
- atenuation is quantified in Hounsfield units
- subsequent computer assisted reconstruction of anatomical structures from the axial plane
- adjusting the "window width" (range of Hounsfield units displayed) and "window level" (midpoint value of the window width) can maximally visualize certain anatomical structures (e.g. CT chest can be viewed using "lung", "soft tissue", and "bone" settings)
- contraindications: pregnancy (relative) contraindications to contrast agents (e.g. allergy, renal failure)
- advantages: delineates surrounding soft tissues, excellent at delineating bones and identifying lung/ liver masses, may be used to guide biopsies, spiral/helical multidetector CT has fast data acquisition and allows 3D reconstruction, CTA is less invasive than conventional angiography
- disadvantages: high radiation exposure, soft tissue characterization is not as good in comparison with MRI, IV contrast injection, anxiety of patient when going through scanner, higher cost, and less available than plain film

### Imaging Modalities

#### Typical Effective Doses from Diagnostic Medical Exposures (in adults)*

<table>
<thead>
<tr>
<th>Diagnostic Procedure Type</th>
<th>Equivalent Number of Chest X-Rays</th>
<th>Approximate Period of Natural Background Radiation** (–300 mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td>Dial-and-energy x-ray absorptiometry (without w/ CT)</td>
<td>0.52/year</td>
</tr>
<tr>
<td></td>
<td>Upper GI series</td>
<td>3.0/year</td>
</tr>
<tr>
<td></td>
<td>Small bowel series</td>
<td>23.0/30mo</td>
</tr>
<tr>
<td></td>
<td>Barium enema</td>
<td>4.0/2.7y</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>6.0/8m</td>
</tr>
<tr>
<td></td>
<td>Head</td>
<td>100/8m</td>
</tr>
<tr>
<td></td>
<td>Neck</td>
<td>20/1yr</td>
</tr>
<tr>
<td></td>
<td>Spine</td>
<td>300/2yr</td>
</tr>
<tr>
<td></td>
<td>Chest</td>
<td>350/2.3yr</td>
</tr>
<tr>
<td></td>
<td>Cervical/thoracic (CT)</td>
<td>750/5yr</td>
</tr>
<tr>
<td></td>
<td>Cor venography</td>
<td>620/5.3yr</td>
</tr>
<tr>
<td></td>
<td>Abdomen</td>
<td>400/2.7yr</td>
</tr>
<tr>
<td></td>
<td>Pelvis</td>
<td>300/2yr</td>
</tr>
<tr>
<td></td>
<td>Radon (NMSA)</td>
<td>98/2.7yr</td>
</tr>
<tr>
<td></td>
<td>Lung (15SA)</td>
<td>105/3.9yr</td>
</tr>
<tr>
<td></td>
<td>Larynx/parietal (15SA)</td>
<td>350/2.9yr</td>
</tr>
<tr>
<td></td>
<td>Esophagus/pancreatic (15SA)</td>
<td>150/3.1yr</td>
</tr>
<tr>
<td></td>
<td>Renal (1SA)</td>
<td>375/2.8yr</td>
</tr>
<tr>
<td></td>
<td>Mammary gland</td>
<td>460/2.9yr</td>
</tr>
<tr>
<td></td>
<td>Penile fossa</td>
<td>105/3.4yr</td>
</tr>
</tbody>
</table>

*Source: Radiology 2000;248:254-263
**Calculated using average natural background exposure in Canada (Health Canada: http://www.hc-sc.gc.ca/alt-vi/vyh-vys/environment/expris-eng.php)
Ultrasound

- high-frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
- reflection (or “echo”) occurs when the sound waves pass through tissue interfaces of different acoustic densities
- structures are described based on their echogenicity; hyperechoic structures appear bright (U/S reflected) whereas hypoechoic structures appear dark (U/S waves not reflected back but pass through)
- higher U/S frequencies result in greater resolution but greater attenuation (i.e. deeper structures more difficult to visualize)
- artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (e.g. tissue/air) or absorbs (e.g. tissue/bone) sound waves; enhancement refers to the increase in reflection amplitude (i.e. increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
- Duplex scan: grey-scale image that utilizes the Doppler effect to visualize the velocity of blood flow past the transducer
- Colour Doppler: assigns a colour based on the direction of blood flow (i.e. red = toward transducer, blue = away)
- advantages: relatively low cost, non-invasive, no radiation, real time imaging, may be used for guided biopsies many different imaging planes (axial, sagittal), determines cystic versus solid
- disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus, poor for bone evaluation

Magnetic Resonance Imaging

- non-invasive imaging technique that does not use ionizing radiation and able to produce images in virtually any plane
- patient is placed in a magnetic field; protons (H⁺) align themselves along the plane of magnetization due to intrinsic polarity. A pulsed radiofrequency beam is subsequently turned on and deflects all the protons off their aligned axes due to absorption of energy from the radiofrequency beam. When the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed. This energy is measured with a detector and interpreted by software to generate MR images
- the MR image reflects the signal intensity picked up by the receiver. This signal intensity is dependent on:
  1. hydrogen density: tissues with low hydrogen density (e.g. cortical bone, lung) generate little to no MR signal compared to tissues with high hydrogen density (e.g. water)
  2. magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment

<table>
<thead>
<tr>
<th>Imaging Techniques</th>
<th>Contrast Enhancements</th>
<th>Main Application</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion-Weighted Imaging</td>
<td>Contrast dependent on the molecular motion of water Decreased diffusion is hyper intense (bright), whereas increased diffusion is hypointense (dark)</td>
<td>Neuroradiology</td>
<td>Sensitive for detection of acute ischemic stroke and differentiating an acute stroke from other neurologic pathologies Acute infarction appears hyperintense Abscess collections also show restricted diffusion</td>
</tr>
<tr>
<td>T1-Weighted</td>
<td>Fluid is hypointense (dark) and fat is hyperintense (bright)</td>
<td>Body soft tissues</td>
<td>Often considered an anatomic scan since they provide a reference for functional imaging</td>
</tr>
<tr>
<td>T2-Weighted</td>
<td>Fluid is hyperintense (bright) and fat is hypointense (dark)</td>
<td>Body soft tissues</td>
<td>Often considered a pathologic scan since they will highlight edematous areas associated with certain pathologies</td>
</tr>
</tbody>
</table>

Positron Emission Tomography Scans

- non-invasive technique that involves exposure to ionizing radiation (~7 mSv)
- nuclear medicine imaging technique that produces images of functional processes in the body
- current generation models integrate PET and CT technologies into a single imaging device (PET-CT) that collects both anatomic and functional information during a single acquisition
- positron-producing radioisotopes, such as ¹⁸FDG, are chemically incorporated into a metabolically active molecule (e.g. glucose). These are then injected into the patient, travel to the target organ, and accumulate in tissues of interest. As the radioactive substance begins to decay, gamma rays are produced, and are then detected by the PET scanner
- contraindications: pregnancy
- advantages: shows metabolism and physiology of tissues (not only anatomic); in oncology, allows for diagnosis staging, and restaging; has predictive and prognostic value; can evaluate cardiac viability
- disadvantages: cost, ionizing radiation
# Contrast Enhancement

## Table 2. Contrast Agents

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Types</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray/CT</td>
<td>1. Barium (oral or rectal)</td>
<td>Radio-opaque substance that helps to delineate intraluminal anatomy; may demonstrate patency, lumen integrity, or large filling defects</td>
<td>Previous adverse reaction to contrast; barium enema is contraindicated in toxic megacolon, acute colitis, and suspected perforation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Iodine (IV injection)</td>
<td>Delineates intraluminal anatomy; may demonstrate patency, lumen integrity, or large filling defects; under fluoroscopy, may also give information on function of an organ</td>
<td>Risk of nephrogenic systemic fibrosis in patients with end-stage renal disease; Previous adverse reaction to contrast, renal failure, DM, pregnancy, multiple myeloma, severe heart failure and dehydration; eGFR &lt;60 may require preventative measures and follow-up</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Gadolinium-Chelates (IV injection)</td>
<td>Shortens T1 relaxation time, thereby increasing signal intensity in T1-weighted sequences; gadolinium has some effect on T2-relaxation time; highlights highly vascular structures (e.g. tumours)</td>
<td>Risk of nephrogenic systemic fibrosis in patients with end-stage renal disease</td>
<td>Previous adverse reaction to contrast or if end-stage renal disease (relative contraindication)</td>
</tr>
<tr>
<td>U/S</td>
<td>Microbubbles (IV injection)</td>
<td>Since gas is highly echogenic, the microbubbles allow for echo-enhancement of a tissue</td>
<td>Contraindicated in individuals with right-to-left cardiac shunts or people with known hypersensitivity reactions</td>
<td></td>
</tr>
</tbody>
</table>

## Chest Imaging

### Chest X-Ray

#### Standard Views
- **PA**: anterior chest against film plate to minimize magnification of the heart size
- **lateral**: better visualization of retrocardiac space and thoracic spine (more sensitive at picking up pleural effusions)
- Helps localize lesions when combined with PA view
- **AP**: for bedridden patients (generally a lower quality film than PA because of enlarged cardiac silhouette)
- **lateral decubitus**: to assess for pleural effusion and pneumothorax in bedridden patients; however, POCUS can also be utilized for both of these purposes
- **lordotic**: angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs

![CXR views](image.png)  
Figure 1. CXR views

### Approach to CXR

#### Basics
- **ID**: patient name, MRN, sex, age
- **date of exam**
- **markers**: right and/or left
- **technique**: view (e.g. PA, AP, lateral), supine or erect
- **indications for the study**
- **comparison**: date of previous study for comparison (if available)
- **quality of film**: inspiration (6th anterior and 10th posterior ribs should be visible), penetration (thoracic spine should be visible) and rotation (clavicles vs. spinous process)
Analysis

- tubes and lines: check position and be alert for pneumothorax or pneumomediastinum
- soft tissues: neck, axillae, pectoral muscles, breasts/nipples, chest wall
  - nipple markers can help identify nipples (may mimic lung nodules)
  - amount of soft tissue, presence of masses and air (subcutaneous emphysema)
- abdomen (see Abdominal Imaging, MI10)
  - free air under the diaphragm, air-fluid levels, distention in small and large bowels
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: C-spine, thoracic spine, shoulders, ribs, sternum, clavicles
  - lytic and blastic lesions and fractures
- mediastinum: trachea, heart, great vessels
  - cardiomegaly (cardiothoracic ratio >0.5), tracheal shift, tortuous aorta, widened mediastinum
- hila: pulmonary vessels, mainstem and segmental bronchi, lymph nodes
  - comment on abnormal lung opacity, pleural effusions or thickening
  - right hemidiaphragm usually higher than left due to liver
- lungs: lung parenchyma, pleura, diaphragm
  - tend to be lower right
- abdomen (see Abdominal Imaging, MI10)
  - free air under the diaphragm, air-fluid levels, distention in small and large bowels
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: C-spine, thoracic spine, shoulders, ribs, sternum, clavicles
  - lytic and blastic lesions and fractures
- mediastinum: trachea, heart, great vessels
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- hila: pulmonary vessels, mainstem and segmental bronchi, lymph nodes
  - comment on abnormal lung opacity, pleural effusions or thickening
  - right hemidiaphragm usually higher than left due to liver
  - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm
- please refer to Toronto Notes website for supplementary material on how to approach a CXR

Anatomy

Localizing Lesions for Parenchymal Lung Disease

- silhouette sign: when two objects of the same radiolucency contact each other, they become indistinguishable on imaging and result in the loss of normal interfaces. It can be used to identify lung pathology (consolidation, atelectasis, mass) and localize disease to specific lung segments. The silhouette sign is not only used in the chest, but can also be an aid to interpreting imaging studies throughout the body
- spine sign: on lateral films, vertebral bodies should appear progressively radiolucent as one moves down the thoracic vertebral column; if they appear more radio-opaque, it is an indication of pathology (e.g. consolidation in overlying left lower lobe)
- air bronchogram: branching pattern of air-filled bronchi on a background of fluid-filled airspaces

### Table 3. Localization Using the Silhouette Sign

<table>
<thead>
<tr>
<th>Interface Lost</th>
<th>Location of Lung Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC/right superior mediastinum</td>
<td>RUL</td>
</tr>
<tr>
<td>Right heart border</td>
<td>RML</td>
</tr>
<tr>
<td>Right hemidiaphragm</td>
<td>RLL</td>
</tr>
<tr>
<td>Aortic knob/left superior mediastinum</td>
<td>LUL</td>
</tr>
<tr>
<td>Left heart border</td>
<td>Lingula</td>
</tr>
<tr>
<td>Left hemidiaphragm</td>
<td>LLL</td>
</tr>
</tbody>
</table>

Legend

a1 anterior 1st rib
a2 anterior 2nd rib
aa aort c arch
apw aorto-pulmonary window
as anterior airspace
carina
cp clavicle
cp coracoid process
cpa costophrenic angle
di diaphragm
g gastric bubble
ipv inferior vena cava
latr left atrium
lbr left mainstem bronchus
lp local pulmonary artery
lv left ventricle
mrf major fissure
mi minor fissure
p3 posterior 3rd rib
p4 posterior 4th rib
pa main pulmonary artery
ratri right atrium
rbr right mainstem bronchus
rpa right pulmonary artery
rv right ventricle
sc scapula
sp spinous process
st sternum
svc superior vena cava
tr trachea
vb vertebral body
Computed Tomography Chest

Approach to CT Chest
- soft tissue window
  - thyroid, chest wall, pleura
  - heart: chambers, coronary artery calcifications, pericardium
  - vessels: aorta, pulmonary artery, smaller vasculature
  - lymph nodes: mediastinal, axillary
  - vertebrae, sternum, manubrium, ribs: fractures, lytic lesions, sclerosis
- bone window
  - trachea: patency, secretions
  - bronchial trees: anatomic variants, mucus plugs, airway collapse
  - lung parenchyma: fissures, nodules, fibrosis/interstitial changes
  - pleural space: effusions
- please refer to Toronto Notes website for supplementary material on how to approach a CT chest

Table 4. Types of CT Chest

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Contrast</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>Scans full lung very quickly (&lt;1 min)</td>
<td>Poor at evaluating diffuse disease ±</td>
<td>CXR abnormality Pleural and mediastinal abnormality Lung cancer staging Follow-up metastases Empyema vs. abscess</td>
</tr>
<tr>
<td>High Resolution</td>
<td>Thinner slices provide high definition of lung parenchyma</td>
<td>Only 5-10% lung is sampled</td>
<td>Hemoptysis Diffuse lung disease (e.g. sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis) Pulmonary fibrosis Normal CXR but abnormal PFTs Characterize solitary pulmonary nodule</td>
</tr>
<tr>
<td>Low Dose</td>
<td>1/5th the radiation</td>
<td>Decreased detail No</td>
<td>Screening Follow-up infections, lung transplant, metastases</td>
</tr>
<tr>
<td>CTA</td>
<td>Iodinated contrast highlights vasculature</td>
<td>Contrast can cause severe allergic reaction and is nephrotoxic Yes</td>
<td>PE Aortic aneurysms Aortic dissection</td>
</tr>
</tbody>
</table>

Lung Abnormalities

Atelectasis
- pathogenesis: collapse of alveoli due to restricted breathing, blockage of bronchi, external compression, or poor surfactant
- findings
  - increased opacity of involved segment/lobe, vascular crowding, silhouette sign, air bronchograms
  - volume loss: fissure deviation, hilar/mediastinal displacement, diaphragm elevation
  - compensatory hyperinflation of remaining normal lung
- differential diagnosis
  - obstructive (most common): air distal to obstruction is reabsorbed causing alveolar collapse
    - post-surgical, endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury), or mucous plug (cystic fibrosis)
  - compressive
  - tumour: bulla, effusion, enlarged heart, lymphadenopathy
  - traction (cicatrization): due to scarring, which distorts alveoli and contracts the lung
  - adhesive: due to lack of surfactant
    - hyaline membrane disease, prematurity
- passive (relaxation): a result of air or fluid in the pleural space
  - pleural effusion, pneumothorax
- management: in the absence of a known etiology, persisting atelectasis must be investigated (i.e. CT thorax) to rule out a bronchogenic carcinoma

**Consolidation**
- pathogenesis: fluid (water, blood), inflammatory exudates, protein, or tumour in alveoli
- findings
  - air bronchograms: lucent branching bronchi visible through opacification
  - airspace nodules: fluffy, patchy, poorly defined margins with later tendency to coalesce, may take on lobar or segmental distribution
  - silhouette sign
- differential diagnosis
  - fluid: pulmonary edema, blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
  - inflammatory exudates: bacterial infections, TB, allergic hypersensitivity alveolitis, BOOP, allergic bronchopulmonary aspergillosis, aspiration, sarcoidosis
  - protein: pulmonary alveolar proteinosis
  - tumour: bronchoalveolar carcinoma, lymphoma
- management: varies depending on the pattern of consolidation, which can suggest different etiologies; should also be done in the context of clinical picture

**Interstitial Disease**
- pathogenesis: pathological process involving the interlobular connective tissue (i.e. “scaffolding of the lung”)
- findings
  - linear: fine lines caused by thickened connective tissue septae
    - Kerley A: long thin lines in upper lobes
    - Kerley B: short horizontal lines extending from the lateral lung margin
    - Kerley C: diffuse linear pattern throughout lung
  - nodular: 1-5 mm well-defined nodules distributed evenly throughout lung
  - reticular: parenchyma replaced by thin-walled cysts suggesting extensive destruction of pulmonary tissue and fibrosis
    - seen in IPF, asbestosis, and CVD
  - reticulonodular: combination of reticular and nodular patterns
- differential diagnosis
  - occupational/environmental exposure
    - inorganic: asbestosis, coal miner’s pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
    - organic: hypersensitivity pneumonitis, bird fancier’s lung, farmer’s lung (mouldy hay), and other organic dust
    - autoimmune: CVD (e.g. rheumatoid arthritis, scleroderma, SLE, polymyositis, mixed connective tissue disease), IB, celiac disease, vasculitis
    - drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, carbamazepine, fluoxetine, amiodarone, chemotherapy (methotrexate), heroin, cocaine, methadone
    - infections: non-tuberculous mycobacteria, aspergillosis, aspiration, sarcoidosis
    - neoplastic: carcinoma, lymphoma, sarcoma, mesothelioma, pulmonary varix, granulomatous disease (e.g. sarcoidosis)
    - vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
    - idiopathic: hypersensitivity pneumonitis, IPF, BOOP
- management: high-resolution CT thorax and biopsy
- for Causes of Interstitial Lung Disease Classified by Distribution see Respirology, R13
- management: high-resolution CT thorax and biopsy

**Pulmonary Nodule**
- findings: round opacity ± silhouette sign
  - note: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers
- differential diagnosis
  - extrapulmonary density: nipple, skin lesion, electrode, pleural mass, bony lesion
  - solitary nodule
    - tumour: carcinoma, hamartoma, metastasis, bronchial adenoma
    - inflammation: histoplasmosis, tuberculosis, coccidioidomycosis
    - vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
  - multiple nodules: metastases, abscess, granulomatous lung disease (TB, fungal, sarcoma, rheumatoid nodules, silicosis, GPA)
- management: clinical information and CT appearance determine level of suspicion of malignancy
  - if high probability of malignancy, invasive testing (fine needle aspiration, transbronchial/thoracoscopic biopsy) is indicated
  - if low probability of malignancy, repeat CXR or CT in 1-3 mo and then every 6 mo for 2 yr; if no change, then >99% chance benign
Table 5. Characteristics of Benign and Malignant Pulmonary Nodules

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin</td>
<td>Well-defined</td>
</tr>
<tr>
<td>Ill-defined/spiculated (&quot;corona radiata&quot;)</td>
<td></td>
</tr>
<tr>
<td>Contour</td>
<td>Smooth</td>
</tr>
<tr>
<td>Lobulated</td>
<td></td>
</tr>
<tr>
<td>Calcification</td>
<td>Diffuse, central, popcorn, concentric</td>
</tr>
<tr>
<td>Eccentric or stippled</td>
<td></td>
</tr>
<tr>
<td>Doubling Time</td>
<td>20-460 d or &gt;460 d</td>
</tr>
<tr>
<td>&lt;20 d or &gt;460 d</td>
<td></td>
</tr>
<tr>
<td>Other Features</td>
<td></td>
</tr>
<tr>
<td>Cavitation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>&lt;3 cm</td>
</tr>
<tr>
<td>Cavitition</td>
<td></td>
</tr>
<tr>
<td>Yes, especially with wall thickness &gt;15 mm, eccentric cavity, and shaggy internal margins</td>
<td>No</td>
</tr>
<tr>
<td>Satellite Lesions</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Pulmonary Vascular Abnormalities

Pulmonary Edema
- Pathogenesis: fluid accumulation in the airspaces of the lungs
- Findings
  - Vascular redistribution/enlargement, cephalization, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
  - Fluid initially collects in interstitium
  - Loss of definition of pulmonary vasculature
  - Peribronchial cuffing
  - Kerley B lines
  - Reticulonodular pattern
  - Thickening of interlobar fissures
- As pulmonary edema progresses, fluid begins to collect in alveoli causing diffuse airspace disease often in a “bat wing” or “butterfly” pattern in perilobar regions with tendency to spare the outermost lung fields
- Differential diagnosis: cardiogenic (e.g. CHF), renal failure, volume overload, non-cardiogenic (e.g. ARDS)

Pulmonary Embolism
- Pathogenesis: arterial blockage in the lungs due to emboli from pelvic or leg veins, rarely from PICC lines, ports, air, fat, or amniotic fluid (difficult to diagnose on imaging except by combination of clinical history and CXR and CT findings of ARDS)
- Findings
  - CXR: Westermark sign (localized pulmonary oligemia), Hampton’s hump (triangular peripheral infarct), enlarged right ventricle and right atrium, atelectasis, pleural effusion, and rarely pulmonary edema
  - Definitive imaging study: CT pulmonary angiography to look for filling defect in contrast-filled pulmonary arteries (emboli can be seen up to 4th order arterial branching)
- V/Q scan: not a diagnostic study

Pleural Abnormalities

Pleural Effusion

Table 6. Sensitivity of Plain Film Views for Pleural Effusion

<table>
<thead>
<tr>
<th>X Ray Projection</th>
<th>Minimum Volume to Visualize</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral decubitus</td>
<td>25 mL; most sensitive</td>
</tr>
<tr>
<td>Upright lateral</td>
<td>50 mL; meniscus seen in the posterior costophrenic sulcus</td>
</tr>
<tr>
<td>PA</td>
<td>200 mL</td>
</tr>
<tr>
<td>Supine</td>
<td>Diffuse haziness</td>
</tr>
</tbody>
</table>

- A horizontal fluid level is seen only in a hydropneumothorax (i.e. both fluid and air within pleural cavity)
- Effusion may exert mass effect, shift trachea and mediastinum to opposite side, or cause atelectasis of adjacent lung
- U/S is superior to plain film for detection of small effusions and may also aid in thoracentesis, and POCUS is now standard of care in acute situations
- Fluid level >1 cm on lateral decubitus film is indication to perform thoracentesis
Pneumothorax
• pathogenesis: gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
• findings
  • upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall
  • separating partially collapsed lung from pleural air
  • more obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiorly)
  • more difficult to detect on supine film; look for the “deep (costophrenic) sulcus” sign, double diaphragm sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  • mediastinal shift may occur if tension pneumothorax
• differential diagnosis: spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, CVP line insertion), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung
• management: needle decompression or chest tube insertion, repeat CXR to ensure resolution

Asbestos
• asbestos exposure may cause various pleural abnormalities including benign plaques (most common; these may calcify), diffuse pleural fibrosis, effusion, and malignant mesothelioma

Mediastinal Mass
• the mediastinum is divided into four compartments; this provides an approach to the differential diagnosis of a mediastinal mass
• anterior border formed by the sternum and posterior border by the heart and great vessels
  • 4 Ts: see sidebar
  • cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
• middle border (extending behind anterior mediastinum to a line 1 cm posterior to the anterior border of the thoracic vertebral bodies)
  • esophageal carcinoma, esophageal duplication cyst, metastatic disease, lymphadenopathy (all causes), hiatus hernia, bronchogenic cyst
• posterior border (posterior to the middle line described above)
  • neurogenic tumour (e.g. neurofibroma, schwannoma), multiple myeloma, pheochromocytoma, neuroenteric cyst, thymic duct cyst, lateral meningocele, Bochdalek hernia, extramedullary hematopoiesis
• superior boundaries (superiorly by thoracic inlet, inferiorly by plane of the sternal angle, anteriorly by manubrium, posteriorly by T1-T4, laterally by pleura)
• in addition, any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, or hematoma

Enlarged Cardiac Silhouette
• heart borders
  • on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
  • on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle
• cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
• using a good quality erect PA chest film in adults, cardiothoracic ratio of >0.5 is abnormal
• differential of ratio >0.5
  • cardiomegaly (myocardial dilatation or hypertrophy)
  • pericardial effusion
  • poor inspiratory effort/low lung volumes
  • pectus excavatum
• ratio <0.5 does not exclude enlargement (e.g. cardiomegaly + concomitant hyperinflation)
• pericardial effusion: globular heart with loss of indentations on left mediastinal border
• RA enlargement: increase in curvature of right heart border and enlargement of SVC
• LA enlargement: flattening of left heart border; increased opacity of lower right side of cardiovascular shadow (double heart border); elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film), distance between left main bronchus and “double” heart border >7 cm, splayed carina (late sign)
• RV enlargement: elevation of cardiac apex from diaphragm; anterior enlargement leading to loss of retrosternal air space on lateral; increased contact of right ventricle against sternum
• LV enlargement: rounding of the cardiac apex; displacement of left cardiac boarder leftward, inferiorly, and posteriorly
**Tubes, Lines, and Catheters**

- ensure appropriate placement and assess potential complications of lines and tubes
- avoid mistaking a line/tube for pathology (e.g. oxygen rebreather mask for pneumothoraces)

**Central Venous Catheter**
- used for fluid and medication administration, vascular access for hemodialysis, and CVP monitoring
- tip must be located proximal to right atrium to prevent inducing arrhythmias or perforating wall of atrium
  - if monitoring CVP, catheter tip must be proximal to venous valves
  - tip of well-positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle, and inferiorly by top of RA
- course should parallel course of SVC; if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

**Endotracheal Tube**
- frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- tip should be located 4 cm above tracheal carina (avoids bronchus intubation and vocal cord irritation)
- maximum inflation diameter <3 cm to avoid necrosis of tracheal mucosa and rupture; ensure diameter of balloon is less than tracheal diameter above and below balloon
- complications: aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

**Nasogastric Tube**
- tip and sideport should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- complications: aspiration (parenchymal opacities), intracranial perforation (trauma patients), pneumothorax

**Swan-Ganz Catheter**
- to monitor pulmonary capillary wedge pressure and to measure cardiac output for suspected LV dysfunction
- tip should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- if tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

**Chest Tube**
- in dorsal and caudal portion of pleural space to evacuate fluid
- in ventral and cephalad portions of pleural space to evacuate pneumothoraces
- tube may lie in fissure as long as functioning
- complications: lung perforation (mediastinal opacities)

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### Abdominal Imaging

#### Abdominal X-Ray

**Indications**
- acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction, large bowel obstruction
- chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
- not useful in: GI bleeds, chronic anemia, vague GI symptoms

**Anatomy**
- abdomen divided into 2 cavities
  - peritoneal cavity: lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
  - retroperitoneal cavity: contains several organs situated posterior to the peritoneal cavity; the contour of these can often be seen on radiographs
### Table 7. Differentiating Small and Large Bowel

<table>
<thead>
<tr>
<th>Property</th>
<th>Small Bowel</th>
<th>Large Bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal Folds</td>
<td>Uninterrupted valvulae conniventes (or plicae circulars)</td>
<td>Interrupted haustra extend only partway across lumen</td>
</tr>
<tr>
<td>Location</td>
<td>Central</td>
<td>Peripheral (picture frame)</td>
</tr>
<tr>
<td>Maximum Diameter</td>
<td>3 cm</td>
<td>6 cm (9 cm at cecum)</td>
</tr>
<tr>
<td>Maximum Fold Thickness</td>
<td>3 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Other</td>
<td>Rarely contains solid fecal material</td>
<td>Commonly contains solid fecal material</td>
</tr>
</tbody>
</table>

### Approach to Abdominal X-Ray

- **mnemonic: “Free ABDO”**
  - **“Free”: free air and fluid**
    - free fluid
      - small amounts of fluid: increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
      - large amounts of fluid: diffuse increased opacification on supine film; bowel floats to centre of anterior abdominal wall
    - ascites and blood (hemoperitoneum) are the same density on the radiograph, and therefore, cannot be differentiated
    - free intraperitoneal air suggests rupture of a hollow viscus (anterior duodenum, transverse colon), penetrating trauma, or recent (<7 d) surgery
  - **“A”: air in the bowel (can be normal, ileus, or obstruction)**
    - volvulus – twisting of the bowel upon itself; from most to least common:
      - sigmoid: ‘coffee bean’ sign (massively dilated sigmoid projects to right or mid-upper abdomen) with proximal dilation
      - cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
      - gastric: rare
    - transverse colon: rare (usually young individuals)
    - small bowel: “corkscrew sign” (rarely diagnosed on plain films, seen best on CT)
    - toxic megacolon
      - manifestation of fulminant colitis
      - extreme dilatation of colon (>6.5 cm) with mucosal changes (e.g. foci of edema, ulceration, pseudopolyps), loss of normal haustral pattern
  - **“B”: bowel wall thickening**
    - increased soft tissue density in bowel wall, thumb-like indentations in bowel wall (“thumb-printing”), or a picket-fence appearance of the valvulae conniventes (“stacked coin” appearance)
    - may be seen in IBD, infection, ischemia, hypoproteineemic states, and submucosal hemorrhage
  - **“D”: densities**
    - bones: look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
    - abnormal calcifications: approach by location
      - RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
      - RLQ: ureteral stone, appendicolith, gallstone ileus
      - LUQ: renal stone, adrenal calcification, tail of pancreas
      - LLQ: ureteral stone
      - central: aorta/aortic aneurysm, pancreas, lymph nodes
      - pelvis: phleboliths (i.e. calcified veins), uterine fibroids, bladder stones
  - **“O”: organs**
    - kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
    - outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)

---

**Figure 16. Normal AXRs:** (left) supine anteroposterior AXR, (middle) upright anteroposterior AXR, and (right) left lateral decubitus AXR
Table 9. Adynamic Ileus vs. Mechanical Obstruction

<table>
<thead>
<tr>
<th>Feature</th>
<th>Adynamic Ileus</th>
<th>Mechanical Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibre of Bowel Loops</td>
<td>Normal or dilated</td>
<td>Usually dilated</td>
</tr>
<tr>
<td>Air-Fluid Levels</td>
<td>Same level in the same single loop</td>
<td>Multiple air fluid levels giving “step ladder” appearance, dynamic (indicating peristalsis present), “string of pearls” (row of small gas accumulations in the dilated valvulae conniventes)</td>
</tr>
<tr>
<td>Distribution of Bowel Gas</td>
<td>Air throughout GI tract is generalized or localized In a localized ileus (e.g. pancreatitis, appendicitis), dilated “sentinel loop” remains in the same location on serial films, usually adjacent to the area of inflammation</td>
<td>Dilated bowel up to the point of obstruction (i.e. transition point)</td>
</tr>
</tbody>
</table>

**Abdominal Computed Tomography**

- indications for plain CT: renal colic, hemorrhage
- indications for CT with contrast
  - IV contrast given immediately before or during CT to allow identification of arteries and veins
  - portal venous phase: indicated for majority of cases
  - biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumours
  - caution: contrast allergy (may premedicate with steroids and antihistamine)
  - contraindication: impaired renal function (based on eGFR)
- oral contrast: barium or water-soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
- rectal contrast: given for investigation of colonic lesions

**Approach to Abdominal Computed Tomography**

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ/structure individually from top to bottom, evaluating size and shape of each area of increased or decreased density
- evaluate the following:
  - soft tissue window
    - liver, gallbladder, spleen and pancreas
    - adrenals, kidneys, ureters, and bladder
    - stomach, duodenum, small bowel mesentery, and colon/appendix
  - retroperitoneum: aorta, vena cava, and mesenteric vessels; look for adenopathy in vicinity of vessels
  - peritoneal cavity for fluid or masses
  - abdominal wall and adjacent soft tissue
  - lung window
    - visible lung (bases)
  - bone window
    - vertebrae, spinal cord, and bony pelvis

**Biliary vs. Portal Venous Air**

- "Go with the flow": air follows the flow of bile or portal venous blood
- Biliary air is most prominent centrally over the liver
- Portal venous air is most prominent peripherally

**Table 8. Abnormal Air on Abdominal X-Ray**

<table>
<thead>
<tr>
<th>Air</th>
<th>Appearance</th>
<th>Common Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraluminal</td>
<td>Upright film: air under diaphragm</td>
<td>Perforated viscus Post-operative (up to 10 d to be resorbed)</td>
</tr>
<tr>
<td>Intrapertoneal (pneumoperitoneum)</td>
<td>Left lateral decubitus film: air between liver and abdominal wall Supine film: gas outlines of structures not normally seen: Inner and outer bowel wall (Rigler’s sign) Falciiform ligament Peritoneal cavity (&quot;football&quot; sign)</td>
<td>Peritonitis (post-op), appendicitis, perforated diverticulitis, bowel obstruction</td>
</tr>
<tr>
<td>Retropertoneal</td>
<td>Gas outlining retroperitoneal structures allowing increased visualization: Psoas shadows Renal shadows</td>
<td>Perforation of retroperitoneal segments of bowel: duodenal ulcer, post-colonoscopy</td>
</tr>
<tr>
<td>Intramural (pneumatosis intestinalis)</td>
<td>Lucent air streaks in bowel wall, 2 types: 1. Linear 2. Rounded (cystoides type)</td>
<td>1. Linear: ischemia, necrotizing enterocolitis 2. Rounded/cystoides (generally benign): prima y (idiopathic), secondary to COPD</td>
</tr>
<tr>
<td>Intraluminal</td>
<td>Dilated loops of bowel, air-fluid levels</td>
<td>Adynamic (paralytic) ileus, mechanical bowel obstruction</td>
</tr>
<tr>
<td>Loculated</td>
<td>Mottled, localized in abnormal position without normal bowel features</td>
<td>Abscess (evaluate with CT)</td>
</tr>
<tr>
<td>Bilary</td>
<td>Air centrally over liver</td>
<td>Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis</td>
</tr>
<tr>
<td>Portal Venous</td>
<td>Air peripherally over liver in branching pattern</td>
<td>Bowel ischemia/infarction</td>
</tr>
</tbody>
</table>

**Conclusion**

93.8%, 97.7%) and OC has a sensitivity of 94.7% (95% CI 90.4%, 97.2%) for the detection of CRC. CTC has a sensitivity of 96.1% (95% CI 93.8%, 97.7%) and OC has a sensitivity of 94.7% (95% CI 90.4%, 97.2%) for the detection of CRC.

**Purpose**

To assess the sensitivity of computed tomography (CT) colonography and optical colonoscopy (OC) for colorectal cancer (CRC) detection.

**Methods**

Systematic review and meta-analysis of diagnostic studies evaluating CT colonography detection of CRC based on a prior eligibility criteria, in particular requiring both OC and histological confirmation of disease. Studies that also assessed true-positive and false-negative diagnoses with OC were used to calculate OC sensitivity. Sensitivity of CTC and OC for CRC was the main outcome.

**Results**

49 studies on 11,151 patients undergoing diagnostic study for detection of CRC were included. CTC has a sensitivity of 96.1% (95% CI 93.8%, 97.7%) and OC has a sensitivity of 94.7% (95% CI 90.4%, 97.2%) for the detection of CRC.

**Conclusion**

CTC is highly sensitive for the detection of CRC and may be a better modality for the initial investigation of suspected CRC, assuming reasonable specificity.
CT and Bowel Obstruction
- cause of bowel obstruction rarely found on plain films; CT is best choice for imaging
- the "3 6,9" rule is a very useful guide to determining when the bowel is dilated; the maximum diameter of the bowel is 3 cm for small bowel, 6 cm for large bowel, and 9 cm for cecum; this can also be useful to distinguish small and large bowel, and to assess for ‘impending’ cecal perforation (e.g. post-untreated Ogilvie’s syndrome)
- closed-loop obstruction: an obstruction in two locations (usually small bowel) creating a loop of bowel segment obstructed both proximally and distally; complications (e.g. ischemia, perforation, necrosis) may occur quickly

CT Colonography (virtual colonoscopy)
- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumours)
- two CT scans of the abdomen (prone and supine) after the instillation of carbon dioxide into a prepped colon
- computer reconstruction of 2D CT images into a 3D intraluminal view of the colon
- lesions seen on 3D images correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, staging of obstructing colonic lesions

Contrast Studies

Table 10. Types of Contrast Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ</th>
<th>Procedure Description</th>
<th>Assessment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine Esophagogram</td>
<td>Cervical esophagus</td>
<td>Contrast agent swallowed recorded for later playback and analysis</td>
<td>Dysphagia, swallowing incoordination, recurrent aspiration, post-operative cleft palate repair</td>
<td>Aspiration, webs (partial occlusion), Zenker’s diverticulum, criopharyngeal bar, laryngeal tumour</td>
</tr>
<tr>
<td>Barium Swallow</td>
<td>Thoracic esophagus</td>
<td>Contrast agent swallowed under fluoroscopy, selective images captured</td>
<td>Dysphagia, rule out GERD, post-esophageal surgery</td>
<td>Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear</td>
</tr>
<tr>
<td>Upper GI Series</td>
<td>Thoracic esophagus, stomach, and duodenum</td>
<td>Double contrast study: 1. Barium to coat mucosa, then 2. Gas pills for distention Patient NPO after midnight</td>
<td>Dyspepsia, investigate possible upper GI bleed, weight loss/anemia, post-gastric surgery</td>
<td>Ulcers, neoplasms, filling defects</td>
</tr>
<tr>
<td>Enterography and Enteroclysis (MRI or CT)</td>
<td>Entire small bowel</td>
<td>Enterography: patient drinks 1-2 L of sorbitol, psyllium, or barium solution to distend small bowel Enteroclysis: NJ tube used to pump barium, psyllium, or sorbitol contrast media directly into small bowel</td>
<td>IBD, malabsorption, weight loss/anemia, Meckel's diverticulum</td>
<td>Neoplasms, IBD, malabsorption, infection</td>
</tr>
</tbody>
</table>
Specific Visceral Organ Imaging

Liver
- U/S: assessment of cysts, abscesses, tumours, biliary tree
- CT ± IV: most popular procedure for imaging the liver parenchyma (primary liver tumours, metastases, cysts, abscesses, trauma, cirrhosis)
- MR: also excellent in evaluation of primary liver tumours, liver metastases, and other parenchymal conditions, and is particularly helpful in differentiating common benign hepatic hemangiomas from primary liver tumours and metastases
- elastography: measures shear wave velocity by U/S (Fibroscan) or MRI (MR elastography) to non-invasively quantify liver fibrosis
- findings
  - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
  - portal HTN: increased portal vein diameter, collateral veins, splenomegaly (≥12 cm), portal vein thrombosis, recanalization of the umbilical vein
  - porto-systemic shunts: caput medusa, esophageal varices, spontaneous spleno-renal shunt
- U/S: cirrhosis appears nodular and hyperechoic with irregular areas of atrophy of the right lobe and hypertrophy of the caudate or left lobes
- CT: fatty infiltration appears hypodense
- in order to be visualized, some masses require contrast
- upon identifying a liver lesion on imaging (e.g. U/S), the follow-up imaging modality should be CT or MR. CT would be four-phase non-contrast, arterial, venous, and delayed to distinguish the common benign liver lesion hemangioma from other tumours

Table 11. Imaging of Liver Masses

<table>
<thead>
<tr>
<th>Mass</th>
<th>U/S</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Adenoma</td>
<td>Most common in young women taking oral contraceptives. Well-defined mass with hyperechoic areas due to hemorrhage</td>
<td>Well-defined hypervascular lesion with enlarged central vessel becoming slightly isoattenuating in venous phase</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Homogeneous hyperechoic mass</td>
<td>PEM peripheral globular enhancement in arterial phase scans; central filling and persistent enhancement on delayed scans</td>
</tr>
<tr>
<td>Focal Nodular Hyperplasia</td>
<td>Well-defined mass, central scar seen in 50%</td>
<td>Hypervascular mass in arterial phase and isoattenuation to liver in portal venous phase</td>
</tr>
<tr>
<td>Abscess</td>
<td>Ill-defined, irregular margin, hypoechoic contents</td>
<td>Low attenuation lesion with an irregular enhancing wall</td>
</tr>
<tr>
<td>Hydatid Cyst</td>
<td>Simple/multiloculated cyst</td>
<td>Low attenuation simple or multiloculated cyst; calcification</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>Single/multiple masses, or diffuse infiltration</td>
<td>Hypervascular; enhances in arterial and washes out in venous phase with portal venous tumour thrombus</td>
</tr>
<tr>
<td>Metastases</td>
<td>Multiple masses of variable echotexture</td>
<td>Usually low attenuation on contrast-enhanced scan</td>
</tr>
</tbody>
</table>

Spleen
- U/S, CT, nuclear medicine scan (nuclear medicine only to distinguish ectopic splenic tissue from enhancing tumours)
- CT for splenic trauma (hemorrhage)

Pancreas
- tumours
  - U/S: mass is more echogenic than normal pancreatic tissue
  - CT: preferred modality for diagnosis/staging
- ductal dilation secondary to stone/tumour
- MRCP: imaging of ductal system using MRI cholangiography; no therapeutic potential
- ERCP: endoscope to inject dye into the biliary tree and x-ray imaging to assess pancreatic and biliary ducts; therapeutic potential (stent placement, stone retrieval); acute pancreatitis is a complication in 5% of diagnostic procedures and 10% of therapeutic procedures

Biliary Tree
- U/S: bile ducts usually visualized only if dilated, secondary to obstruction (e.g. choledocholithiasis, benign stricture mass)
- CT: dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- MRCP, ERCP, PTC: further evaluation of obstruction and possible intervention

Figure 18. ERCP: biliary tree
**Acute Cholecystitis**
- Pathogenesis: inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or, in the case of acalculous cholecystitis, due to gallbladder ischemia or cholestasis (see *General Surgery, GS47*)
- Best imaging modality: U/S (best sensitivity and specificity), nuclear medicine (HIDA scan can help diagnose cases of acalculous or chronic cholecystitis)
- Findings: Most sensitive findings are presence of gallstones and positive sonographic Murphy's sign (tenderness from pressure of US probe over visualized gallbladder). Secondary findings include thickened gallbladder wall (>3 mm), dilated gallbladder and pericholecystic fluid.
- Management: admit, NPO, IVF analgesia, cefazolin, early laparoscopic cholecystectomy

**Acute Appendicitis**
- Pathogenesis: luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess or peritonitis (see *General Surgery, GS27*)
- Best imaging modality: U/S or CT
- Findings:
  - U/S: thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible; may also demonstrate other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
  - CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage management: admit, NPO, IVF, analgesia, cefazolin + metronidazole, appendectomy

**Acute Diverticulitis**
- Pathogenesis: erosion of the intestinal wall (most commonly rectosigmoid) by increased intraluminal pressure or ininspired food particles → inflammation and focal necrosis → micro- or macroscopic perforation (see *General Surgery, GS31*)
- Best imaging modality: CT although U/S is sometimes used
- Contrast: oral and rectal contrast given before CT to opacify bowel
- Findings:
  - Cardinal signs: thickened wall, mesenteric infiltration, gas-filled diverticula, abscess
  - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
  - Sometimes difficult to distinguish from perforated cancer (therefore send abscess fluid for cytology and follow-up with colonoscopy)
  - If chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)
- Management: ranges from antibiotic treatment to surgical intervention; can use imaging to follow progression

**Acute Pancreatitis**
- Pathogenesis: activation of proteolytic enzymes within pancreatic cells leading to local and systemic inflammatory response (see *Gastroenterology, G44*); a clinical/biochemical diagnosis
- Best imaging modality: imaging used to support diagnosis and evaluate for complications (diagnosis cannot be excluded by imaging alone)
  - U/S good for screening and follow-up
  - CT is useful in advanced stages and in assessing for complications (1st line imaging test)
- Findings:
  - U/S: hypoechoic enlarged pancreas (if ileus present, gas obscures pancreas)
  - CT: enlarged pancreas, edema, stranding changes in surrounding fat with indistinct fat planes, mesenteric and Gerota's fascia thickening, pseudocyst in lesser sac, abscess (gas or thick-walled fluid collection), pancreatic necrosis (low attenuation gas-containing non-enhancing pancreatic tissue), hemorrhage
- Management: supportive therapy
  - CT-guided needle aspiration and/or drainage done for abscess when clinically indicated
  - Pseudocyst may be followed by CT and drained if symptomatic

**Chronic Pancreatitis**
- Pathogenesis: (see *Gastroenterology, G45*)
- Best imaging modality: MRCP (can show calcification and duct obstruction)
- Findings: U/S, CT scan, and MRI may show calcifications, ductal dilatation, enlargement of the pancreas and fluid collections (e.g. pseudocysts) adjacent to the gland
Genitourinary System and Adrenal

Angiography of Gastrointestinal Tract

- anatomy of the GI tract arterial blood supply branches
  - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
  - superior mesenteric artery: jejunal, ileal, ileo-colic, right colic, middle colic
  - inferior mesenteric artery: left colic, superior rectal
- imaging modalities
  - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
    - flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
  - CT angiogram: modality of choice, non-invasive using IV contrast (no catheterization required)

Genitourinary System and Adrenal

Urological Imaging

KUB (Kidney, Ureter, and Bladder X-ray)
- a frontal supine radiograph of the abdomen
- indication: useful in evaluation of radio-opaque renal stones (all stones but uric acid and indinavir) indwelling ureteric stents/catheters, and foreign bodies in abdomen
- findings: addition of IV contrast excreted by the kidney (intravenous urogram) allows greater visualization of the urinary tract, but has been largely replaced by CT urography

Abdominal CT

Renal Masses
- Bosniak classification for cystic renal masses
  - class I-II: benign and can be disregarded
  - class III: should be followed
  - class III-IV: suspicious for malignancy, requiring additional workup

Table 12. Bosniak Classification for Cystic Renal Masses

<table>
<thead>
<tr>
<th>Classes</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Renal Cysts</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>Fluid-attenuating well-defined lesion no septation, no calcification, no solid components, hair thin wall</td>
</tr>
<tr>
<td>Class II</td>
<td>Same as class I + fine calcification or moderately thickened calcification in septae or walls also includes hyperdense cysts (&lt;3 cm) that do not enhance with contrast</td>
</tr>
<tr>
<td>Complex Renal Cysts</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>Thick irregular walls ± calcifications ± septated, enhancing walls or septa with contrast</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>Same as class III + soft tissue enhancement with contrast (defined as &gt;10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase ± areas of necrosis</td>
</tr>
</tbody>
</table>

- plain CT KUB indications: general imaging of renal anatomy, renal colic symptoms, assessment of renal calculi (size and location), and hydronephrosis prior to urological treatment
- CT urography indications: investigation of cause of microscopic/gross hematuria, detailed assessment of urinary tracts (excretory phase), high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts, assessment of renal calculi
  - phases: unenhanced, excretory
  - renal triphasic CT indications: standard imaging for renal masses, allows accurate assessment of renal arteries and veins, better characterization of suspicious renal masses, especially in differentiating renal cell carcinoma from more benign masses, and pre-operative staging
  - phases: unenhanced, arterial and venous (nephrographic), excretory

Ultrasound
- indications: initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic renal masses vs. complicated cysts); technique of choice for screening patients with suspected hydronephrosis (no IV contrast injection, no radiation to patient, and can be used in patients with renal failure); TRUS useful to evaluate prostate gland and guide biopsies; Doppler U/S to assess renal vasculature
- findings: solid renal masses are echogenic (bright on U/S), cystic renal masses have smooth well-defined walls with anechoic interior (dark on U/S), and complicated cysts have internal echoes within a thickened, irregular wall
Retrograde Pyelography
- **indications**: visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium, visualized by radiograph or fluoroscopy; ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction)
- **findings**: only yields information about the collecting systems (renal pelvis and associated structures), no information regarding the parenchyma of the kidney

Voiding Cystourethrogram
- bladder filled with contrast to the point where voiding is triggered
- fluoroscopy (continuous, real-time) to visualize bladder
- indications: children with recurrent UTIs, hydrenephrosis, hydroureret, suspected lower urinary tract obstruction or vesicoureteral reflux
- findings: contractility and evidence of vesicoureteric reflux

Retrograde Urethrogram
- a small Foley catheter placed into penile urethral opening
- indications: used mainly to study strictures or trauma to the male urethra; first-line study if trauma with blood present at urethral meatus

MRI
- **advantages**: high spatial and tissue resolution, lack of exposure to ionizing radiation and nephrotoxic contrast agents
- **indications**: indicated over CT for depiction of renal masses in patients with previous nephron sparing surgery, patients requiring serial follow-up (less radiation dosage), patients with reduced renal function, patients with solitary kidneys, clinical staging of prostate cancer (endorectal coil MRI)

Renal Nuclear Scan

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Uses</th>
<th>Radionuclide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renogram</td>
<td>Assess renal function and collecting system: evaluation of renal failure, workup of urinary tract obstruction and renovascular HTN, investigation of renal transplant</td>
<td>IV 99mTc-pentetate (DTPA) or mertidate (MAG3), and imaged at 1-3 s intervals with a gamma camera over the first 60 s to assess perfusion</td>
</tr>
<tr>
<td>Morphological</td>
<td>Assess renal anatomy: investigation of pyelonephritis and cortical scars</td>
<td>99mTc-DMSA, 99mTc-glucloheptonate</td>
</tr>
</tbody>
</table>

Gynecological Imaging

Ultrasound
- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air-containing loops of bowel
  - indications: good initial investigation for suspected pelvic pathology
- TVUS provides enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves at reduced distances
  - indications: improved assessment of ovaries, first trimester development, and ectopic pregnancies

Hysterosalpingogram
- performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent
- **indications**: useful for assessing pathology of the uterine cavity and fallopian tubes, evaluating uterine abnormalities (e.g. bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)

CT/MRI
- **indications**: evaluating pelvic structures, especially those adjacent to the adnexa and uterus
  - invaluable for staging gynecological malignancies and detecting recurrence

Sonohysterogram
- saline infusion sonohysterogram involves injecting fluid into the uterine cavity transcervically to provide enhanced endometrial visualization during TVUS examination
- indications: abnormal uterine bleeding, uterine cavity abnormalities that are suspected or noted on TVUS (e.g. leiomyomas, polyps, synchieae), congenital abnormalities of the uterine cavity, infertility, recurrent pregnancy loss
- contraindications: pregnancy, pelvic infection
Table 14. Typical and Atypical Findings on a Sonohysterogram

<table>
<thead>
<tr>
<th>Finding</th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>Mobile, thin, echogenic bands that cut across the endometrial cavity</td>
<td>Thick, broad-based bands that can completely obliterate the endometrial cavity, as in Asherman’s syndrome</td>
</tr>
<tr>
<td>Adhesions</td>
<td>Mobile, thin, echogenic bands that cut across the endometrial cavity</td>
<td>Thick, broad-based bands that can completely obliterate the endometrial cavity, as in Asherman’s syndrome</td>
</tr>
</tbody>
</table>

Table 15. Adrenal Mass Findings on CT and MRI

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adrenocortical Adenoma</th>
<th>Adrenocortical Carcinoma</th>
<th>Pheochromocytoma</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (CT)</td>
<td>Usually &lt;3 cm</td>
<td>Usually &gt;3 cm</td>
<td>Usually &gt;3 cm</td>
<td>Variable around &lt;3 cm</td>
</tr>
<tr>
<td>Shape (CT)</td>
<td>Smooth margins and round/oval</td>
<td>Irregular with unclear margins</td>
<td>Round/oval with clear margins</td>
<td>Oval/irregular with unclear margins</td>
</tr>
<tr>
<td>Texture (CT)</td>
<td>Homogeneous</td>
<td>Heterogeneous with mixed densities</td>
<td>Heterogeneous with cystic areas</td>
<td>Heterogeneous with mixed densities</td>
</tr>
<tr>
<td>Vascularity (CT)</td>
<td>Not highly vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
</tr>
<tr>
<td>Washout of Contrast Medium on CT</td>
<td>≥50% at 10 min</td>
<td>&lt;50% at 10 min</td>
<td>&lt;50% at 10 min</td>
<td>&lt;50% at 10 min</td>
</tr>
<tr>
<td>Growth Rate (cm/yr)</td>
<td>Stable or very slow (&lt;1 cm/yr)</td>
<td>Usually rapid (&gt;2 cm/yr)</td>
<td>Slow (0.5-1 cm/yr)</td>
<td>Variable</td>
</tr>
<tr>
<td>Other Findings</td>
<td>Usually low density due to intracellular fat</td>
<td>Necrosis, calcifications, and hemorrhage</td>
<td>Hemorrhage</td>
<td>Occasionally hemorrhage</td>
</tr>
<tr>
<td>MRI on T2 Weighted Imaging</td>
<td>Isointense in relation to liver</td>
<td>Hyperintense in relation to liver</td>
<td>Markedly hyperintense in relation to liver</td>
<td>Hyperintense in relation to liver</td>
</tr>
</tbody>
</table>

Modality Based on Neuropathology

- Cognitive decline = CT
- Cord compression = MRI
- Decreased level of consciousness = CT
- Fish bone/other swallowed foreign body = CT
- Low back pain, radiculopathy = MRI
- Multiple sclerosis = MRI
- Neck infection = CT
- Orbital infection = CT
- Rule out bleed = CT
- Rule out aneurysm = CTA, MRA
- Seizure = CT
- Sinusitis = CT
- Stroke = CT, MRI
- Trauma = CT
- Weakness, systemically unwell = CT

Adrenal Mass

- Imaging modality: most often identified on CT scan as ‘incidentaloma,’ can also use CT/MRI to distinguish benign from malignant masses

Neuroradiology

Modalities

- CT is the modality of choice for most neuropathology; even under circumstances where MRI is preferred, CT is frequently the initial study performed because of its speed, availability, and lower cost
- Acute head trauma: CT is best for visualizing “bone and blood”; MRI is used only when CT fails to detect an abnormality despite strong clinical suspicion
- Acute stroke: MRI ideal, CT most frequently used
- Suspected subarachnoid or intracranial hemorrhage
- Meningitis: rule out mass effect (e.g. cerebral herniation, shift) prior to lumbar puncture
- Tinnitus and vertigo: CT and MRI are used in combination to detect bony abnormalities and CN VIII tumors, respectively

Skull Films

- Rarely performed, generally not indicated for non-penetrating head trauma
- Indications: screening for destructive bony lesions (e.g. metastases), metabolic disease, skull anomalies, post-operative changes and confirmation of hardware placement, skeletal surveys, multiple myeloma

CT

- Indications: excellent study for evaluation of bony and intracranial abnormalities
- Often done first and then with IV contrast to show vascular structures or anomalies
- Vascular structures and areas of blood-brain barrier impairment are opaque (e.g. hyperattenuating or white/show enhancement) with contrast injection
- When in doubt, look for Circle of Willis or confluence of sinuses to determine presence of contrast enhancement
• posterior fossa can be obscured by extensive bony-related streak artifact
• rule out skull fracture, epidural hematoma (lenticular shape), subdural hematoma (crescentic shape), subarachnoid hemorrhage, space occupying lesion, hydrocephalus, and cerebral edema
• multiplanar imaging can be performed with newer generation of multidetector CT scanners

Myelography
• introduction of water-soluble, low-osmotic contrast media into subarachnoid space using lumbar puncture followed by x-ray or CT scan
• indications: excellent study for disc herniations, traumatic nerve root avulsions, patients with contraindication to MRI

MRI
• indications: shows brain and spinal soft tissue anatomy in fine detail, clearly distinguishes white from grey matter (especially T1-weighted series), multiplanar reconstruction helpful in pre-operative assessment

Cerebral Angiography/CT Angiography/MR Angiography
• indications: evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissection
• conventional digital subtraction angiography remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (femoral) puncture; catheter manipulation has risk of vessel injury (e.g. dissection, occlusion, vasospasm, emboli)
• MRA methods (phase contrast, time of flight, gadolinium-enhanced) and CTA are much less invasive without actual risk to intracranial or neck vessels
• MRA and CTA are often used first as ‘screening tests’ for the assessment of subarachnoid hemorrhage, vasospasm, aneurysms

Table 16. Two Types of Hydrocephalus

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicating/Extra-Ventricular</td>
<td>Obstruction distal to the ventricles (e.g. at the level of the arachnoid granulations); imaging shows all ventricles dilated</td>
</tr>
<tr>
<td>Non-Communicating</td>
<td>Obstruction within the ventricular system (e.g. mass obstructing the aqueduct or foramen of Monro); imaging shows dilatation of ventricles proximal to the obstruction</td>
</tr>
</tbody>
</table>

Nuclear Medicine
• SPECT using 99mTc-exametazime (HMPAO) and 99mTc-bisicat (ECD) imaging assesses cerebral blood flow by diffusing rapidly across the blood brain barrier and becoming trapped within neurons proportional to cerebral blood flow
• 18FDG PET imaging assesses cerebral metabolic activity
• indications: differentiation of residual tumour vs. radiation necrosis; localizing of epileptic seizure foci; evaluation of atypical dementia

Approach to CT Head
• think anatomically, work from superficial to deep
• scan: confirm that the imaging is of the correct patient, whether contrast was used, if the patient is aligned properly, if there is artifact present
• skin/soft tissue: examine the soft tissue superficial to the skull, looking for thickening suggestive of hematoma or edema; also evaluate the ear, orbital contents (globe, fat, muscles), parotid gland, muscles of mastication (masseter, temporalis, pterygoids), visualize pharynx
• bone and airspace (use the bone window): check calvarium, visualize mandible, visualize C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for opacity that may suggest fluid, pus, blood, tumour, or fracture; status of the orbital floor in cases of facial trauma (coronal series best)
Multiple Sclerosis (see Neurology, N52)
- best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
- findings
  - characteristic lesion on MRI is cerebral or spinal plaque
  - plaques typically found in periventricular region, corpus callosum (arranged at right angles to the corpus callosum) centrum semiovale, and to a lesser extent in deep white matter structures and basal ganglia
  - “Dawson’s fingers” refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  - plaques usually have ovoid appearance, hyperintense on T2 and hypointense on T1
  - conventional T2 may underestimate plaque size and overall plaque burden – advanced techniques (diffusion tensor imaging and MR spectroscopy) can be used

Selected Pathology
- see Neurosurgery, NS20 for intracranial mass lesions
- see Neurosurgery, NS29 and Plastic Surgery, PL29 for head trauma
- see Emergency Medicine, ER7 for vertebral trauma
- see Neurosurgery, NS27 and Orthopedics, OR22 for degenerative spinal abnormalities

Cerebrovascular Disease (see Neurology, N6 and Neurosurgery, NS17)
- pathogenesis of stroke: see Neurology, N48
- best imaging modality: infarcts best detected by MRI > CT

Table 17. Temporal Findings of Infarction with CT and MRI

<table>
<thead>
<tr>
<th>Time from Stroke Onset</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute (0-24 h)</td>
<td>Usually normal within 6 h</td>
<td>Hyperintensity on DWI within minutes of</td>
</tr>
<tr>
<td></td>
<td>Edema (loss of grey-white matter differentiation – “insular ribbon sign”, effacement of sulci, mass effect)</td>
<td>arterial occlusion due to restriction of water movement indicative of cytotoxic edema</td>
</tr>
<tr>
<td></td>
<td>Hyperattenuating artery “hyperdense MCA sign” representing intravascular thrombus/emboli may be seen in ischemic stroke</td>
<td>Hypointensity on ADC within minutes</td>
</tr>
<tr>
<td></td>
<td>Hyperattenuating acute blood surrounded by edema may be seen in hemorrhagic stroke</td>
<td>Hyperintensity upon T2/FLAIR approximately 6 h after onset due to edema (loss of grey-white matter differentiation, effacement of sulci, mass effect)</td>
</tr>
<tr>
<td>Acute (24 h-1 wk)</td>
<td>Increasing edema (seen as hypodensity) may result in significant positive mass effect</td>
<td>Continued hyperintensity on DWI</td>
</tr>
<tr>
<td>Subacute (1-3 wk)</td>
<td>Resolution of edema leads to increased attenuation of infarcted area that may regain near-normal density and mask stroke “fogging phenomenon”</td>
<td>Continued hyperintensity on DWI due to “T2 shine through”</td>
</tr>
<tr>
<td></td>
<td>Intensity on ADC continues to rise, pseudonormalizes at 10-15 d, and then surpasses that of sur-rounding normal tissue</td>
<td>Intensity on ADC continues to rise, pseudonormalizes at 10-15 d, and then surpasses that of sur-rounding normal tissue</td>
</tr>
<tr>
<td>Chronic (&gt;3 wk)</td>
<td>Encephalomalacia (parenchymal volume loss) appears as hypodensity with negative mass effect</td>
<td>Continued hyperintensity on T2/FLAIR</td>
</tr>
<tr>
<td></td>
<td>ADC intensity progressively decreases</td>
<td>Continued hyperintensity on T2/FLAIR</td>
</tr>
</tbody>
</table>

- carotid artery disease
  - best imaging modality: Duplex Doppler U/S
  - other modalities: MRA or CTA if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)

Multiple Sclerosis (see Neurology, N52)
- best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
- findings
  - characteristic lesion on MRI is cerebral or spinal plaque
  - plaques typically found in periventricular region, corpus callosum (arranged at right angles to the corpus callosum) centrum semiovale, and to a lesser extent in deep white matter structures and basal ganglia
  - “Dawson’s fingers” refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  - plaques usually have ovoid appearance, hyperintense on T2 and hypointense on T1
  - conventional T2 may underestimate plaque size and overall plaque burden – advanced techniques (diffusion tensor imaging and MR spectroscopy) can be of use
Musculoskeletal System

Modalities

- see Imaging Modalities, MI2 for advantages and disadvantages of the following

Plain Film/X-Ray
- usually initial study used in evaluation of bone and joint disorders
- indications: fractures and dislocations, arthritis, assessment of malalignment, orthopedic hardware, and bone tumours (initial)
- minimum of two films orthogonal to each other (usually AP and lateral) to rule out a fracture
- image proximal and distal joints, particularly important with paired bones (e.g. radius/ulna)
- minimally effective in evaluating soft tissue injury

CT
- evaluation of fine bony detail
- indications: assessment of complex, comminuted, intra-articular, or occult fractures including distal radius, scaphoid, skull, spine, acetabulum, calcaneus, and sacrum
- evaluation of soft tissue calcification/ossification

MRI
- indications: evaluation of internal derangement of joints (e.g. ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses

CNS Infections

- leptomeningitis
  - pathogenesis: inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via organisms gaining access across areas not protected by the blood-brain barrier (choroid plexus or circumventricular organs)
  - pathogens include: S. pneumoniae, H. influenzae, N. meningitidis, L. monocytogenes
  - best imaging modality: MRI (T2-weighted/FLAIR) superior to CT
  - findings:
    - meningeal enhancement (following the gyri/sulci and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
    - a normal MRI does not rule out leptomeningitis

- herpes simplex encephalitis (see Infectious Diseases, ID19)
  - pathogenesis: inflammation of the brain parenchyma secondary to infection with herpes simplex virus, asymmetrically affects the limbic regions of the brain (i.e. temporal lobes, orbitofrontal region, insula, and cingulate gyrus)
  - best imaging modality: MRI (T1- and T2 weighted)
  - findings:
    - acute (within 4-5 d): asymmetric high intensity lesions on T2 MRI in temporal and inferior frontal lobes strongly suggestive
    - DDx: infarct, tumour, status epilepticus, limbic encephalitis
    - CT may show low density in temporal lobe and insula; rarely basal ganglia involvement
    - long-term may show parenchymal loss to affected areas

- cerebritis/cerebral abscess
  - pathogenesis: an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms, commonly located in the distribution of the MCA
  - pathogens include: S. aureus (often in IV drug users, nosocomial), Streptococcus, Gram negative bacteria, Bacteroides
  - best imaging modality: MRI including DWI imaging series (abscess will be DWI positive); CT still used as a viable alternative
  - findings according to one of four stages of abscess formation
    - early cerebritis (1-3 d): inflammatory infiltrate with necrotic centre, low intensity on T1, high intensity on T2
    - late cerebritis (4-9 d): ring enhancement may be present
    - early capsule (10-13 d): ring enhancement
    - late capsule (14 d or greater): well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperintensity on T2

Figure 35. T2-weighted FLAIR: (A) sagittal (B) axial images of multiple sclerosis with periventricular “Dawson’s Fingers”

Figure 36. T2-weighted (FLAIR) coronal image of herpes simplex virus encephalitis affecting temporal lobes
Ultrasound
- indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection of soft tissue masses and to determine whether cystic or solid, detection of foreign bodies, U/S-guided biopsy and injections
- Doppler determines vascularity of structures

Nuclear Medicine (Bone Scintigraphy)
- determine the location and extent of bony lesions
  - ⁹⁹mTc-methylene diphosphonate localizes to areas of increased bone turnover or calcification – growth plate in children, tumours, infections, fractures, metabolic bone disease (e.g. Paget’s), sites of reactive bone formation, and periostitis
- advantages: very sensitive, capable of imaging entire body with relatively low dose radiation
- disadvantages: low specificity, not widely available due to special requirements (e.g. gamma camera, radiopharmaceuticals)

Approach to Bone X-Rays
- identification: name, MRN, age of patient, type of study, region of investigation
- soft tissues: swelling, calcification/ossification
- joints: alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, and symmetry of affected joint
- bone: periosteum, cortex, medulla, trabeculae, density articular surfaces, bone destruction, bone production, appearance of the edges or borders of any lesions

Trauma

Fracture/Dislocation
- description of fractures
- site of fracture (bone, region of bone, intra-articular vs. extra-articular)
- pattern of fracture line (simple vs. comminuted)
- displacement (distal fragment with reference to the proximal fragment)
- soft tissue involvement (calcification, gas, foreign bodies)
- type of fracture (stress vs. pathologic)
- for specific fracture descriptions and characteristics of fractures, see Orthopedics, OR4

Arthritis

Radiographic Hallmarks of Osteoarthritis
- joint space narrowing – typically non-uniform
- subchondral sclerosis
- subchondral cyst formation
- osteophytes

Radiographic Hallmarks of Rheumatoid Arthritis
- joint space narrowing – typically uniform
- soft tissue swelling
- erosions
- periarticular osteopenia

Bone Tumour

Approach
- metastatic tumours to bone are much more common than primary bone tumours, particularly if age >40 yr
  - diagnosis usually requires a biopsy if primary not located
  - few benign tumours/lesions have potential for malignant transformation
  - MRI is good for tissue delineation and pre-operative assessment of surrounding soft tissues, neurovascular structures, and medullary/marrow involvement
  - plain film is less sensitive than other modalities but useful for assessing aggressiveness and constructing differential diagnosis

Considerations and Tumour Characteristics
- for specific bone tumours, see Orthopedics, OR45
- age: most common tumours by age group
  - <1 yr of age: metastatic neuroblastoma
  - 1-20 yr of age: Ewing’s sarcoma in tubular bones
  - 10-30 yr of age: osteosarcoma and Ewing’s tumour in flat bones
  - >40 yr of age: metastases, multiple myeloma, and chondrosarcoma
- multiplicity: metastases, myeloma, lymphoma, fibrous dysplasia, enchondromatosis
- location within bone
  - epiphysis: giant cell tumour, chondroblastoma, geode, eosinophilic granuloma, infection
  - metaphysis: simple bone cyst, aneurysmal bone cyst, enchondroma, chondromyxoid fibroma, nonossifying fibroma, osteosarcoma, chondrosarcoma
  - diaphysis: fibrous dysplasia, aneurysmal bone cyst, brown tumours, eosinophilic granuloma, Ewing’s sarcoma

Figure 37. X-ray of first carpometacarpal joint: normal image (left) and osteoarthritis (right) with joint space narrowing and subchondral sclerosis

Figure 38. Rheumatoid arthritis (A) compared with osteoarthritis (B) changes on X-ray
• expansile
  - aneurysmal bone cyst, giant cell tumour, enchondromas, brown tumours, metastases (especially renal and thyroid), plasmacytoma
• matrix mineralization
  - chondroid (popcorn calcification) or osseous
• margin/zone of transition: area between lesion and normal bone
• cortex: intact, disturbed
• periosteal reaction: onion-skinning, sunburst, Codman’s triangle, periosteal neocortex
• soft tissue mass

![Figure 39. Radiographic appearance of bone remodelling and destruction processes](image)

**Table 18. Characteristics of Benign and Malignant Bone Lesions**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin sclerotic margin/sharp delineation of lesion</td>
<td>Poor delineation of lesion – wide zone of transition</td>
</tr>
<tr>
<td>Overlying cortex intact</td>
<td>Loss of overlying cortex/bony destruction</td>
</tr>
<tr>
<td>No or simple periosteal reaction</td>
<td>Periosteal reaction</td>
</tr>
<tr>
<td>No soft tissue mass</td>
<td>Soft tissue mass</td>
</tr>
</tbody>
</table>

**Metastatic Bone Tumours**

- all malignancies have potential to metastasize to bone
- metastases are 20-30x more common than primary bone tumours
- metastasis can cause a lytic or a sclerotic reaction when seeding to bone
- when a primary malignancy is first detected, a bone scan is often part of the initial workup
- may present with pathological fractures or pain
- biopsy or determination of primary is the only way to confirm the diagnosis
- most common metastatic bone tumours: breast, prostate, lung, see Orthopedics, OR45

**Table 19. Characteristic Bone Metastases of Common Cancers**

<table>
<thead>
<tr>
<th>Lytic</th>
<th>Sclerotic</th>
<th>Expansile</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Prostate</td>
<td>Thyroid</td>
<td>Kidney</td>
</tr>
<tr>
<td>Lung</td>
<td>Breast</td>
<td>Renal</td>
<td>Lung</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Lymphoma</td>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td>Kidney</td>
<td>Lung</td>
<td>(KLM: flies to the periphery)</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bowel</td>
<td>Medulloblastoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treated tumours</td>
<td></td>
</tr>
</tbody>
</table>

**Infection**

**Osteomyelitis**

- MRI is the imaging modality of choice for demonstrating bone, bone marrow, and soft tissue abnormalities
- $^{99m}$Tc, followed by $^{111}$In-labeled white cell scan or gallium radioisotope scan
- plain film changes visible 8-10 d after process has begun
  - soft tissue swelling
  - local periosteal reaction
  - pockets of air (from anaerobes) may be seen in the tissues, may also suggest necrotizing fasciitis
  - mottled and nonhomogeneous with a classic “moth-eaten” appearance
  - cortical destruction

**Benign Lesions which may have Aggressive Features**

- Osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Myositis ossificans

**Periosteal Reaction**

- “Onion skinning” = Ewing’s sarcoma
- “Sunburst”, “hair on end” = osteosarcoma
- “Codman’s triangle” = osteosarcoma, Ewing’s sarcoma, subperiosteal abscess
Bone Abscess
- overlying cortex has periosteal new bone formation
- sharply outlined radiolucent area with variable thickness in zone of transition
- variable thickness periosteal sclerosis
- sequestrum: a piece of dead bone within a Brodie's abscess
- a sinus tract or cloaca may communicate between the abscess through the cortex to the surface of the bone
- best modality: MRI for bone, bone marrow, and soft tissue abnormalities; CT for sequestra and cortical erosions

Metabolic Bone Disease

Osteoporosis
- reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
- DEXA: gold standard for measuring bone mineral density
  - T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - osteopenia: $-2.5 < \text{T-score} < -1$
    - osteoporosis: $\text{T-score} \leq -2.5$
  - Z-score: the number of standard deviations from the age-matched mean
  - risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy
  - diagnostic sensitivity of DEXA highest when bone mineral density measured at lumbar spine and proximal femur
- appearance on plain film
  - osteopenia: reduced bone density on plain films
  - may also be seen with osteomalacia, hyperparathyroidism, and disuse
  - compression of vertebral bodies
  - biconcave vertebral bodies ("codfish" vertebrae)
  - long bones have appearance of thinned cortex and increased medullary cavity
  - look for complications of osteoporosis (e.g. insufficiency fractures: hip, vertebrae, sacrum, pubic rami)
- see Endocrinology, E40

Osteomalacia/Rickets
- reduction in bone mineral density; normal amount of bone but reduced mineralization of normal osteoid
- usually due to vitamin D deficiency, resulting in softening and bowing of long bones
- similar to osteoporosis, initial radiological appearance of osteopenia (coarse and poorly defined bone texture)
  "fuzzy", ill-defined trabeculae
- Looser’s zones (pseudofracture)
  - characteristic radiologic feature
  - fissures or clefts at right angles to long bones and extending through cortex
  - DDx: chronic renal disease, fibrous dysplasia, hyperparathyroidism, Paget’s, osteodystrophy, X-linked hypophosphatemia

Figure 40. Osteomalacia, osteopenia, and osteoporosis
**Hyperparathyroidism**
- most common cause is renal failure (secondary hyperparathyroidism)
- chondrocalcinosis
- calcium crystal deposition in hyaline cartilage or fibrocartilage (including arteries and peri-articular soft tissue)
- resorption of bone typically in hands (subperiosteal and at tufts), sacroiliac joints (subchondral), skull (“salt and pepper” appearance), osteoclastoma (brown tumours)
- "rugger jersey spine": band-like osteosclerosis at superior/inferior margins of vertebral bodies

**Paget’s Disease**
- abnormal remodelling involving single or multiple bones – especially skull, spine, pelvis
- 3 phases: 1st phase = lytic, 2nd phase = mixed (lytic/sclerotic), 3rd phase = sclerotic
- features
  - coarsening of the trabeculae with bone expansion
  - bone softening/bowing
  - bone scan will reveal high activity, especially at bone ends
  - thickened cortex
- see Endocrinology, E44

**Nuclear Medicine**

**Brain**
- 99mTc-exametazime (HMPAO) and 99mTc-bicsate (ECD) imaging used in SPECT to assess cerebral blood flow and cellular metabolism, taken up predominantly in grey matter
  - used for dementia, traumatic brain injury, and to a lesser extent vasculitis, neuropsychiatric disorders, and occasionally stroke
  - most commonly used tracers to confirm brain death (i.e. absent blood flow to the brain and absent uptake on delayed planar and SPECT images in brain and brainstem, assuming study is technically adequate)
  - either tracer can be used for seizure imaging to assess for the most likely location of epileptogenic focus but usually must be made available for 24 h and the patient followed by a nurse who is competent to administer the activity at the time of seizure
- PET imaging assesses metabolic activity most commonly with 18FDG; used for dementia imaging, grade and stage of brain tumours, occasionally for seizure disorder imaging, and vasculitis; PET imaging with amyloid tracers for diagnosis of Alzheimer’s disease is becoming more common
- CSF imaging, intrathecal administration of 111In DTPA to evaluate CSF leak or to differentiate normal pressure hydrocephalus from brain atrophy
- CSF shunt evaluation for obstruction (most commonly ventriculoperitoneal) with sterile or pyrogen free 99mTc (usually) or 111In-DTPA; small quantity of activity is injected into the reservoir under sterile conditions and should flow freely into the peritoneal cavity by 45 min; maneuvers such as pumping the shunt, sitting the patient upright or ambulating are acceptable to encourage flow during this time
- adrenergic imaging of the heart with MIBG has been used to differentiate dementias with autonomic dysfunction (i.e. Lewy Body and Parkinson’s disease) from other forms of dementia (i.e. autonomic impairment associated with decreased MIBG activity in the heart)

**Thyroid**

**Radioactive Iodine Uptake** (see Endocrinology, E21)
- index of thyroid function (trapping and organification of iodine)
- radioactive 131I given PO to fasting patient (small quantity)
- measure percentage of administered iodine taken up by thyroid
- increased RAU: toxic multinodular goitre, toxic adenoma, Graves’ disease
- decreased RAU: subacute thyroiditis, late Hashimoto’s disease, exogenous thyroid hormone or iodine, falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed, taking a “thyroid vitamin”)
- important – iodine uptake helps in the differential of hyperthyroidism only, not hypothyroidism (exception is pediatrics)

**Thyroid Imaging (Scintiscan)**
- 99mTc-pertechnetate IV or radioactive iodine (123I); most Canadian sites use pertechnetate to reduce cost
- provides functional anatomic detail
- hot (hyperfunctioning) lesions: usually benign (e.g. adenoma, toxic multinodular goitre), cancer very unlikely (less than 1%)
- cold (hypofunctioning) lesions: cancer must be considered until biopsy negative even though only 6-10% are cancerous; decision to biopsy should be based on clinical and sonographic features
- isointense i.e. “warm” lesions: cancer must be considered as an isointense lesion may represent cold nodules superimposed on normal tissue; if cyst suspected, correlate with U/S

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Figure 41. Multinodular goitre (top). Cold nodule (bottom)
Radioiodine Ablation
- $^{131}$I for Graves' disease, multinodular goitre, thyroid cancer (in the case of thyroid cancer, ablation performed at higher dose and after thyroidectomy)
- serum thyroglobulin used to detect recurrent thyroid cancer in a patient that has received ablation
- advice should be given for patient-specific precautions to remain away from family members and caregivers to reduce radiation exposure after thyroid ablation, do not initiate pregnancy for 6 mo, small risk of exophthalmos, thyroid storm, secondary malignancy

Pediatric Hypothyroidism
- pertechnetate thyroid scan can differentiate thyroid agenesis, hemiagenesis, lingular thyroid, organization defect, however should not wait for a diagnosis to start thyroid hormone replacement in a neonate; start immediately

Respiratory
V/Q Scan
examine areas of lung in which ventilation and perfusion do not match
- ventilation scan
  - patient breathes radioactive gas (nebulized $^{99m}$Tc-DTPA, $^{133}$Xe, or most commonly Technegas) through a closed system, filling alveoli proportionally to ventilation
  - ventilation scan defects indicate: airway obstruction (i.e. air trapping), chronic lung disease, bronchospasm, tumour mass obstruction
- perfusion scan
  - radiotracer injected IV ($^{99m}$Tc-MAA) → trapped in pulmonary capillaries (0.1% of arterioles occluded) according to blood flow
  - relatively contraindicated in severe pulmonary HTN, right-to-left shunt, previous history of pneumonectomy, small child. In these cases fewer particles are usually given
- to rule out PE
  - indications: some institutions favour in pregnancy (lower radiation dose to breast than CT), or where CT contrast contraindicated (e.g. contrast allergy, renal failure)
  - areas of lung that are well-ventilated but not perfused (unmatched defect) are suspicious for acute infarction
  - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
  - often reported as high probability (> 2 large i.e. segmental mismatched perfusion defects), intermediate, low, very low, or normal according to modified PIOPED II criteria although now are increasingly reported as PE present, indeterminate or normal
  - useful in finding clinically important emboli
  - decreased detection of incidentalomas commonly found on CT
- not valid for assessment of PE when patients have consolidation and the test can be limited by ventilatory problems (e.g. COPD), much like CT
- modified V/Q scan (perfusion only, lower dose contrast) may be used for pregnant patients if CXR is normal or if there are ventilatory problems

Myocardial Perfusion Scanning
- to investigate coronary artery disease (CAD), assess treatment of CAD pre-op risk stratification, viability testing
- $^{99m}$Tc-sestamibi, or $^{99m}$Tc-tetrofosmin are used most commonly; thallium 201 was used previously but largely discontinued due to high radiation doses to patients and unfavourable imaging characteristics; today thallium still used for viability studies
- injected at peak exercise (85% max predicted heart rate by the Bruce protocol, chest pain, ECG changes) or after persantine challenge (vasodilator), or after dobutamine infusion (chronotropic, again to 85% predicted heart rate); can be done as stress only protocol with optional rest or as stress and rest combined protocol (i.e. as 1 day or 2 day protocol)
- patients with left bundle usually given pharmacologic stress because ECG is difficult to interpret for ST changes and avoids a characteristic artifact
- pharmacologic stress contraindicated if sBP is <90; persantine exacerbates asthma, so patients with asthma and wheeze who cannot exercise usually get dobutamine infusion; reverse persantine with aminophylline or caffeine
- persistent defect (at rest and stress) suggests infarction or myocardial scar; reversible defect (only during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- Courage trial indicates that patients with >10% ischemic myocardium benefit most from revascularization
- see Cardiology and Cardiac Surgery C13
Radionuclide Ventriculography
• $^{99m}$Tc-tagged to red blood cells, tagged albumin is also acceptable
• first pass through RV $\rightarrow$ pulmonary circulation $\rightarrow$ LV; provides information about RV function, presence of shunts
• cardiac MUGA scan sums multiple cardiac cycles, usually at least 200 beats
• evaluation of LV function and regional wall motion, ejection fraction
• images are obtained by gating (synchronizing) the count acquisitions to the ECG signal
• can assess diastolic dysfunction
• provides information on ejection fraction (normal = 50-65%), ventricular volume, and wall motion
• indications: most commonly to monitor potential cardiac toxicity with chemotherapy or herceptin, as a gold standard of ejection fraction in defibrillator workup

Abdomen and Genitourinary System

HIDA Scan (Cholescintigraphy)
• IV injection of $^{99m}$Tc-disofenin (DISIDA) or $^{99m}$Tc-mebrofenin which is bound to protein, taken up, and excreted by hepatocytes into biliary system
• can be performed in non-fasting state but prefer NPO after midnight
• indicated in workup of cholecystitis when abdominal ultrasound result is equivocal:
  • acute cholecystitis: no visualization of gallbladder at 4 h or 1 h after administration of morphine
  • chronic cholecystitis: no visualization of gallbladder at 1 h but seen at 4 h or after morphine administration
• gallbladder visualized when cystic duct is patent (rules out acute cholecystitis with >99% certainty), usually seen by 30 min-1 h
• differential diagnosis of obstructed cystic duct: acute/chronic cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting less than 4 h or more than 24 h
• also used to assess bile leaks post-operatively or in trauma
• gallbladder ejection fraction (>38% is normal) can be measured after a fatty meal or CCK to assess for biliary dyskinesia

RBC Scan
• IV injection of radiotracer with sequential images of the abdomen ($^{99m}$Tc RBCs)
• GI bleed
  • if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed, look for a change in shape and location on sequential image, requires active bleeding to localize
  • if bleeding acutely at >0.5 mL/min, use angiography (more specific)
• liver lesion evaluation
  • hemangioma has characteristic appearance: cold early (limited blood flow to lesion), fills later (accumulation of tagged cells greater than surrounding liver parenchyma)

Other Important Nuclear Medicine Abdominal Tests
• Meckel's Scan: uses $^{99m}$m pertechnetate; give patient ranitidine premedication; Meckel's diverticulum contains gastric mucosa which will light up at the same time as the stomach and get brighter with time like stomach
• $^{111}$In octreoscan: a somatostatin analog used for evaluation and staging of neuroendocrine tumours including carcinoid; gastrinoma and carcinoid tend to be more octreotide avid than insulinoma.
• iodinated MIBG: a norepinephrine analogue, used for pheochromocytoma, neuroblastoma and medullary thyroid cancer most commonly; limited cardiac applications as above
• solid and liquid gastric emptying: a standardized solid or liquid meal is labelled, usually with $^{99m}$Tc sulfur colloid and gastric emptying studied over time. There are normal ranges for solids and liquids

Urea Breath Test
• indication: diagnosis of gastric Helicobacter pylori infection
• patient administered 14C-labelled urea orally, urea metabolized by H. pylori to ammonia and $^{14}$CO$_2$, $^{14}$C-labelled CO$_2$ is measured via plastic filament detectors or liquid scintillation

Functional Renal Imaging
• evaluation of renal function and anatomy using $^{99m}$Tc DTPA or $^{99m}$Tc MAG3
• frequently used to provide index of relative function between two kidneys
• frequently used in adults to assess for UPJ obstruction (by assessing the clearance half time with lasix), and assess renal transplants or as a nuclear GFR study in patients wanting to donate kidneys
• in children, imaging with $^{99m}$Tc DMSA is used to assess for pyelonephritis
• in children, the injection of tracer into the bladder via foley catheter is often used to assess for reflux
Bone Scan
- isotopes, usually 99mTc-diphosphonate
- radioactive tracer binds to hydroxyapatite of bone matrix
- increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
- indications: bone pain of unknown origin, staging or restaging of cancer with bone mets (or primary bone cancer), imaging of arthroplasty complications like loosening or infection, osteomyelitis imaging
- when used to assess for osteomyelitis, usually done in combination with gallium or white blood cell scan
- differential diagnosis of positive bone scan: bone metastases (breast, prostate, lung, thyroid), primary bone tumour, arthritis, fracture, infection, anemia, Paget's disease
- lytic lesions like multiple myeloma, renal cell cancer, eosinophilic granuloma: typically normal or cold (false negative); need a skeletal survey
- "superscan": increased bone uptake and poor renal uptake due to diffuse metastases (breast, prostate) or metabolic causes (e.g. renal osteodystrophy)

Interventional Radiology

Vascular Procedures

Angiography
- injection of contrast material through a catheter placed directly into an artery or vein to delineate vascular anatomy
- catheter can be placed into a large vessel (e.g. aorta, vena cava) for a "flush" or selectively placed into a branch vessel for more detailed examination of smaller vessels and specific organs
- indications: diagnosis of primary occlusive or stenotic vascular disease, aneurysms, coronary, carotid and cerebral vascular disease, PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (endovascular aneurysm repair, thrombolysis, stenting, and angioplasties)
- complications (<5% of patients): puncture site hematoma, infection, pseudoaneurysm, AV fistula, dissection, thrombosis, embolic occlusion of a distal vessel
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (colour Doppler U/S, CTA, and MRA)
- see Neuroradiology, MI18

Percutaneous Transluminal Angioplasty and Stents
- introduction and inflation of a balloon into a stenosed or occluded vessel to restore distal blood supply
- common alternative to surgical bypass grafting with 5yr patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary, and carotid artery stenoses are amenable to treatment
- vascular stents may help improve long-term results by keeping the vessel wall patent after angioplasty; also used for angioplasty failure or complications
- stent grafts (metal mesh covered with durable fabric) may provide an alternative treatment option for AV fistulas
- complications: similar to angiography, but also includes vessel rupture

Thrombolytic Therapy
- may be systemic (IV) or catheter directed
- infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
- can restore blood flow in a vessel obstructed with a thrombus or embolus
- indications: treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of venous thromboembolism (DVT or PE)
- complications: bleeding, stroke, distal embolus, reperfusion injury with myoglobinuria and renal failure if advanced ischemia present

Embolization
- injection of occluding material into vessels
- permanent agents: amplatzer plugs, coils, glue, and onyx
- temporary: gel foam, autologous blood clots
- indications: management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of arteriovenous malformation, pre-operative treatment of vascular tumours (bone metastases, renal cell carcinoma), varicocele embolization for infertility, symptomatic uterine fibroids
- complications: post-embolization syndrome (pain, fever, leukocytosis), unintentional embolization of a non-target organ with resultant ischemia

Thrombolytic Therapy for Pulmonary Embolism

Purpose: To assess the effects of thrombolytic therapy in patients with acute pulmonary embolism (PE).

Methods: Systematic review of RCTs evaluating thrombolytic therapy followed by heparin versus heparin alone, heparin plus placebo or surgical intervention in patients with acute PE. Studies comparing two different thrombolytic agents or different doses of the same thrombolytic drug were not considered eligible. Main outcomes of interest were death, recurrence of PE, and major and minor hemorrhagic events.

Results: Eighteen trials with 2,197 participants were included. Thrombolytics plus heparin were associated with a reduction in odds of death relative to heparin alone or heparin plus OR 0.57, 95% CI 0.37 to 0.87, P = 0.02) and recurrence of PE (OR 0.53, 95% CI 0.39 to 0.78, P < 0.001). Length of hospital stay (mean difference (MD) 1.35, 9.27 to 1.58) and quality of life were similar between groups. Based on one study, stroke occurred more often in the thrombolytics group (OR 12.10, 1.57 to 93.39).

Conclusion: Low-quality evidence suggests thrombolytics reduce death following acute PE compared with heparin and may be helpful in reducing PE recurrence, but may cause more major and minor hemorrhagic events and stroke events.
Inferior Vena Cava Filter
- insertion of temporary or permanent metallic “umbrellas” to mechanically trap emboli and prevent PE
- inserted via femoral, jugular, or antecubital vein
- usually placed infrarenally to avoid renal vein thrombosis
- indications: contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation

Central Venous Access
- variety of devices available
- PICC, external tunneled catheter (Hickman or dialysis catheters), subcutaneous port (Portacath™)
- indications: chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
- complications: venous thrombosis, central venous stenosis, infection including sepsis, and pneumothorax

Nonvascular Interventions

Percutaneous Biopsy
- replaces open surgical procedure
- many sites are amenable to biopsy using U/S, fluoroscopy, CT or MR guidance
- complications: false negative (sampling error or tissue necrosis), pneumothorax in 30% of lung biopsies (chest tube required in ~5%), acute pancreatitis (pancreatic biopsies), bleeding from liver biopsies in patients with uncorrectable coagulopathies or ascites (can be minimized with transjugular approach)

Abscess Drainage
- placement of a drainage catheter into an infected fluid collection
- administer broad spectrum IV antibiotics prior to procedure
- routes: percutaneous (most common), transgluteal, transvaginal, transrectal
- complications: hemorrhage, injury to intervening structures (e.g. bowel), bacteremia, sepsis

Percutaneous Biliary Drainage/Cholecystostomy
- placement of drainage catheter ± metallic stent into obstructed biliary system (PBD) or gallbladder (cholecystostomy) for relief of jaundice or infection
- percutaneous gallbladder access can be used to crush or remove stones
- indications
  - cholecystostomy: acute cholecystitis
  - PBD biliary obstruction secondary to stone or tumour, cholangitis
- complications
  - acute: sepsis, hemorrhage
  - long-term: tumour ingrowth and stent occlusion

Percutaneous Nephrostomy
- placement of catheter into renal collecting system
- indications: hydronephrosis, pyonephrosis, ureteric injury with or without urinary peritonitis (traumatic or iatrogenic)
- complications: bacteria and septic shock, hematuria due to pseudoaneurysm or AV fistulas, injury to adjacent organs

Gastrostomy/Gastrojejunostomy
- percutaneous placement of catheter directly into either stomach (gastrostomy) or through stomach into small bowel (transgastric jejunostomy)
- indications: inability to eat (most commonly CNS lesion, e.g. stroke), esophageal obstruction, or decompression in gastric outlet obstruction
- complications: gastroesophageal reflux with aspiration peritonitis, hemorrhage, bowel or solid organ injury

Radiofrequency Ablation
- U/S- or CT-guided probe is inserted into tumour, radiofrequency energy delivered through probe causes heat deposition and tissue destruction
- indications: hepatic tumours (HCC and metastases), renal tumours
- complications: destruction of neighbouring tissues and structures, bleeding
**Breast Imaging**

**Modalities**

**Mammography**

**Description**
- x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities (see General Surgery, GS56)
- routine evaluation involves two standard views: cranio-caudal and medial-lateral-oblique

**Indications**
- screening
  - begin screening from age 50 q2-3yr
  - no strong data to support screening >70 yr, but may continue screening if in good general health
  - if <50, screening is only recommended for those with high risk of breast cancer
  - screening detects 2-8 cancers/1,000 women screened
- surveillance
  - follow-up of women with previous breast cancer
- diagnostic: includes mammography with special views and/or ultrasound
  - workup of an abnormality that may be suggestive of breast cancer including a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, and spontaneous serous or sanguinous nipple discharge from a single duct
  - women with abnormal screening mammograms
  - suspected complications of breast implants

**Table 20. Breast Imaging Reporting and Data System (BI-RADS®) Mammography Categories**

<table>
<thead>
<tr>
<th>Assessment Categories</th>
<th>Imaging Findings</th>
<th>Follow-Up Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS 0</td>
<td>Incomplete</td>
<td>Additional imaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison to prior films</td>
</tr>
<tr>
<td>BI-RADS 1</td>
<td>Negative</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 2</td>
<td>Benign</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 3</td>
<td>Probably benign</td>
<td>Unilateral mammogram at 6 mo</td>
</tr>
<tr>
<td></td>
<td>Likelihood of malignancy is &lt;2%</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 4</td>
<td>Suspicious abnormality</td>
<td>Biopsy</td>
</tr>
<tr>
<td>BI-RADS 5</td>
<td>Highly suspicious of malignancy</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Likelihood of malignancy is 95%</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 6</td>
<td>Malignancy confirmed by biopsy</td>
<td>Definitive therapy</td>
</tr>
</tbody>
</table>

**Breast Ultrasound**

**Indications**
- characterization of palpable abnormalities
  - ultrasound is 1st line <30 yr and in lactating and pregnant women
  - >30 yr need mammogram first
- further characterization of mammographic findings
- guidance for interventional procedures

**Breast MRI**

**Description**
- contrast-enhanced MRI of the breasts
- sensitive for detecting invasive breast cancer (95-100%) but specificity variable (37-97%)
- for diagnosis, used only after mammography and U/S investigation
- use as a screening modality is limited to high-risk patients, in conjunction with mammography

**Indications**
- “problem-solving” of indeterminate findings following complete mammographic and ultrasound workup
- evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
- evaluation of previously diagnosed breast cancer: positive margins, recurrence, response to chemotherapy
• high-risk screening
  • known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer, or untested first-degree relative of a carrier of such a gene mutation
  • family history consistent with a hereditary breast cancer syndrome and/or estimated personal lifetime cancer risk >25%
  • high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ)
  • radiation therapy to chest (before age 30)

**Breast Intervventional Procedures**

**Description**
• includes fine needle aspirate biopsy, core needle biopsy, stereotactic biopsy, MRI guided biopsy, abscess drainage, and cyst aspiration (see General Surgery, GS59)

**Indications**
• cystic mass: complex cyst, symptomatic, suspected abscess
• solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5)
• suspicious calcifications: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) – stereotactic biopsy
• initial percutaneous biopsy procedure that was insufficient or discordant with imaging
• presurgical wire localization of a lesion

**Breast Findings**

**Breast Masses**
• **definition:** a space-occupying lesion seen in two different projections; if seen in only a single projection it should be called an “asymmetry” until its three-dimensionality is confirmed

<table>
<thead>
<tr>
<th>Table 21. Mammographic Features of Benign and Malignant Breast Masses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Margin</td>
</tr>
<tr>
<td>Density</td>
</tr>
<tr>
<td>Calcifications (± mass)</td>
</tr>
</tbody>
</table>

**Other Findings**
• tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
• intramammary lymph node: typical lymph nodes are circumscribed, reniform and often have a fatty notch and centre; usually less than 1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty centre or notch) are well seen, the lesion is almost always benign and insignificant
• focal asymmetry: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
• if focal compression shows mass-like character – or if the area can be palpated – biopsy generally recommended
References


Canadian Association of Radiologists (CAR) standard for breast imaging. Ottawa: Canadian Association of Radiologists, 1998.


Acronyms ............................................. 2
Basic Anatomy Review .......................... 2
Anatomy of the Kidney
Renal Structure and Function
Renal Hemodynamics
Assessment of Renal Function .......... 5
Measurement of Renal Function
Urinalysis
Urine Microscopy
Urine Biochemistry
Electrolyte Disorders ..................... 7
Sodium Homeostasis
Hyponatremia
Hypernatremia
Diabetes Insipidus
Potassium Homeostasis
Hypokalemia
Hyperkalemia
Hyperphosphatemia
Hypophosphatemia
Hypermagnesemia
Hypomagnesemia
Acid-Base Disorders .................... 15
Metabolic Acidosis
Metabolic Alkalosis
Acute Kidney Injury ..................... 18
Approach to AKI
Parenchymal Kidney Diseases .......... 19
Glomerular Diseases
Glomerular Syndromes
Tubulointerstitial Disease
Vascular Diseases of the Kidney
Analgescic Nephropathies
Systemic Disease with Renal Manifestation 31
Diabetes
Scleroderma
Multiple Myeloma
Malignancy
Chronic Kidney Disease ............. 33
Management of Chronic Kidney Disease
Hypertension ......................... 35
Hypertensive Nephrosclerosis
Renovascular Hypertension
Renal Parenchymal Hypertension
Cystic Diseases of the Kidney .......... 35
Adult Polycystic Kidney Disease
Autosomal Recessive Polycystic Kidney Disease
Medullary Sponge Kidney
End Stage Renal Disease ............. 37
Presentation of End Stage Renal Disease
Renal Replacement Therapy .......... 38
Dialysis
Renal Transplantation
Common Medications ............. 39
Landmark Nephrology Trials ........ 40
References ....................... 42
Acronyms

ACEI angiotensin converting enzyme
ACEI angiotensin-converting enzyme inhibitor
ACR albumin to creatinine ratio
ADH antidiuretic hormone
AG anion gap
AIN acute interstitial nephritis
AKI acute kidney injury
ANA antinuclear antibody
ARB angiotensin receptor blocker
ASA acetylsalicylic acid
ASOT anti-streptolysin-O titer
ATN acute tubular necrosis
AVM arteriovenous malformation
c-ANCA cytoplasmic antineutrophil cytoplasmic antibody
C&S culture and sensitivity
CHF congestive heart failure
CKD chronic kidney disease
Ct creatinine
cr creatinine clearance
DDAVP 1-desamino-8-d-arginine vasopressin
DI diabetes insipidus
DIC disseminated intravascular coagulation
DM diabetes mellitus
D5W 5% dextrose in water
DCT distal convoluted tubule
DDAVP 1-desamino-8-d-arginine vasopressin
HCTZ hydrochlorothiazide
HPS Henoch-Schönlein purpura
HTN hypertension
HUS hemolytic uremic syndrome
INA intravenous pyelogram
LOC level of consciousness
MDRD modification of diet in renal disease
NS normal saline
p-ANCA perinuclear anti-neutrophil cytoplasmic antibody
PCKD polycystic kidney disease
Pt parathyroid hormone
R&R routine and microscopy
RAAS renin-angiotensin-aldosterone system
RBF renal blood flow
RFP renal plasma flow
RCC renal cell carcinoma
RPGN rapidly progressive glomerulonephritis
RRT renal replacement therapy
RTA renal tubular acidosis
SIADH syndrome of inappropriate antidiuretic hormone
SLE systemic lupus erythematosis
TBW total body water
TIN tubulointerstitial nephritis
TTP thrombotic thrombocytopenic purpura
UAG urine anion gap
UTI urinary tract infection

Basic Anatomy Review

Anatomy of the Kidney

- see Urology, U2

Renal Structure and Function

The Nephron
- basic structural and functional unit of the kidney, approximately 1 million per kidney
- 2 main components: glomerulus and attached renal tubule
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

Table 1. Major Kidney Functions

<table>
<thead>
<tr>
<th>Function</th>
<th>Mechanism</th>
<th>Affected Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Waste Excretion</td>
<td>Glomerular filtration</td>
<td>Excretion of nitrogenous products of protein metabolism (urea, Cr)</td>
</tr>
<tr>
<td></td>
<td>Tubular secretion</td>
<td>Excretion of organic acids (urate) and organic bases (Cr)</td>
</tr>
<tr>
<td></td>
<td>Tubular catabolism</td>
<td>Breakdown and excretion of drugs (antibiotics, diuretics) and peptide hormones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(most pituitary hormones, insulin, glucagon)</td>
</tr>
<tr>
<td>2. Electrolyte Balance and Osmoregulation</td>
<td>Tubular NaCl and water reabsorption</td>
<td>Controls volume status and osmolar balance</td>
</tr>
<tr>
<td></td>
<td>Tubular K⁺ secretion</td>
<td>Controls potassium concentration</td>
</tr>
<tr>
<td></td>
<td>Tubular H⁺ secretion</td>
<td>Acid-base balance</td>
</tr>
<tr>
<td></td>
<td>Tubular Ca²⁺, Mg²⁺, PO₄³⁻ transport</td>
<td>Alters Ca²⁺, Mg²⁺, PO₄³⁻ homeostasis</td>
</tr>
<tr>
<td></td>
<td>Synthesize osmolytes</td>
<td>Increase osmolality of medullary cytoplasm to match medullary concentration gradient</td>
</tr>
<tr>
<td>3. Hormonal Synthesis</td>
<td>Erythropoietin production (cortex)</td>
<td>Red blood cell production</td>
</tr>
<tr>
<td></td>
<td>Vitamin D activation: 25(OH)D/Vitamin D converted to 1,25(OH)D/1,25(OH)D (proximal tubule)</td>
<td>Calcium homeostasis</td>
</tr>
<tr>
<td></td>
<td>Renin production (juxtaglomerular apparatus)</td>
<td>Alters vascular resistance and aldosterone secretion</td>
</tr>
<tr>
<td>4. Blood Pressure Regulation</td>
<td>Na⁺ excretion</td>
<td>Alters ECF volume</td>
</tr>
<tr>
<td></td>
<td>Renin production</td>
<td>Alters vascular resistance</td>
</tr>
<tr>
<td>5. Glucose Homeostasis</td>
<td>Gluconeogenesis (from lactate, pyruvate, and amino acids)</td>
<td>Glucose supply maintained in prolonged starvation</td>
</tr>
<tr>
<td></td>
<td>Clearance and degradation of circulating insulin</td>
<td>Maintains glucose homeostasis</td>
</tr>
</tbody>
</table>

The Glomerulus
- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman’s space
- particles are selectively filtered by size (<60 kDa) and charge (negative charge repelled)
• consists of following cell types:
  1. Mesangial cells
     • structural cells that support the vascular tree; they are also contractile and produce vasoactive substances to help control blood flow
  2. Capillary endothelial cells
     • one of the cells of the glomerular filtration barrier; help form the plasma filtration apparatus due to their sinusoidal nature and glycosylation; contribute to the production of the GBM
  3. Visceral epithelium (podocytes)
     • one of the cells of the glomerular filtration barrier; help form the plasma filtration apparatus due to their interdigitated foot process that form slit diaphragms; contribute to the production of the GBM
  4. Parietal epithelium
     • lines the interior of Bowman’s capsule and contains a podocyte progenitor population
  5. Juxtaglomerular cells
     • smooth muscle cells in lining of afferent arteriole; produce, store and secrete renin

The Renal Tubules
• reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion
• each segment of the tubule selectively transports various solutes and water and is targeted by specific diuretics
Renal Hemodynamics

- **GFR**
  - is the sum of the filtration across all nephrons
  - the rate of fluid transfer between glomerular capillaries and Bowman's space
  - average 180 L/d, of which 99% is reabsorbed, giving a urine output of 1.0-1.5 L/d to match oral fluid intake
  - normal urine output is 0.5-2.0 ml/kg/h in adults
  - GFR is highest in early adulthood, and decreases thereafter starting around age 40

- **2 mechanisms of autoregulation**
  - myogenic mechanism: release of vasoactive factors such as prostaglandins in response to changes in perfusion pressure (e.g. → perfusion pressure → afferent arteriolar constriction → decreased GFR)
  - tubuloglomerular feedback: changes in Na+ delivery to macula densa lead to changes in afferent arteriolar tone (e.g. increased delivery causes afferent constriction)

- **FF**
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio: FF = GFR/RPF; normal = 0.2 or 20%
  - renin is released from juxtaglomerular apparatus in response to decreased RPF and maintain sodium balance
  - renin is an important enzyme in the renin angiotensin aldosterone system (RAAS), that converts angiotensinogen to angiotensin I

Glomerular Filtration Rate

\[
GFR = K_f (\Delta P - \Delta \Pi) 
\]

- \( K_f \) = ultrafiltration coefficient
- \( \Delta P \) = hydrostatic pressure difference between glomerular capillaries and Bowman’s space
- \( \Delta \Pi \) = osmotic pressure difference between glomerular capillaries and Bowman’s space
- \( \Delta P - \Delta \Pi = \text{net outward pressure} \)

Angiotensin II Effects:

1. Vasoconstriction
2. \( \uparrow \) vascular smooth muscle growth
3. \( \uparrow \) Na+ reabsorption
4. \( \uparrow \) aldosterone
5. \( \uparrow \) bicarbonate products
# Measurement of Renal Function

## Limitations of Using Serum Cr Measurements

1. **must be in steady state**
   - constant GFR and rate of production of Cr from muscle; however, serum Cr will not immediately reflect sudden reduction in GFR until new Cr steady-state is reached
2. **GFR must fall substantially before Cr rises above normal laboratory range**
   - with progressive renal failure, remaining nephrons compensate with hyperfiltration
   - GFR is relatively preserved despite significant structural damage
3. **plasma [Cr] is influenced by the rate of Cr production**
   - lower production with smaller muscle mass (e.g. female, elderly, low weight)
     - for example, consider plasma [Cr] of 100 µmol/L in both of these patients
       - 20 yr old man who weighs 100 kg, GFR = 144 mL/min
       - 80 yr old woman who weighs 50 kg, GFR = 30.6 mL/min
     - clinical correlation: GFR decreases with age but would not be reflected as a rise in serum Cr due to the age-associated decline in muscle mass
4. **tubular secretion of Cr increases as GFR decreases**
   - serum Cr and CrCl overestimate low GFR
   - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
5. **errors in Cr measurement**
   - very high bilirubin level causes [Cr] to be falsely low
   - acetooacete (a ketone body) and certain drugs (cefoxitin) create falsely high [Cr]

## Measurement of Urea Concentration

- urea is the major end-product of protein metabolism
- plasma urea concentration reflects renal function but should not be used alone as it is modified by a variety of other factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) causes urea level to rise
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in hypernatreemic states
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mmol/L for urea and µmol/L for Cr)
**Urinalysis**

- Use dipstick in freshly voided urine specimen to assess the following:

1. **Specific Gravity**
   - Ratio of the mass of equal volumes of urine/H₂O
   - Range is 1.001-1.030
   - Values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
   - Value usually 1.010 in ESRD (isosthenuria: same specific gravity as plasma)

2. **pH**
   - Urine pH is normally between 4.5-7.0; if persistently alkaline, consider
     - RTA
     - UTI with urease-producing bacteria (e.g. Proteus)

3. **Glucose**
   - Freely filtered at glomerulus and reabsorbed in proximal tubule
   - Causes of glucosuria include:
     1. Hyperglycemia >9-11 mmol/L leads to filtration that exceeds tubular resorption capacity
     2. Increased GFR (e.g. pregnancy)
     3. Proximal tubule dysfunction (e.g. Fanconi's syndrome)

4. **Protein**
   - Dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
   - Microalbuminuria (morning ACR of 2.0 - 20 mg/mmol) is not detected by standard dipstick; greater than these ranges would be macroalbuminuria (see Diabetes, NP31)
   - Sulfosalicylic acid detects all protein in urine by precipitation
   - Gold standard: 24 h timed urine collection for total protein

5. **Leukocyte Esterase**
   - Enzyme found in WBC and detected by dipstick
   - Presence of WBCs indicates infection (e.g. UTI) or inflammation (e.g. AIN)

6. **Nitrites**
   - Nitrates in urine are converted by some bacteria to nitrites
   - High specificity but low sensitivity for UTI

7. **Ketones**
   - Positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

8. **Hemoglobin**
   - Positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis), and true hematuria (RBCs seen on microscopy)

### Urine Microscopy

<table>
<thead>
<tr>
<th>Active Sediment = Suggestive of Parenchymal Kidney Disease</th>
<th>Bland Sediment = Less Likely Parenchymal Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any one or more of the following seen on microscopy</strong></td>
<td></td>
</tr>
<tr>
<td>Red cell casts</td>
<td>Only hyaline casts</td>
</tr>
<tr>
<td>White cell casts</td>
<td>Small quantities of crystals</td>
</tr>
<tr>
<td>Muddy-brown granular or epithelial cell casts</td>
<td>Small amount of bacteria</td>
</tr>
<tr>
<td>&gt;2 red cells per HPF</td>
<td>&lt;2 red cells per HPF</td>
</tr>
<tr>
<td>&gt;4 white cells per HPF</td>
<td>&lt;4 white cells per HPF</td>
</tr>
</tbody>
</table>

1. **CELLS**

   **Erythrocytes**
   - Hematuria = greater than normal range of 2-3 RBCs per HPF
   - Dysmorphic RBCs and/or RBC casts suggest glomerular bleeding (e.g. proliferative GN)
   - Isomorphic RBCs, no casts suggest extraglomerular bleeding (e.g. bladder Ca)

   **Leukocytes**
   - Pyuria = greater than upper limit of normal: 3 WBCs per HPF
   - Indicates inflammation or infection
   - If persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, papillary necrosis, renal TB, viral infections
**Eosinophils**
- detected using Wright's or Hansel's stain (not affected by urine pH)
- consider AIN, atheroembolic disease

**Oval Fat Bodies**
- renal tubular cells filled with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

**2. CASTS**
- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein

<table>
<thead>
<tr>
<th>Table 3. Interpretation of Casts</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaline casts</td>
<td>Physiologic (concentrated urine, fever, exercise)</td>
</tr>
<tr>
<td>RBC casts</td>
<td>Glomerular bleeding (GN, vasculitis)</td>
</tr>
<tr>
<td>WBC casts</td>
<td>Infection (pyelonephritis)</td>
</tr>
<tr>
<td>Pigmented granular casts (heme granular casts, muddy brown)</td>
<td>ATN</td>
</tr>
<tr>
<td>Fatty casts</td>
<td>Acute GN</td>
</tr>
<tr>
<td>Nephrotic Syndrome ( &gt;3.5 g/d)</td>
<td></td>
</tr>
</tbody>
</table>

**3. CRYSTALS**
- uric acid: consider acid urine, hyperuricosuria
- calcium phosphate: alkaline urine
- calcium oxalate: consider hyperoxaluria, ethylene glycol poisoning
- sulfur: sulfa-containing antibiotics

**Urine Biochemistry**
- commonly measure: Na⁺, K⁺, Cl⁻, osmolality, and pH
- no "normal" values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient's current state, for example:
  1. ECF volume depletion: expect low urine [Na⁺] (kidneys should be retaining Na⁺)
     - urine [Na⁺] >20 mmol/L suggests a renal problem or the action of a diuretic
     - urine [Na⁺] <20 mmol/L suggests a prerenal problem
  2. daily urinary potassium excretion rate should be decreased (<20 mmol/d) in hypokalemia
     - if higher than 20 mmol/d, suggests renal contribution to hypokalemia
- osmolality is useful to estimate the kidney's concentrating ability
- FENa refers to the fractional excretion of Na⁺
  - FENa <1% suggests the pathology is prerenal
- urine pH is useful to grossly assess renal acidification
  - low pH (<5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (e.g. RTA)

**Electrolyte Disorders**

**Sodium Homeostasis**
- hyponatremia and hypernatremia are disorders of water balance
  - hyponatremia usually suggests too much water in the ECF relative to Na⁺ content
  - hypernatremia usually suggests too little water in the ECF relative to Na⁺ content
- solutes (such as Na⁺, K⁺, glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
  - water moves out of cells in response to increased ECF osmolality
  - water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by Na⁺ content rather than concentration
  - Na⁺ deficiency leads to ECF volume contraction
  - Na⁺ excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially in the brain) shrinking (hyponatremia) or swelling (hypernatremia)
Table 4. Clinical Assessment of ECF Volume (Total Body Na+)

<table>
<thead>
<tr>
<th>Fluid Compartment</th>
<th>Hypovolemic</th>
<th>Hypervolemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JVP</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Orthostatic drop</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Auscultation of heart</td>
<td>Tachycardia</td>
<td>S3</td>
</tr>
<tr>
<td>Auscultation of lungs</td>
<td>Normal</td>
<td>Inspiratory crackles</td>
</tr>
<tr>
<td><strong>Interstitial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin turgor</td>
<td>Decreased</td>
<td>Normal/increased</td>
</tr>
<tr>
<td>Edema (dependent)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td>Decreased*</td>
<td>Variable</td>
</tr>
<tr>
<td>Body weight</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Hematocrit, serum protein</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

*If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia.

**Hyponatremia**

- hyponatremia: serum [Na+] <135 mmol/L
- can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality
- consider if it is “appropriate” vs. “inappropriate” ADH secretion
- if appropriate ADH secretion, is it real vs. effective volume loss?

**Figure 4. Approach to hyponatremia**

**Hypovolemic**

- $U_{osm}<20$ and $F_{Na}<1\%$ (renal losses)
- CHF
- Cirrhosis and ascites
- Nephrotic syndrome
- Pregnancy
- $U_{Na}>20$
- AKI, CKD

**Hypervolemic**

- $U_{osm}>100$
- SIADH (normal $U_{Na}$)
- Adrenal insufficiency
- Hypothyroidism
- $U_{Na}<100$
- Psychogenic polydipsia
- Low solute - “tea & toast”
- $U_{Na}>20$
- Diuretics (especially thiazides)
- Salt-wasting nephropathy
- Diarrhea
- Excessive sweating
- Third spacing (e.g. peritonitis, pancreatitis, burns)

**Iso-Osmolar**

- (280-295 mOsm/kg)
- Retention in ECF of large volumes of isotonic fluids that do not contain sodium (e.g. mannitol)
- Pseudohyponatremia – lab artifact seen with severe hyperlipidemia or paraproteinemia (e.g. multiple myeloma)

**Hypo-Osmolar (dilutional)**

- (<280 mOsm/kg)
- Most common cause of hyponatremia
- Excess water in relation to sodium stores which can be decreased, normal, or increased
- Categorized by volume status as determined by clinical assessment

**Hyper-Osmolar (translocational)**

- (>295 mOsm/kg)
- Extra osmoles in ECF draw water out of cells diluting the Na+ in ECF
- Usually glucose (rarely hypertonic mannitol)
- Every 10 mmol/L increase in blood glucose results in 3 mmol/L decrease in Na

**Symptoms of Central Pontine Myelinolysis**

- Cranial nerve palsies
- Quadriplegia
- Decreased LOC

**Complications**

- seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death
- risk of brain cell shrinkage with rapid correction of hyponatremia
- can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible (e.g. central pontine myelinolysis: cranial nerve palsies, quadriplegia, decreased LOC)
Risk Factors for Osmotic Demyelination
- rise in serum [Na+] with correction >8 mmol/L/24 hr if chronic hyponatremia
- associated hypokalemia and/or malnutrition (e.g. low muscle mass)
- if patient with hyponatremia and hypovolemia is given large volume of isotonic fluid (ADH is stimulated by hypovolemia; when hypovolemia is corrected, the ADH level falls suddenly causing sudden brisk water diuresis, and therefore rapid rise in serum Na+ level)
- patient with psychogenic polydipsia, deprived of water

Investigations
- ECF volume status assessment (see Table 4)
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine Na+ (urine Na+ < 10-20 mmol/L suggests volume depletion as the cause of hyponatremia)
- assess for causes of SIADH (see Table 5)
- TSH, free T4, and cortisol levels
- consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. paraneoplastic syndrome by small cell lung cancer)
- consider CT head if suspect CNS cause of SIADH

Treatment of Hyponatremia
- general measures for all patients
  1. treat underlying cause (e.g. restore ECF volume if volume depleted, remove offending drug, treat pain, nausea, etc.)
  2. restrict free water intake
  3. promote free water loss
  4. carefully monitor serum Na+, urine volume, and urine tonicity
  5. ensure frequently that correction is not occurring too rapidly
     - monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia

A. Known Acute (known to have developed over <24-48 h)
- commonly occurs in hospital (dilute IV fluid, post-operative increased ADH)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
  - correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum [Na+] = 125-130 mmol/L
  - may need furosemide to address volume overload
- if asymptomatic, treatment depends on severity
  - if marked fall in plasma [Na+], treat as symptomatic

B. Chronic or Unknown
  1. if severe symptoms (seizures or decreased LOC)
     - must partially correct acutely
     - aim for increase of Na+ by 0.5-1 mmol/L/h for 4-6 h
     - limit total rise to 8 mmol/L in 24 h
     - IV 3% NaCl at 1-2 cc/kg/h
     - may need furosemide
  2. if asymptomatic
     - water restrict to <1 L/d fluid intake
     - consider IV 0.9% NS + furosemide (reduces urine osmolality augments excretion of H2O)
     - consider NaCl tablet or Oxo cubes® as a source of Na+
  3. refractory
     - furosemide and oral salt tablets
     - oral urea (osmotic aquaresis)
     - V2 receptor antagonists (e.g. tolvaptan)
  4. always pay attention to patient’s ECF volume status  if already volume-expanded, unlikely to give NaCl (tablet or IV); if already volume-depleted, almost never appropriate to give furosemide

C. Options for Treatment of Overly-Rapid Correction
- give water (IV D5W)
- give ADH to stop water diuresis (DDAVP 1-2 µg IV)

Impact of IV Solution on Serum [Na+] 
- formula to estimate the change in serum [Na+] caused by retention of 1 L of any infusate
  \[ \text{change in serum [Na+] = \text{infusate [Na+] - serum [Na+] \over TBW + 1 L}} \]
- formula assumes there are no losses of water or electrolytes
SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION
1. urine that is inappropriately concentrated for the serum osmolality
2. high urine sodium (>20-40 mmol/L)
3. high FE\textsubscript{Na}

Table 5. Disorders Associated with SIADH

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Pulmonary</th>
<th>CNS</th>
<th>Drugs</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell cancer</td>
<td>Pneumonia</td>
<td>Mass lesion</td>
<td>Antidepressants</td>
<td>Post-operative state</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Lung abscess</td>
<td>Encephalitis</td>
<td>TCAs</td>
<td>Pain</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>TB</td>
<td>Subarachnoid hemorrhage</td>
<td>SSRIs</td>
<td>Severe nausea</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>Acute respiratory failure</td>
<td>Stroke</td>
<td>Antineoplastics</td>
<td>HIV</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Asthma</td>
<td>Head trauma</td>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>COPD</td>
<td>Acute psychosisis</td>
<td>Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive pressure ventilation</td>
<td>Acute intermittent porphyria</td>
<td>Anti-epileptics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barbiturates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorpropamide</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ACEI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DDAVP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxytocin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nicotine</td>
<td></td>
</tr>
</tbody>
</table>

Hypernatremia

- hypernatremia: serum [Na\textsuperscript{+}] >145 mmol/L
- too little water relative to total body Na\textsuperscript{+}; always a hyperosmolar state
- usually due to NET water loss, rarely due to hypertonic Na\textsuperscript{+} gain
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

![Hypernatremia Diagram](image)

Figure 5. Approach to hypernatremia

**Signs and Symptoms**
- with acute hypernatremia there is no time for adaptation, therefore more likely to be symptomatic
- adaptive response: cells import and generate new osmotically active particles to normalize size
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- ± polyuria, thirst, signs of hypovolemia

**Complications**
- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema due to ongoing brain hyperosmolality

**Treatment of Hypernatremia**
- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum Na\textsuperscript{+} frequently to ensure correction is not occurring too rapidly
- if evidence of hemodynamic instability, must first correct volume depletion with NS bolus
- loss of water is often accompanied by loss of Na\textsuperscript{+}, but a proportionately larger water loss
- use formula to calculate free water H\textsubscript{2}O deficit and replace
- encourage patient to drink pure water, as oral route is preferred for fluid administration

**H\textsubscript{2}O Deficit and TBW Equations**

\[
\text{H}_{2}\text{O deficit} = \text{TBW} \times (\text{Na}\textsuperscript{+}\text{plasma} - 140) / 140
\]

\[
\text{TBW} = 0.6 \times \text{wt (kg)} \quad \text{men}
\]

\[
\text{TBW} = 0.5 \times \text{wt (kg)} \quad \text{women}
\]

1 L 0.9% NS approximately equals 500 mL of free water
Electrolyte Disorders

• if unable to replace PO or NG, correct H₂O deficit with hypotonic IV solution (IV D5W, 0.45% NS [half normal saline], or 3.3% dextrose with 0.3% NaCl [1/2/3 and 1/3])
  • use formula (see Hyponatremia, NP8) to estimate expected change in serum Na⁺ with 1 L infusate
  • aim to lower [Na⁺] by no more than 12 mmol/L in 24 h (0.5 mmol/L/h)
  • must also provide maintenance fluids and replace ongoing losses
  • general rule: give 2 cc/kg/h of free water to correct serum [Na⁺] by about 0.5 mmol/L/h or 12 mmol/L/d

Diabetes Insipidus

• collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
• defect in central release of ADH (central DI) or renal response to ADH (nephrogenic DI)

Etiology

• central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
• nephrogenic DI: lithium (most common), hypokalemia, hypercalcemia, and congenital

Diagnosis

• urine osmolality inappropriately low in patient with hypernatremia (Uosm <300 mOsm/kg)
• serum vasopressin concentration may be absent or low (central), or elevated (nephrogenic)
• dehydration test: H₂O deprivation until loss of 3% of body weight or until urine osmolality rises above plasma osmolality; if urine osmolality remains <300 (fails to concentrate urine), most likely DI
• administer DDAVP (exogenous ADH) (10 µg intranasally or 2 µg SC or IV)
  • central DI: diagnosed if there is rise in urine osmolality, fall in urine volume
  • treat with DDAVP
  • nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
  • treat with water (IV D5W or PO water), thiazides may help as well (reduced ECF volume stimulates proximal tubular reabsorption of sodium and water, leading to less delivery of glomerular filtrate to ADH sensitive parts of renal tubule, and therefore lower urine volume results)

Potassium Homeostasis

• approximately 98% of total body K⁺ stores are intracellular
• normal serum K⁺ ranges from 3.5-5.0 mEq/L
• in response to K⁺ load, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia
• insulin, catecholamines, and acid-base status influence K movement into cells
  • aldosterone has a minor effect
• potassium excretion is regulated at the distal nephron
  • K⁺ excretion = urine flow rate x urine [K⁺]

Factors which Increase Renal K⁺ Loss

• hyperkalemia
• increased distal tubular urine flow rate and Na⁺ delivery (thiazides and loop diuretics)
• increased aldosterone activates epithelial sodium channels in cortical collecting duct, causing Na⁺ reabsorption and K⁺ excretion
• metabolic alkalosis (increases K⁺ secretion)
• hypomagnesemia
• increased non-reabsorbable anions in tubule lumen: HCO₃⁻, penicillin, salicylate (increased tubular flow rate increases K⁺ secretion)

Hypokalemia

• serum [K⁺] <3.5 mEq/L

Signs and Symptoms

• usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
• N/V, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
• if severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
• arrhythmias occur at variable levels of K⁺; more likely if digoxin use, hypomagnesemia, or CAD
• ECG changes are more predictive of clinical picture than serum [K⁺]
  • U waves most important (low amplitude wave following a T wave)
  • flattened or inverted T waves
  • depressed ST segment
  • prolongation of Q T interval
  • sinus bradycardia
  • with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity
• common arrhythmias seen with hypokalemia: Ventricular fibrillation, Ventricular tachycardia's
**Electrolyte Disorders**

**NP12 Nephrology**

**Toronto Notes 2018**

---

**Figure 6. ECG changes in hypokalemia**

**Approach to Hypokalemia**

1. emergency measures: obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of $K^+$ as cause of hypokalemia
3. assess contribution of dietary $K^+$ intake
4. spot urine $K:Cr$ (should be less than 1 in setting of hypokalemia)
   - if <1 consider GI loss
   - if >1 consider a renal loss
5. consider 24 h $K^+$ excretion
6. if renal $K^+$ loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum $[Mg^{2+}]$

---

**Figure 7. Approach to hypokalemia**

**Treatment**

- treat underlying cause
- if true $K^+$ deficit, potassium repletion
  - oral sources – food, tablets (K-Dur®), KCl liquid solutions (preferable route if the patient tolerates PO medications)
  - IV – usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
- max 40 mmol/L via peripheral vein, 60 mmol/L via central vein, max infusion 20 mmol/h
- $K^+$-sparing diuretics (triamterene, amiloride, spironolactone) can prevent renal $K^+$ loss
- restore $Mg^{2+}$ if necessary
- if urine output and renal function are impaired, correct with extreme caution
- risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
- use of ACE inhibitor or ARB for CHF (reduces angiotensin II action and therefore aldosterone)
- beware of excessive potassium repletion, especially if transcellular shift caused hypokalemia

---

**Figure 6**

**Hypokalemia**

1. Decreased Intake
   - Limited dietary intake
   - Clay ingestion
2. Increased Loss
   - Spot urine K:Cr
     - Spot urine K:Cr < 1
     - Spot urine K:Cr > 1
3. Redistribution into Cells (transcellular shifts)
   - Metabolic alkalosis ($K^+/H^+$ exchange across cell membrane)
   - Insulin (stimulates Na+/K+ ATPase)
   - Catecholamines, β₂-agonists (salbutamol), theophylline (stimulates Na+/K+ ATPase)
   - Tocolytic agents
   - Uptake into newly forming cells
     - Vitamin B₁₂ injections in pernicious anemia
     - Colony stimulating factors 
4. Hypo- or normotensive
   - Check acid base status
5. Hypertensive
   - 1º hyperaldosteronism (e.g. Conn’s syndrome)
   - 2º hyperaldosteronism (renovascular disease, renin tumour)
   - Non-aldosterone mineralocorticoid (Cushing’s, exogenous)
6. Acidemic
   - DKA
   - RTA
7. Variable
   - HypoK
   - Vomiting/NG
8. Alkalemic
   - Diuretics (furosemide, HCTZ) manifest as renal losses due to hyperaldosteronism, metabolic alkalosis and increased flow to collecting duct
   - Inherited renal tubular lesions
     - Barter’s (loop of Henle dysfunction: furosemide-like effect)
     - Gitelman’s (DCT dysfunction: thiazide-like)
Hyperkalemia

- serum \([K^+] >5.0 \text{ mEq/L}\)

Signs and Symptoms
- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniagenesis and metabolic acidosis
- ECG changes and cardioxicity (do not correlate well with serum \([K^+]\))
- peaked and narrow T waves
- decreased amplitude and eventual loss of P waves
- prolonged PR interval
- widening of QRS and eventual merging with T wave (sine-wave pattern)
- AV block
- ventricular fibrillation, asystole

![Figure 8. ECG changes in hyperkalemia](image)

Table 6. Causes of Hyperkalemia

<table>
<thead>
<tr>
<th>Factitious</th>
<th>Increased Intake</th>
<th>Transcellular Shift</th>
<th>Decreased Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample hemolysis*</td>
<td>Diet</td>
<td>Intravascular hemolysis</td>
<td>Decreased GFR</td>
</tr>
<tr>
<td>Sample taken from vein where IV KCl is running</td>
<td>KCI tabs</td>
<td>Rhabdomyolysis</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Prolonged use of tourniquet</td>
<td>IV KCl</td>
<td>Tumour lysis syndrome</td>
<td>Low effective circulating volume</td>
</tr>
<tr>
<td>Leukocytosis (extreme)</td>
<td>Salt substitute</td>
<td>Insulin deficiency</td>
<td>NSAIDs in renal insufficiency</td>
</tr>
<tr>
<td>Thrombocytosis (extreme)</td>
<td></td>
<td>Acidemia</td>
<td>Normal GFR but hypoaldosteronism</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>KCl tabs</td>
<td></td>
<td>β-blockers</td>
<td></td>
</tr>
<tr>
<td>IV KCl</td>
<td></td>
<td>Digitalis ove dose (blocks Na⁺/K⁺ ATPase)</td>
<td></td>
</tr>
<tr>
<td>Salt substitute</td>
<td></td>
<td>Succinylcholine</td>
<td></td>
</tr>
</tbody>
</table>

*Most common

Table 7. Causes of Hyperkalemia with Normal GFR

<table>
<thead>
<tr>
<th>Decreased Aldosterone Stimulus (low renin, low aldosterone)</th>
<th>Decreased Aldosterone Production (normal renin, low aldosterone)</th>
<th>Aldosterone Resistance (decreased tubular response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV</td>
<td>Adrenal insufficiency of any cause (e.g. Addison's disease, AIDS, metastatic cancer) ACEI Angiotensin II receptor blockers</td>
<td>K⁺-sparing diuretics Spironolactone Amiloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triamterene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal tubulointerstitial disease</td>
</tr>
</tbody>
</table>

Approach to Hyperkalemia
1. emergency measures: obtain ECG, if life threatening begin treatment immediately
2. rule out factitious hyperkalemia; repeat blood test
3. hold exogenous K⁺ (PO and IV) and any K⁺ retaining medications
4. assess potential causes of transcellular shift
5. estimate GFR (calculate CrCl using Cockcroft-Gault)

Treatment
- acute therapy is warranted if ECG changes are present or if patient is symptomatic regardless of \([K^+]\)
- tailor therapy to severity of increase in \([K^+]\) and ECG changes
  - \([K^+] <6.5\) and normal ECG
    - treat underlying cause, stop K⁺ intake, increase the loss of K⁺ via urine and/or GI tract
  - \([K^+]\) between 6.5 and 7.0, no ECG changes: add insulin to above regimen
  - \([K^+] >7.0\) and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

1. Stabilize Myocardium
- calcium gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes the membrane action of hyperkalemia, protects cardiac conduction system, no effect on serum \([K^+]\)
- onset within minutes, lasts 30-60 min (may require repeat doses during treatment course of hyperkalemia)
2. Shift K⁺ into Cells
- regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
  - onset of action 15-30 min, lasts 1-2 h
  - monitor capillary blood glucose q1h because of risk of hypoglycemia
  - can repeat every 4-6 h
  - caution giving D50W before insulin if hyperkalemia is severe as it can cause a serious arrhythmia
- NaHCO₃ 1-3 ampules (given as 3 ampules of 7.5% or 8.4% NaHCO₃ in 1L D5W)
  - onset of action 15-30 min, transient effect, drives K⁺ into cells in exchange for H⁺
  - more effective if patient has metabolic acidosis
- β₂-agonist (Ventolin⁺) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  - onset of action 30-90 min, stimulates Na⁺/K⁺ ATPase
  - caution if patient has heart disease as may result in tachycardia

3. Enhance K⁺ Removal from Body
- via urine (preferred approach)
  - furosemide (≥40 mg IV), may need IV NS to avoid hypovolemia
  - fludrocortisone (synthetic mineralocorticoid) if suspect aldosterone deficiency
- via gastrointestinal tract
  - cation exchange resins: calcium resonium or sodium polystyrene sulfonate (Kayexalate⁺)
    - increasingly falling out of favour due to risk of colonic necrosis; works by binding Na⁺ in exchange for K⁺, and controversial how much K⁺ is actually removed
  - lactulose or sorbitol PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered - main benefit may be the diarrhea caused by lactulose)
  - Kayexalate⁺ enemas with tap water
- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

---

**Hyperphosphatemia**

**Definition**
- serum phosphate >1.45 mmol/L
- critical role in the development of secondary hyperparathyroidism and renal osteodystrophy in patients with advanced CKD and on dialysis

**Table 8. Etiology of Hyperphosphatemia**

<table>
<thead>
<tr>
<th>Increased Phosphate Load</th>
<th>Reduced Renal Clearance</th>
<th>Pseudohyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI intake (rectal enema, GI bleeding)</td>
<td>Acute/chronic renal failure</td>
<td>Hyperglobulinemia</td>
</tr>
<tr>
<td>IV phosphate load (K-Phos⁺, blood transfusion)</td>
<td>Hypoparathyroidism</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis, lactic acidosis)</td>
<td>Acromegaly</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Tumour calcinosis (ability of kidney to clear phosphate is defective)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Features**
- non-specific, include ectopic calcification, renal osteodystrophy

**Treatment**
- acute: hemodialysis if symptomatic; aluminum hydroxide (use with extreme caution in renal failure)
- chronic: low PO₄³⁻ diet, phosphate binders (e.g. CaCO₃ or lanthanum carbonate or sevelamer with meals)

---

**Hypophosphatemia**

**Definition**
- serum phosphate <0.85 mmol/L

**Table 9. Etiology of Hypophosphatemia**

<table>
<thead>
<tr>
<th>Inadequate Intake</th>
<th>Renal Losses</th>
<th>Excessive Skeletal Mineralization</th>
<th>Shift into ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starvation</td>
<td>Hyperparathyroidism</td>
<td>Osteoblastic metastases (referred to as ‘hungry bone syndrome’)</td>
<td>Recovery from metabolic acidosis</td>
</tr>
<tr>
<td>Malabsorption (diarrhea, steatorrhea)</td>
<td>Diuretics</td>
<td>Post parathyroidectomy (referred to as ‘hungry bone syndrome’)</td>
<td>Respiratory alkalosis</td>
</tr>
<tr>
<td>Antacid use</td>
<td>X-linked or AD</td>
<td></td>
<td>Stavation preceding (stimulated by insulin)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>hypophosphatemic rickets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fanconi syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early post-kidney transplant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Features**
- non-specific (CHF, coma, hypotension, weakness, defective clotting)
Acid-Base Disorders

Treatment
- treat underlying cause
  - Oral PO$^43$ 2-4 g/d divided bid-qid (start at 1 g/d to minimize diarrhea)
  - IV PO$^43$: only for severely symptomatic patients or inability to tolerate oral therapy

Hypermagnesemia

Definition
- serum magnesium >0.85 mmol/L

Etiology
- AKI/CRF
- Mg$^{2+}$-containing antacids or enemas
- IV administration of large doses of MgSO$_4$ (e.g. for Preeclampsia; see Obstetrics, OB24)

Clinical Features
- rarely symptomatic
- drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest, hypotension

Treatment
- discontinue Mg$^{2+}$-containing products
- IV calcium (Mg$^{2+}$-antagonist) for acute reversal of magnesium toxicity
- dialysis if renal failure

Hypomagnesemia

Definition
- serum magnesium <0.70 mmol/L

Etiology

<table>
<thead>
<tr>
<th>GI losses</th>
<th>Excess renal loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starvation/malabsorption</td>
<td>2$^{nd}$ hyperaldosteronism due to cirrhosis and CHF</td>
</tr>
<tr>
<td>Vomiting/diarrhea</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Loop and thiazide-type diuretics</td>
</tr>
<tr>
<td></td>
<td>Nephrotoxic medications</td>
</tr>
<tr>
<td></td>
<td>Proton-pump inhibitors</td>
</tr>
<tr>
<td></td>
<td>Early post-renal transplant</td>
</tr>
</tbody>
</table>

Clinical Features
- seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities), and arrhythmias including Torsades de Pointes

Treatment
- treat underlying cause
- encourage increased dietary intake e.g. fruits
- oral Mg$^{2+}$ salts unless patient has seizures or other severe symptoms
- Mg$^{2+}$ IM/IV; cellular uptake of Mg$^{2+}$ is slow, therefore repletion requires sustained correction
- discontinue diuretics
  - in patients requiring diuretics, use a K$^+$-sparing diuretic to minimize magnesuria

Acid-Base Disorders
- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic, and CNS function
- see Respirology, R6 for more information on respiratory acidosis/alkalosis
- normal concentration of HCO$_3^-$ = 24 mEq/L (range: 22-30 mEq/L)
- normal pCO$_2$ = 40 mmHg (range: 36-44 mmHg)
- each acid base disorder has an appropriate compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder (e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis)
Acid-Base Disorders

Figure 9  Approach to acid-base disorders

**Approach**

1. **Identify the primary disturbance**
   - respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis

2. **Evaluate compensation. If compensation is not appropriate, a second acid-base disorder is likely present**
   - compensation occurs in the same direction as the primary disturbance

3. **Calculate Plasma AG**
   - AG = [Na+] – ([HCO3-] + [Cl–])
   - baseline = 12, normal range 10-14 mEq/L
   - AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 mEq/L (e.g. if plasma [albumin]= 20 g/L, expect AG = 6 mEq/L)

4. **If AG elevated, compare increase in AG with decrease in HCO3-**
   - if increase in AG < decrease in HCO3-, there is a coexisting non-AG metabolic acidosis
   - if increase in AG > decrease in HCO3-, there is a coexisting metabolic alkalosis

5. **Calculate Osmolar Gap**
   - osmolar gap = measured osmolality – calculated osmolality
   - calculated osmolality = (2 x [Na+]) + [urea] + [glucose] (all units are in mmol/L)
   - calculated osmolality <10
   - if OG >10, consider: methanol poisoning, ethylene glycol poisoning, or another cause of acidosis plus ethanol ingestion

**Metabolic Acidosis**

**Etiology and Pathophysiology**

1. **Increased AG Metabolic Acidosis (4 types)**
   - L-lactic acidosis (2 types)
     - type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
     - type B: non-hypoxic – multiple causes; the most common is failure to metabolize normally produced lactic acid in the liver due to severe liver disease; other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain anti-retrovirals, large tumours, mitochondrial myopathies
     - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
     - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria metabolize carbohydrate load into D-lactic acid, diminished colonic motility and impaired D-lactate metabolism
   - diabetic
   - starvation
   - alcoholic (decreased carbohydrate intake and vomiting)

   **Useful Equations**
   - AG = [Na+] - ([HCO3-] + [Cl–]) (normal range = 10-14 mEq/L)
   - Osmolar Gap = measured serum osmolality – calculated osmolality (normal <10 mEq/L)
   - calculated osmolality = (2 x [Na+]) + [urea] + [glucose] + [Ethanol] (all units are in mmol/L)

   **Causes of Increased AG Metabolic Acidosis**
   - Methanol
   - Ethylene glycol
   - Ethanol
   - Polyethylene glycol
   - Mannitol
   - Sorbitol
3. toxins
   • methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
   • ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
   • salicylate (e.g. ASA) overdose: causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacid (salicylate activates fat breakdown)

4. advanced renal failure (e.g. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)

2. Normal AG Metabolic Acidosis (Hyperchloremic Acidosis)
   • diarrhea (HCO₃⁻ loss from GI tract)
   • RTA
     ◆ type I RTA (distal): inability to secrete H⁺ in collecting duct, leading to impaired excretion of ammonium into urine
     ◆ type II RTA (proximal): impaired HCO₃⁻ reabsorption
     ◆ type III RTA: combination of Types I and II and is extremely rare
     ◆ type IV RTA: defective ammoniagenesis due to decreased aldosterone, hyporesponsiveness to aldosterone, or hyperkalemia
   • to help distinguish renal causes from non-renal causes, use Urine AG = (Na⁺ + K⁺) – Cl⁻
   • calculation establishes the presence or absence of unmeasured positive ions (e.g. NH₄⁺) in urine
     ◆ if UAG <0, suggests adequate NH₄⁺ excretion in urine (likely nonrenal cause: diarrhea)
     ◆ if UAG >0, suggests problem is lack of NH₄⁺ in urine (e.g. distal RTA)

Treatment of Metabolic Acidosis
1. treat underlying cause:
   • fluid resuscitation and insulin for DKA
   • restore tissue perfusion for Type A lactic acidosis
   • ethanol/fomepizole ± dialysis for methanol or ethylene glycol poisoning
   • alkaline diuresis ± dialysis if ASA overdose
2. correct coexisting disorders of K⁺ (see Hyperkalemia, NP13)
3. consider treatment with exogenous alkali (e.g. NaHCO₃) if:
   • severe reduction in [HCO₃⁻] e.g. <8 mmol/L, especially with very low pH (<7)
   • no metabolizable anion (e.g. salicylate, formate, oxalate, or sulphate); note that lactate and ketoacid anions can be metabolized to HCO₃⁻
   • note: risks of sodium bicarbonate therapy
     ◆ hypokalemia: causes K⁺ to shift into cells (correct K⁺ deficit first)
     ◆ ECF volume overload: Na⁺ load given with NaHCO₃ can exacerbate pulmonary edema
     ◆ overshoot alkalemia: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to HCO₃⁻, and persisting hyperventilation

Metabolic Alkalosis

Pathophysiology
   • requires initiating event and maintenance factors
   • precipitating factors
     ◆ GI (vomiting, NG tube) or renal loss of H⁺
     ◆ exogenous alkali (oral or parenteral administration), milk alkali syndrome
     ◆ diuretics (contraction alkalosis): decreased excretion of HCO₃⁻, decreased ECF volume, therefore increased [HCO₃⁻]
     ◆ post-hypercapnia: renal compensation for respiratory acidosis is HCO₃⁻ retention, rapid correction of respiratory disorder results in transient excess of HCO₃⁻
   • maintenance factors
     ◆ volume depletion: reduced GFR and increase proximal reabsorption of NaHCO₃ and increased aldosterone
     ◆ hyperaldosteronism (1º or 2º): distal Na⁺ reabsorption in exchange for K⁺ and H⁺ excretion leads to HCO₃⁻ generation; aldosterone also promotes hypokalemia
     ◆ hypokalemia: transcellular K⁺/H⁺ exchange, stimulus for ammoniagenesis and HCO₃⁻ generation

Evaluate Compensation (identify co-existing respiratory acid-base disorders)
   • hypoventilation (an upper limit to compensation exists – breathing cannot be stopped)

Treatment
   • treat underlying cause
   • correct underlying disease, replenish K⁺ and Mg²⁺ deficits, and possibly K⁺-sparing diuretic
   • saline sensitive metabolic alkalosis (most common)
     ◆ volume repletion ± carbonic anhydrase inhibitor (e.g. acetazolamide) to facilitate loss of HCO₃⁻ in urine
   • saline resistant metabolic alkalosis
     ◆ remove source of aldosterone or glucocorticoid ± spironolactone

Causes of Non-AG Metabolic Acidosis

HARDUP
   • Hyperalimentation
   • Acetazolamide
   • RTA *
   • Diarrhea *
   • Ureterointestinal fistula
   • Pancreaticoduodenal fistula

*Most common
**Acute Kidney Injury**

**Definition**
- abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
- formerly known as acute renal failure

**Clinical Presentation**
- azotemia (increased BUN, Cr)
- abnormal urine volume: formally <0.5 ml/kg/h for >6 h but can manifest as anuria, oliguria, or polyuria

**Approach to AKI**

**Investigations**
- blood work: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), Ca²⁺, PO₄³⁻
- urine dipstick: albumin, hemoglobin, WBC's, others: glucose, pH, urobilinogen, specific gravity
- urine volume. C&S, R&M: sediment, casts, crystals
- urinary indices: electrolytes, osmolality
- Foley catheterization (rule out bladder outlet obstruction)

**Clues to Prerenal Etiology**
- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
- Increased [urea] >> Increased [Cr]
- Urine (Na⁺) <10-20 mmol/L
- Urine osmolality >500 mOsm/kg
- Fractional excretion of Na⁺ <1%

**Clues to Renal Etiology**
- Appropriate clinical context
- Urinalysis positive for casts:
  - Pigmented granular – ATN
  - WBC – AIN
  - RBC – GN
- Systemic features, anemia, thrombocytopenia, HTN, mild-moderate ECF volume overload

**Clues to Postrenal Etiology**
- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis

**Differentiating Prerenal from ATN**

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis Normal</td>
<td>RBC, pigmented granular casts</td>
</tr>
<tr>
<td>Urine [Na⁺] &lt;20</td>
<td>&gt;20 mEq/L</td>
</tr>
<tr>
<td>Urine [Na⁺]/[Cr] &lt;20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Urine osmolality &gt;500</td>
<td>&lt;350 mOsm/kgH₂O</td>
</tr>
<tr>
<td>FeNa &lt;1%</td>
<td>&gt;1%</td>
</tr>
</tbody>
</table>
Parenchymal Kidney Diseases

• fluid challenge (e.g. fluid bolus to rule out most prerenal causes)
• imaging: abdomen U/S (assess kidney size, hydronephrosis, postrenal obstruction)
• indications for renal biopsy
  • diagnosis is not certain
  • prerenal azotemia or ATN is unlikely
  • oliguria persists > 2-4 days

Treatment
1. preliminary measures
   ■ prerenal
     • correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEI/ARB (gently rehydrate when needed, e.g. CHF) and NSAIDs
   ■ renal
     • address reversible renal causes: discontinue nephrotoxic drugs, treat infection, and optimize electrolytes
     • correct ECF volume, supportive care, consider corticosteroid or immunosuppressive therapy
   ■ postrenal
     • consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
     • for obstruction to cause AKI, must have functional solitary kidney or obstruction affecting both kidneys:
       treat with Foley catheter insertion, indwelling bladder catheter, nephrostomy, stenting
2. treat complications
   ■ fluid overload
     • NaCl restriction
     • high dose loop diuretics
     • hyperkalemia (see Approach to Hyperkalemia, NP13)
     • adjust dosages of medications cleared by kidney (e.g. amiodarone, digoxin, cyclosporin, tacrolimus, some antibiotics, and chemotherapeutic agents)
   ■ dialysis
3. definitive therapy depends on etiology

Prognosis
• high morbidity and mortality in patients with sustained AKI and multi-organ failure

Parenchymal Kidney Diseases

Glomerular Diseases

HISTOLOGICAL TERMS OF GLOMERULAR CHANGES

Extent of Changes
• histological term describing the number of glomeruli affected in a given condition:
  ■ diffuse: majority of glomeruli abnormal
  ■ focal: some glomeruli affected
• histological term describing the extent to which individual glomeruli are affected in a given condition
  ■ global: entire glomerulus abnormal
  ■ segmental: only part of the glomerulus abnormal

Types of Changes
• proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
• crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration form crescent-shape in Bowman’s space
• membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane

CLINICAL PRESENTATION OF GLOMERULAR DISEASE

Important Points to Remember
• glomerular diseases have diverse clinical presentations including hematuria, proteinuria, HTN, edema, and decreased GFR
• each glomerulopathy presents as one of four major glomerular syndromes (these are NOT diagnoses)
  1. asymptomatic urinary abnormalities
     - proteinuria
     - hematuria
  2. nephritic syndrome
     - acute GN
     - rapidly progressive GN
  3. nephrotic syndrome
  4. ESRD

Avoid NSAIDs in patients with diarrhea, heart failure or renal failure
Renal transplant is not a therapy for AKI
Drugs Implicated in Prerenal Azotemia
  • Diuretics
  • NSAIDs
  • ACEI/ARBs
• glomerulopathies can be caused by a primary disease or can occur secondary to a systemic disease
• some glomerulopathies can present as more than one syndrome at different times

The Nephritic-Nephrotic Spectrum
• glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes

PROTEINURIA
• hallmark of nephrotic syndromes
• composition of normal urine protein: albumin, lower molecular proteins (such as immunoglobulin light chain) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)
• 24 h urine protein: gold standard to assess degree of proteinuria
• urine ACR: used to screen for diabetic nephropathy
• microalbuminuria: ACR ≥2.0mg/mmol
  • marker of vascular endothelial function
  • an important prognostic marker for kidney disease in DM and HTN (see Diabetes, NP31)
  • microalbuminuria is the earliest sign of diabetic nephropathy
• composition of normal total urine protein
• upper limit of normal daily excretion of total protein is 150 mg/d
• upper limit of normal daily excretion of albumin is 30 mg/d
• the other normally excreted proteins are either filtered low molecular weight proteins (such as immunoglobulin light chains or β-2 microglobulin) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)

Pathologic Proteinuria
Tubulointerstitial
• Normally low molecular weight proteins (<60 kDa) pass through glomerular filtration barrier and are reabsorbed in proximal tubule
• Proximal tubule dysfunction causes impaired reabsorption and increased excretion of low molecular weight proteins
• Albumin (>60 kDa) is not affected; thus, edema is partly secondary to salt and water retention

Glomerular
• Normally, the filtration barrier is selectively permeable to size (<60 kDa) and charge (repels negative particles); thus, albumin is filtered to a very limited extent through a normal glomerulus
• Damage to any component of the glomerular filtration barrier results in loss of albumin and other high molecular weight proteins; thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (possibly due to filtered proteins stimulating the action of cortical collecting duct epithelial sodium channel)

Overflow
• Increased production of low molecular weight proteins which exceeds the reabsorptive capacity of the proximal tubule
• Plasma cell dyscrasias: produce light chain Ig (multiple myeloma, Waldenstrom’s macroglobulinemia, monoclonal gammopathy of undetermined significance)
Table 10. Daily Excretion of Protein

<table>
<thead>
<tr>
<th>Daily Excretion</th>
<th>Stage of Nephropathy</th>
<th>ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 mg total protein (and &lt;30 mg albumin)</td>
<td>Normal</td>
<td>Less than 2.0 mg/mmol</td>
</tr>
<tr>
<td>30-300 mg albumin</td>
<td>Microalbuminuria</td>
<td>Greater than 2.0 mg/mmol</td>
</tr>
<tr>
<td>&gt;3500 mg total protein/1.73m² BSA</td>
<td>Nephrotic range proteinuria</td>
<td></td>
</tr>
<tr>
<td>Variable amount of proteinuria</td>
<td>Can be seen with glomerular disease</td>
<td></td>
</tr>
<tr>
<td>Up to 2000 mg per d</td>
<td>Possible tubular disease because of failure to reabsorb filtered proteins</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
- urine R&M, C&S, urea, Cr
- further workup (if degree of proteinuria >0.5 g/d, casts, and/or hematuria)
  - CBC, glucose, electrolytes, 24 h urine protein, and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic U/S
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA (PR3), Hep B, Hep C, HIV, ASOT
- indications for nephrology referral
  - generally if there is "heavy" proteinuria (ACR >30 mg/mmol), should refer to nephrologist
  - definitely if there is nephrotic syndrome: marked proteinuria >3.5 g/1.73m²/d with hypoalbuminemia (<35 g/L)

HEMATURIA
- hallmark of nephritic syndromes
- presence of blood or RBCs in urine
  - gross hematuria: pink, red, or tea-coloured urine
    - if the sediment is red, true hematuria
    - if the supernatant is red, test for heme with a dipstick
    - if supernatant positive for heme: myoglobinuria or hemoglobinuria
    - if negative for heme; pseudohematuria; consider medications (e.g. rifampin), food dyes (e.g. beets), or metabolites (e.g. porphyria)
  - microscopic hematuria: blood in the urine that is invisible to the naked eye, >2-3 RBCs/HPF on microscopy

Figure 14. Approach to red urine

Investigations for Hematuria
- Hx and P/E: family history of nephrolithiasis, hearing loss (Alport Syndrome), cerebral aneurysm (PCKD), diet, recent URTI, irritative and obstructive urinary symptoms (UTI)
- urine R&M, C&S, urea, Cr
- renal U/S
- 24 h urine stone workup if there is a history of stone formation or if there is a stone noted on imaging: calcium, oxalate, titrate, magnesium, uric acid, cystine
- further workup (if casts and/or proteinuria): CBC, electrolytes, 24 h urine protein and Cr, serology (ANA, RF, C3, C4, p-ANCA, c-ANCA, ASOT)
- consider urology consult and possible cystoscopy if not clearly a nephrologic source for hematuria or if >50 yr of age
**Glomerular Syndromes**

### 1. ASYMPTOMATIC URINARY ABNORMALITIES

**Clinical/Lab Features**
- often have rapid decline in GFR, anemia, elevated inflammatory markers, ECF volume replete or mildly overloaded
  - proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
    - isolated proteinuria
      - can be postural
      - occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
    - hematuria with or without proteinuria
      - IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, usually presents after viral URTI
      - hereditary nephritis (Alport Syndrome – Type IV collagen mutation): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/d
      - benign thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
      - benign recurrent hematuria: hematuria associated with febrile illness, exercise, or immunization; a diagnosis of exclusion after other possibilities are ruled out

### 2 NEPHRITIC SYNDROME

#### Anti-GBM Mediated (RPGN Type I) (15%)
- Linear IF pattern due to IgG and C3 deposition along capillary loops
- anti-GBM +ve
- With lung hemorrhage: Goodpasture's disease
- Without lung hemorrhage: Anti-GBM disease

#### Immune Complex Mediated (RPGN Type II) (24%)
- Granular pattern due to subendothelial or subepithelial deposits of IgG and C3
- C3 normal
- IgA nephropathy
- Henoch-Schönlein purpura
- Membranoproliferative GN
- SLE
- Infective endocarditis
- Post-infectious GN
- Cryoglobulinemia
- c-ANCA +ve
- Granulomatosis with polyangiitis

#### Non-Immune Mediated (RPGN Type III) (60%)
- Pauci-immune: no immune staining
- Decreased C3
- p-ANCA +ve
- Churg-Strauss
- Microscopic polyangiitis

#### Double Antibody Positive Disease (RPGN Type IV)
- Has features of Type I and Type III
- Double antibody positive

---

**Figure 15. Approach to nephritic syndrome**

**ACUTE NEPHRITIC SYNDROME**
- a subset of nephritic syndrome in which the clinical course proceeds over days
- etiology can be divided into low and normal complement levels
- frequently immune-mediated, with Ig and C3 deposits found in GBM

**Clinical/Lab Features**
- proteinuria (but <3.5 g/1.73 m²/d)
- abrupt onset hematuria (microscopic or macroscopic)
- azotemia (increased Cr and urea)
- RBC casts and/or dysmorphic RBCs in urine
- oliguria, HTN (due to salt and water retention)
- peripheral edema/puffy eyes
- smoky urine

**Treatment**
- depends on etiology
- pulse steroid therapy and other immunosuppression, BP control, monitoring for progression to end stage renal disease

**RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS**
- a subset of nephritic syndrome in which the clinical course proceeds over weeks to months
- clinical diagnosis, not histopathological
- any cause of GN can present as RPGN (except minimal change disease)
- additional etiologies seen only as RPGN: anti-GBM Disease and granulomatosis with polyangiitis (previously called Wegener's granulomatisis)
- crescentic GN (identified by pathology) results from proliferation of parietal epithelial cells and is the most aggressive form of glomerular disease
**Clinical/Lab Features**
- Fibrous crescents typically present on renal histopathology
- RBC casts and/or dysmorphic RBCs in urine
- Classified by immunofluorescence staining
- Type I: Anti-GBM mediated (15% of cases)
- Type II: Immune complex mediated (24% of cases)
- Type III: Non-immune mediated (60% of cases)
- Type IV: Double antibody positive

**Treatment and Prognosis**
- Treatment: underlying cause for postinfectious; corticosteroids + cyclophosphamide or other cytotoxic agent + plasmapheresis in management of cases such as Anti-GBM Ab
- Prognosis: 50% recovery with early treatment, depends on underlying cause

**3. NEPHROTIC SYNDROME**

**Clinical/Lab Features**
- Heavy proteinuria (>3.5 g/1.73 m²/d)
- Hypoalbuminemia
- Edema
- Hyperlipidemia (elevated LDL cholesterol), lipiduria (fatty casts and oval fat bodies on microscopy)
- Hypercoagulable state (due to antithrombin III, Protein C, and protein S urinary losses)
- Patient may report frothy urine
- Glomerular pathology on renal biopsy
  - Minimal change disease (or minimal lesion disease or nil disease) – e.g. glomeruli appear normal on light microscopy
  - Membranous glomerulopathy
  - Focal segmental glomerulosclerosis (FSGS)
  - Membranoproliferative GN
  - Nodular glomerulosclerosis
- Each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause proteinuria without obvious glomerular pathology)

**Table 11. Nephrotic Syndrome**

<table>
<thead>
<tr>
<th>Secondary Causes</th>
<th>Membranous Glomerulopathy</th>
<th>Focal Segmental Glomerulosclerosis</th>
<th>Membranoproliferative Glomerulonephritis</th>
<th>Nodular Glomerulosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>HBV, SLE, solid tumours (lung, breast, GI)</td>
<td>Reflux nephropathy, HIV, HBV, obesity, sickle cell disease</td>
<td>HDV, malaria, SLE, leukemia, lymphoma, shunt nephritis</td>
<td>DM, amyloidosis</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Gold, penicillamine</td>
<td>Heroin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>Steroids</td>
<td>Reduce BP, ACEI, steroids</td>
<td>Steroids, ACEI/ARB for proteinuria</td>
<td>Aspirin®, ACEI, dipyridamole (Persantine®) – controversial</td>
</tr>
</tbody>
</table>

**4. END STAGE RENAL DISEASE**
- See *End Stage Renal Disease*, NP36

**INVESTIGATIONS FOR GLOMERULAR DISEASE**
- Blood work
  - First presentation: electrolytes, Cr, urea, albumin, fasting lipids
  - Determining etiology: CBC, ESR, serum immunoelectrophoresis, anti-GBM Disease, C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV
- Urinalysis: RBCs, WBCs, casts, protein
- 24 h urine for protein and CrCl
- Radiology
  - CXR (infiltrates, CHF, pleural effusion)
  - Renal US
- Renal biopsy (percutaneous or open) if heavy proteinuria or renal insufficiency and cause is not obviously diabetic nephropathy
- Urine immunoelectrophoresis
  - For Bence-Jones protein if proteinuria present
SECONDARY CAUSES OF GLOMERULAR DISEASE

Amyloidosis
- nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
- presents as nephrotic range proteinuria with progressive renal insufficiency
- can be primary or secondary
- secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy

Systemic Lupus Erythematosus (see Rheumatology, RH11)
- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- GN caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement, ANA, anti-DNA levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis

Henoch-Schönlein Purpura
- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia, and fever
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

Anti-GBM Disease
- Goodpasture Syndrome when lung and renal both involved
- antibodies against type IV collagen present in lungs and GBM
- present with RPGN type I and hemoptysis/dyspnea
- pulmonary hemorrhage more common in smokers and males
- treat with plasma exchange, cyclophosphamide, prednisone

ANCA Associated Vasculitis
- c-ANCA most commonly associated with the clinical picture of granulomatosis with polyangiitis
- p-ANCA most commonly associated with the clinical picture of microscopic polyangiitis
- focal segmental necrotizing RPGN with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treatment typically involves cyclophosphamide and prednisone

Cryoglobulinemia
- cryoglobulins: monoclonal IgM and polyclonal IgG which precipitate at reduced temperatures
- presents as purpura, fever, Raynaud’s phenomenon, and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

Figure 16. International Society of Nephrology/Renal Pathology Society classification of lupus nephritis 2003

Henoch-Schönlein Purpura
- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia, and fever
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD
Shunt Nephritis
- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients
- treat by removing shunt and administering appropriate antibiotics

HIV-Associated Renal Disease
1. direct nephrotoxic effect of HIV infection, anti-retroviral drugs (e.g. tenofovir, indinavir), and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy
   - histology: focal and segmental glomerular collapse with mesangial sclerosis; “collapsing FSGS”
   - tubular cystic dilation and tubulo-reticular inclusions
   - clinical features: predominant in African American men, heavy proteinuria, progressive renal insufficiency (apo-l-1 risk genotypes)
   - prognosis: kidney failure within 1 yr without treatment
   - therapy: short term, high dose steroids, ACEI, HAART

Infective Endocarditis
- manifests as mild form of acute nephritic syndrome with decreased serum complement
- S. aureus is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

Hepatitis B
- can result in membranous nephropathy, polyarteritis nodosa, membranoproliferative GN

Hepatitis C
- can result in membranous nephropathy, cryoglobulinemia, and membranoproliferative GN

Syphilis
- can result in membranous GN

Tubulointerstitial Disease

TUBULOINTERSTITIAL NEPHRITIS

Definition
- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

Signs and Symptoms
- manifestation of disease depends on site of tubule affected
  1. proximal tubule (e.g. multiple myeloma, heavy metals)
     - Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hyperuricosuria
     - proximal RTA (decreased bicarbonate absorption): Type II RTA
  2. distal tubule (e.g. amyloidosis, obstruction)
     - distal RTA (Type I RTA), usually hypokalemic
     - Na+-wasting nephropathy
     - ± hyperkalemia leading to type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
  3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
     - urinary concentrating defect leading to mild nephrogenic DI
     - polyuria

1 ACUTE TUBULOINTERSTITIAL NEPHRITIS

Definition
- rapid (days to weeks) decline in renal function
- 10-20% of all AKI

Etiology
- hypersensitivity
  1. antibiotics: β-lactams, sulfonamides, rifampin, quinolones, cephalosporins, fluoroquinolones
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
Parenchymal Kidney Diseases

• infections
  • immune
    • SLE, acute allograft rejection, Sjögren’s syndrome, sarcoidosis, mixed essential cryoglobulinemia
  • idiopathic

Pathophysiology
• acute inflammatory cell infiltrates into renal interstitium

Clinical Features
• AKI
  • if hypersensitivity reaction: may see fever, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
  • if pyelonephritis: flank pain and costovertebral angle (CVA) tenderness
  • if drug reaction, AKI usually occurs 7-10 days after exposure
  • other signs and symptoms based on underlying etiology
  • HTN and edema are uncommon

Findings
• urine
  • mild, non-nephrotic range proteinuria and microscopic hematuria
  • sterile pyuria, WBC casts
  • eosinophilia if AIN
• blood work
  • increased Cr and urea
  • eosinophilia if drug reaction
  • normal AG metabolic acidosis (RTA)
  • hypophosphatemia, hyperkalemia, hyponatremia
  • gallium scan often shows intense signal due to inflammatory infiltrate
  • renal biopsy definitive

Treatment
• treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
• corticosteroids (may be indicated in allergic or immune disease)

Prognosis
• recovery within 2 wk if underlying insult can be eliminated
• the longer the patient is in renal failure, the less likely they will have a full renal recovery

2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Definition
• characterized by slowly progressive renal failure, moderate proteinuria, and signs of abnormal tubule function

Etiology
• persistence or progression of acute TIN
• urinary tract obstruction: most important cause of chronic TIN (tumours, stones, bladder outlet obstruction, vesicoureteral reflux)
• chronic pyelonephritis due to vesicoureteral reflux or UTI with obstruction
• nephrotoxins
  • exogenous
    • analgesics: NSAIDs (common), acetaminophen
    • cisplatin, lithium, cyclosporine, tacrolimus
    • heavy metals (lead, cadmium, copper, lithium, mercury, arsenic)
    • Chinese herbs (aristolochic acid)
  • endogenous
    • hypercalcemia, hypokalemia, oxalate, uric acid
• vascular disease: ischemic nephrosclerosis, atheroembolic disease
• malignancies: multiple myeloma, lymphoma
• granulomatous: TB, sarcoidosis granulomatosis with polyangiitis
• immune: SLE, Sjögren’s, cryoglobulinemia, Anti-GBM Disease, amyloidosis, renal graft rejection, vasculitis
• hereditary: cystic diseases of the kidney, sickle cell disease
• others: radiation, Balkan (endemic) nephropathy

Pathophysiology
• fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

Signs and Symptoms
• dependent on underlying etiology
**Findings**
- normal AG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi's syndrome
- progressive renal failure with azotemia and uremia
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- U/S: shrunken kidneys with irregular contours

**Treatment**
- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders (Ca\(^{2+}\), PO\(_{4}^{3-}\)) and anemia

### 3. ACUTE TUBULAR NECROSIS

**Definition**
- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

**Clinical Presentation**
- typically presents as an acute rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
- most common cause of non-prerenal AKI in hospitalized patients
- urine: high FE\(_{\text{Na}}\), pigmented-granular casts

**Risk Factors**
- pre-existing chronic kidney disease, pre-existing cardiovascular disease, ECF volume depletion, multiple renal insults

**Complications**
- hyperkalemia: can occur rapidly and cause serious arrhythmias
- metabolic acidosis, decreased Ca\(^{2+}\), increased PO\(_{4}^{3-}\), hypoalbuminemia

**Investigations**
- blood work: CBC, electrolytes, Cr, urea, Ca\(^{2+}\), PO\(_{4}^{3-}\), blood gases
- urine: R&M, electrolytes, osmolality, microscopic urinalysis searching for pigmented granular casts
- ECG
- abdominal U/S
- rule out other causes of prerenal/postrenal azotemia and intrinsic AKI (GN, AIN, vasculitis)

**Treatment**
- largely supportive once underlying problem is corrected
- loop diuretics may help manage volume overload and reduce tubular metabolic requirements to allow for recovery (controversial)
- consider early dialysis in severe/rapidly progressing cases to prevent uremic syndrome

---

**Figure 17. Etiology of ATN**

**Etiology**
- Acute Tubular Necrosis
  - **Toxins**
    - Exogenous
      - Antibiotics
        - Aminoglycosides
        - Cephalosporins
        - Amphotericin B
    - Antiviral (cidofovir)
    - Antineoplastics
      - Cisplatin
      - Methotrexate
    - Contrast media
    - Heavy metals
    - Other
      - Fluorinated anesthetic
      - Ethylene glycol
  - Endogenous
    - Endotoxins (bacterial)
    - Myoglobin
    - Hemoglobin
  - Decreased Circulating Volume
    - Hemorrhage including post-surgical
    - Skin losses
    - GI losses
    - Renal losses
    - Decreased Effective Circulating Volume
      - Heart failure
      - Liver failure
      - Sepsis
      - Anaphylaxis
    - Vessel Occlusion
      - Large or small renal artery involvement

---

**Meta-Analysis: Effectiveness of Drugs for Preventing Contrast-Induced Nephropathy**

- **Ann Intern Med** 2008; 148: 84-96
- **Purpose**: To determine the effectiveness of N-acetyl cysteine, theophylline, fenoldopam, dopamine, lisinopril, statin, furosemide, or mannitol on preventing nephropathy.
- **Study Selection**: RCTs that used these agents in patients receiving iodinated contrast.
- **Results**: In the 41 RCTs included, N-acetyl cysteine (RR=0.62 [0.44-0.88]) and theophylline (RR=0.49 [0.25-0.92]) reduced the risk of nephropathy more than saline alone. Furosemide increased the risk (RR=3.27 [1.48-7.26]). Other agents did not affect risk of nephropathy.
- **Conclusion**: N-acetyl cysteine is more renoprotective than hydration alone.
Prevention
- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast:
  - give N-acetylcysteine 600-1200 mg PO bid before and day of procedure, give intravenous isotonic fluid (either NaCl or NaHCO₃)
  - isotonic NaHCO₃ at 3 mL/kg over 1 h before procedure and 1 mL/kg/h for 6 h post-procedure if not contraindicated
  - avoid giving diuretics, ACEI, cyclosporine on morning of procedure if possible
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency

Vascular Diseases of the Kidney

LARGE VESSEL DISEASE

Table 12. Summary of Vascular Diseases

<table>
<thead>
<tr>
<th>Large Vessel Disease</th>
<th>Medium Vessel Disease</th>
<th>Small Vessel Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal artery occlusion (infarct)</td>
<td>Kawasaki disease</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td>Renal artery stenosis (ischemia)</td>
<td>Polyarteritis nodosa</td>
<td>Atheroembolic renal disease</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>Thrombotic microangiopathy</td>
<td>Scleroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcineurin inhibitor nephropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemolytic Uremic Syndrome (HUS)</td>
</tr>
</tbody>
</table>

1. RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)
- important, potentially reversible cause of renal failure

Etiology
- abdominal trauma, surgery, embolism, vasculitis, extra-renal compression, hypercoagulable state, aortic dissection
- kidney transplant recipients more vulnerable

Signs and Symptoms (depend on presence of collateral circulation)
- fever, N/V, flank pain
- leukocytosis, elevated AST, ALP
- marked elevated LDH (LDH >4x upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
- acute onset HTN (activation of RAAS) or sudden worsening of long-standing HTN
- renal dysfunction, e.g. elevated Cr (if bilateral, or solitary functioning kidney)

Investigations
- renal arteriography (more reliable but risk of atheroembolic renal disease)
- contrast-enhanced CT or MR angiography, duplex Doppler studies (operator dependent)

Treatment
- prompt localization of occlusion and restoration of blood flow
- anticoagulation thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
- medical therapy in the long-term to reduce risk (e.g. antihypertensives)

2. ISCHEMIC RENAL DISEASE (RENAral Artery STenosis)
- chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
- significant cause of ESRD: 15% in patients >50 yr (higher prevalence if significant vascular disease)
- usually associated with large vessel disease elsewhere
- causes of renal artery stenosis
  - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males >55 yr, smokers
  - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset <30 yr)
- when there is decreased RBF, GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the FF (GFR/RBF)
- most common cause of secondary HTN (“renovascular HTN”), 1-2% of all hypertensive patients
- etiology
  - decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
  - increased angiotensin raises blood pressure in two ways
    1. causes generalized arteriolar constriction
    2. release of aldosterone increases Na⁺ and water retention
- elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN
# Risk Factors
- >50 yr
- smoking
- other atherosclerotic disease (dyslipidemia, DM, diffuse atherosclerosis)

# Signs and Symptoms
- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

# Investigations
- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (e.g. captopril renal scan)
- renal arteriography (gold standard)

# Treatment
- surgical: percutaneous angioplasty ± stent, surgical revascularization, occasionally surgical bypass
- medical: BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- little or no benefit if therapy is late (e.g. kidney is already shrunken), however, therapy can be considered to save the opposite kidney if normal

### 3. RENAL VEIN THROMBOSIS

#### Etiology
- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical presentation determined by rapidity of occlusion and formation of collateral circulation

#### Signs and Symptoms
- acute: N/V, flank pain, hematuria, elevated plasma LDH, ± rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria and/or tubule dysfunction

#### Investigations
- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

#### Treatment
- thrombolytic therapy ± percutaneous thrombectomy for acute renal vein thrombosis
- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

### MEDIUM VESSEL DISEASE

1. **KAWASAKI DISEASE**
   - see Pediatrics, P87

2. **POLYARTERITIS NODOSA**
   - see Rheumatology, RH19
   - kidneys most commonly involved organ
   - heterogenous impact on renal function
   - pathologically can cause glomerular ischemia which manifests as mild proteinuria and hypertension

### SMALL VESSEL DISEASE

1. **HYPERTENSIVE NEPHROSCLEROSIS**
   - see Hypertension, NP35

2. **ATHEROEMBOLIC RENAL DISEASE**
   - progressive renal insufficiency due to embolic obstruction of small- and medium-sized renal vessels by atheromatous emboli
   - spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
• anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
• investigations
  • cosinophilia, eosinophiluria, and hypocomplementemia
  • ren 1 biopsy: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small-/medium-sized vessels
• treatment
  • no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
  • prognosis: poor overall, at least one third will develop ESRD

3. THROMBOTIC MICROANGIOPATHY
  • see Hematology, H22
  • etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia
  • renal involvement more common in HUS than TTP
  • renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
  • treatment
    • depends on cause
    • supportive therapy
    • TTP-HUS: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)
  • avoid platelet transfusions and ASA

4. CALCINEURIN INHIBITOR NEPHROPATHY
  • cyclosporine and tacrolimus
  • causes both acute reversible and chronic, largely irreversible nephrotoxicity
  • major cause of kidney failure in other solid organ transplants (e.g. heart)
  • acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
  • preglomerular azotemia
  • treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
  • chronic: result of obliterator arteriopathy causing interstitial nephritis and CKD (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors

### Analgesic Nephropathies

1. Vasomotor AKI
   • clinically: develop preglomerular azotemia within a few days of starting NSAID
   • normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
   • NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
   • more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
   • treatment: discontinue NSAID, dialysis rarely needed

2. Acute Interstitial Nephritis
   • fenoprofen (60%), ibuprofen, naproxen
   • may be associated with minimal change glomerulopathy and nephrotic range proteinuria
   • resolves eventually with discontinuation of NSAID, may require interval dialysis
   • short-term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

3. Chronic Interstitial Nephritis
   • due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
   • seen in patients who also have emotional stress, psychiatric symptoms, and GI disturbance
   • papillary necrosis
     • gross hematuria, flank pain, declining renal function
     • calyceal filling defect seen with IVP – “ring sign”
   • increased risk of transitional cell carcinoma of renal pelvis
   • good prognosis if discontinue analgesics

4. Acute Tubular Necrosis
   • can be caused by acetaminophen
   • incidence of renal dysfunction is related to the severity of acetaminophen ingestion
   • vascular endothelial damage can also occur
   • both direct toxicity and ischemia contribute to the tubular damage
   • renal function spontaneously returns to baseline within 1–4 wk
   • dialysis may be required during the acute episode of ingestion

5. Other Effects of NSAIDs
   • sodium retention (2° to reduced GFR)
   • hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
   • excess water retention (2° to loss of antagonistic effect of prostaglandins on ADH)
Systemic Disease with Renal Manifestation

Diabetes

- diabetic nephropathy: presence of microalbuminuria or overt nephropathy (e.g. macroalbuminuria) in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 50% of patients with diabetes will develop nephropathy
- at diagnosis up to 30% of patients with type 2 DM have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once macroalbuminuria is established, renal function declines, 50% of patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially type 1 DM) and/or neuropathy (especially type 2 DM)
- indication of possible non-diabetic cause of renal disease in patients with DM
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of systemic disease
  - inappropiate time course; rapidly rising Cr, renal disease in a patient with short duration of DM
  - family history of non-diabetic renal disease (e.g. PCKD, Alport’s)

DIABETIC RENAL COMPLICATIONS

1. Progressive Glomerulosclerosis
   - classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
   - more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix

<table>
<thead>
<tr>
<th>Table 13. Stages of Diabetic Progressive Glomerulosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>↑ GFR (120-150%) – compensatory hyperfiltration</td>
</tr>
<tr>
<td>± slightly increased mesangial matrix</td>
</tr>
<tr>
<td>(ACR) 2.0-20 mg/mmol (18-180 mg/d)</td>
</tr>
<tr>
<td>↑ mesangial matrix</td>
</tr>
<tr>
<td>↑↑↑ mesangial matrix</td>
</tr>
</tbody>
</table>

2. Accelerated Atherosclerosis
   - common finding
   - decreased GFR
   - may increase angiotensin II production resulting in increased BP
   - increased risk of ATN secondary to contrast media

3. Autonomic Neuropathy
   - affects bladder leading to functional obstruction and urinary retention
   - residual urine promotes infection
   - obstructive nephropathy

4. Papillary Necrosis
   - type 1 DM susceptible to ischemic necrosis of medullary papillae
   - sloughed papillae may obstruct ureter
   - can present as renal colic or with obstructive features ± hydronephrosis
Figure 19. Clinical practice guidelines on chronic kidney disease in diabetes

Priorities in the Management of Patients with DM
1. vascular protection for all patients with DM
   • ACEI, antiplatelet therapy (as indicated)
   • BP control, glycemic control, lifestyle modification, lipid control
   • Canagliflozin provides renoprotection independent of its glycemic effects
2. optimization of BP in patients who are hypertensive
   • treat according to HTN guidelines
3. renal protection for DM patients with nephropathy (even in absence of HTN)
   • type 1 DM: ACEI or ARB
   • type 2 DM: CrCl >60 mL/min: ACEI or ARB – CrCl <60 mL/min: ARB
   • 2nd line agents: nondihydropyridine calcium channel blockers (diltiazem verapamil)
   • combination of ACEI and ARB not recommended for proteinuria
   • check serum Cr and K+ levels within 1 wk of initiating ACEI or ARB and at time of acute illness
   • serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
   • if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
   • consider holding ACEI, ARB, and/or diuretic with acute illness and in women before becoming pregnant
   • consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive kidney function loss, unable to achieve BP targets, or unable to stay on ACEI or ARB

Scleroderma
• see Rheumatology, RH13
• 50% of scleroderma patients have renal involvement (mild proteinuria, high Cr, HTN)
• renal involvement usually occurs early in the course of illness
• histology: media thickened, “onion skin” hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
• 10-15% of scleroderma patients have a “scleroderma renal crisis” (occurs in first few years of disease): malignant HTN, ARE, microangiopathy, volume overload, visual changes, HTN encephalopathy
• treatment: BP control with ACEI slows progression of renal disease

Renal Outcomes with Telmisartan, Ramipril, or Both in People at High Vascular Risk (ONTARGET Study)
Lancet 2008;372:547-553
Study: Prospective, multicentre, double-blind, RCT.
Participants: 25,620 patients with median follow-up of 56 mo.
Intervention: Patients received either ramipril (10 mg/d; n=8,576), telmisartan (80 mg/d; n=8,542), or a combination of both drugs (n=8,502).
Primary Outcome: Composite of dialysis, doubling of creatinine level, and death.
Results: The number of outcome events was similar for telmisartan (n=1,147) and ramipril (1,150; HR 1.00, 95% CI 0.92-1.09), but was increased with combination therapy (1,233; HR 1.09, 1.01-1.18, p=0.037). The need for dialysis or doubling of serum creatinine, was similar with telmisartan (189) and ramipril (174; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212; HR 1.24, 1.01-1.51, p=0.038). Estimated GFR declined least with ramipril compared with telmisartan or combination therapy (p<0.001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) and combination therapy (p<0.001) than with ramipril.
Conclusion: Renal outcomes were similar in both telmisartan and ramipril monotherapy. Combination therapy reduced proteinuria to a greater extent than monotherapy, but was associated with poorer renal outcomes.

Order random urine ACR and serum creatinine for eGFR
Screen annually when no transient causes of albuminuria or low eGFR are present, and when acute kidney injury or non-diabetic kidney disease is not suspected
Type 1 diabetes: Annually in postpubertal individuals with duration of diabetes ≥5 years
Type 2 diabetes: At diagnosis and annually thereafter

Chronic Kidney Disease Diagnosed
## Multiple Myeloma

- see Hematology, H49
- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms
  - hypercalcemia
  - light chain cast nephropathy or "myeloma kidney"
  - hyperuricemia
  - infection
  - secondary amyloidosis
  - monoclonal Ig deposition disease
  - diffuse tubular obstruction
- light chain cast nephropathy
  - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
  - proteinuria and renal insufficiency, can progress rapidly to kidney failure
- monoclonal Ig deposition disease
  - deposits of monoclonal Ig in kidney, liver, heart, and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

## Malignancy

- cancer can have many different renal manifestations
- kidney transplantation cannot be performed unless malignancy is cured
  - solid tumours: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
  - renal cell carcinoma
  - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction, hyperkalemia, hyperphosphatemia, hypocalcemia, lactic acidosis
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumours/mets: postrenal failure secondary to obstruction
  - amyloidosis
  - radiotherapy (radiation nephritis)

## Chronic Kidney Disease

### Definition
- progressive abnormalities of kidney function for >3 months, with either
  - GFR <60 mL/min/1.73 m²; or
  - markers of kidney damage, including
  - albuminuria; or
  - small shrunken kidney <9 cm with increased cortical echogenicity on ultrasound; or
  - pathology on biopsy

### Clinical Features
- volume overload and HTN
- electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
- uremia (e.g. nausea/vomiting, pruritus, encephalopathy)
- anemia
- bone mineral disorders

### Incidence of Etiologies of CKD

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>42.9%</td>
</tr>
<tr>
<td>HTN</td>
<td>26.4%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>9.9%</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>7.7%</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>4.0%</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td></td>
</tr>
<tr>
<td>Cystic/Hereditary/Congenital</td>
<td>3.1%</td>
</tr>
<tr>
<td>Secondary GN/Vasculitis</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

### Management of Complications of CKD

<table>
<thead>
<tr>
<th>N</th>
<th>Low-nitrogen diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Electrolytes: monitor K⁺</td>
</tr>
<tr>
<td>P</td>
<td>pH metabolite acidosis</td>
</tr>
<tr>
<td>H</td>
<td>HTN</td>
</tr>
<tr>
<td>R</td>
<td>RBCs: manage anemia with</td>
</tr>
<tr>
<td>C</td>
<td>erythropoietin</td>
</tr>
</tbody>
</table>
| O | Osteodystrophy: give calcium between meals (to increase Ca²⁺)
  and calcium with meals (to bind and decrease PO₄³⁻)
| N | Nephrotoxins: avoid nephrotoxic drugs (ASA, gentamicin) and adjust doses of renally excreted medications |
Table 14. Stages of CKD (KDIGO, 2013)

<table>
<thead>
<tr>
<th>Persistent Albuminuria Categories</th>
<th>GFR (mL/min/1.73m²)</th>
<th>A &lt; 30 mg/g</th>
<th>A2 30-300 mg/g</th>
<th>A3 &gt; 300 mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR Categories (mL/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>≥90</td>
<td>1 if CKD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>1 if CKD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>3</td>
<td>3</td>
<td>4+</td>
</tr>
<tr>
<td>G5 (kidney failure)</td>
<td>&lt; 15</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
</tr>
</tbody>
</table>

The numbers in the boxes are a reflection of the risk of progression and are a guide to the frequency of monitoring/year.

Management of Chronic Kidney Disease

- **diet**
  - preventing HTN and volume overload
  - Na⁺ and water restriction
  - preventing electrolyte imbalances
  - K⁺ restriction (40-60 mmol/d)
  - PO₄³⁻ restriction (1 g/d)
  - avoid extra-dietary Mg²⁺ (e.g. antacids)
  - preventing uremia and potentially delaying decline in GFR
  - protein restriction with adequate caloric intake in order to limit endogenous protein catabolism

- **medical**
  - adjust dosages of renally excreted medications
  - HTN: ACEI (target 140/90 mmHg without DM and 130/80 mmHg with DM), loop diuretics when GFR <25 mL/min
  - dyslipidemia: statins (target LDL <2 mmol/L)
  - calcium and phosphate disorders
    - calcium supplements (e.g. TUMS®) treats hypocalcemia when given between meals and binds phosphate when given with meals
    - consider calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic, but hold if hyperphosphatemic (reduces PTH)
    - sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
    - cinacalcet for hyperparathyroidism (sensitizes parathyroid to Ca²⁺, decreasing PTH)
  - metabolic acidosis: sodium bicarbonate
  - anemia: erythropoietin injections for Hb <90 g/L (9 g/dL) and target Hb between 90-105 g/L (9-10.5 g/dL)
  - clotting abnormalities: DDAVP if patient has clinical bleeding or invasive procedures (acts to reverse platelet dysfunction)

- **dialysis** (hemodialysis, peritoneal dialysis)
  - indications include persistent and refractory hyperkalemia or metabolic acidosis, fluid overload, encephalopathy, persistent nausea and vomiting, evidence of malnutrition, pericarditis
  - renal transplantation for end stage kidney disease

Prevention of Progression

- as above
  - control of HTN, DM (HbA1c <7%), cardiovascular risk factors (e.g. smoking cessation, physical activity, weight loss)
  - avoid nephrotoxins such as NSAID’s, COXIB’s, IV contrast in patients with eGFR < 60 mL/min/1.73 m²
  - address reversible causes of AKI
Hypertension

- see Family Medicine, FM34
- HTN occurs in about 20% of population
- etiology classified as primary (‘essential’; makes up 90% of cases) or secondary
- primary HTN can cause kidney disease (hypertensive nephrosclerosis), which may in turn exacerbate the HTN
- secondary HTN can be caused by renal parenchymal or renal vascular disease

Hypertensive Nephrosclerosis

Table 15. Chronic vs. Malignant Nephrosclerosis

<table>
<thead>
<tr>
<th></th>
<th>Chronic Nephrosclerosis</th>
<th>Malignant Nephrosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles</td>
<td>Fibrinoid necrosis of arterioles, disruption of vascular endothelium</td>
</tr>
<tr>
<td><strong>Clinical Picture</strong></td>
<td>Black race, underlying CKD, chronic hypertensive disease</td>
<td>Acute elevation in BP (dBP &gt;120 mmHg) HTN encephalopathy</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>Mild proteinuria, normal urine sediment</td>
<td>Proteinuria and hematuria (RBC casts)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Blood pressure control, (target &lt;140/90) with frequent follow-up</td>
<td>Lower dBP to 100-110 mmHg within 6-24 h More aggressive treatment can cause ischemic event Identify and treat underlying cause of HTN</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Can progress to renal failure despite patient adherence</td>
<td>Lower survival if renal insufficiency develops</td>
</tr>
</tbody>
</table>

Renovascular Hypertension

- see Vascular Diseases of the Kidney, NP28

Renal Parenchymal Hypertension

- HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include:
  - excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective sodium excretion with fluid overload

Investigations

- as well as investigations for renovascular HTN, additional tests may include
  - 24 h urinary estimations of CrCl and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy (very rarely if at all)

Treatment

- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na⁺ restriction (2 g/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor K⁺ and Cr) if there is significant proteinuria (>300 mg/d)

Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population >50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive), and acquired cystic kidney disease (in chronic hemodialysis patients)

Adult Polycystic Kidney Disease

- autosomal dominant; at least 2 genes: PKD1 (chr 16p) and PKD2 (chr 4q)
- PKD1 (1:400), PKD2 (1:1,000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant PKD gene but accumulate a series of second ‘somatic hits’ precipitating the condition
- PKD gene defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth

Hypercalcemia complicates many cancers and can cause multiple kinds of renal disorders (renal vasoconstriction with reduced GFR, salt-wasting with volume depletion, risk of calcium kidney stones)
Cystic Diseases of the Kidney

• most common extrarenal manifestations: multiple asymptomatic hepatic cysts (33%), mitral valve prolapse (25%), cerebral aneurysm (10%), diverticulosis
• polycystic liver disease rarely causes liver failure
• less common extrarenal manifestations: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta

Signs and Symptoms
• often asymptomatic; discovered incidentally on imaging or by screening those with FHx
• acute abdominal flank pain/dull lumbar back pain
• hematuria (frequently initial sign is microscopic hematuria, otherwise gross hematuria)
• nocturia (urinary concentrating defect)
• rarely extra-renal presentation (e.g. ruptured berry aneurysm, diverticulitis)
• HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
• ± palpable kidneys

Common Complications
• urinary tract and cyst infections, HTN, chronic renal failure, nephrolithiasis (5-15%), flank and chronic back pain

Clinical Course
• polycystic changes are always bilateral and can present at any age
• clinical manifestations rare before age 20-25
• kidneys are normal at birth but may enlarge to 10x normal size
• variable progression to renal functional impairment (ESRD in up to 50% by age 60)

Investigations
• radiographic diagnosis: best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
• CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
• gene linkage analysis for PKD1 for asymptomatic carriers
• Cr, BUN, urine R&M (to assess for hematuria)

Treatment
• goal: to preserve renal function by prevention and treatment of complications
• educate patient and family about disease, its manifestations, and inheritance pattern
• genetic counselling: transmission rate 50% from affected parent
• prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
• TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
• adequate hydration to prevent stone formation
• avoid contact sports due to greater risk of injury to enlarged kidneys
• screen for cerebral aneurysms if family history of aneurysmal hemorrhages
• monitor blood pressure and treat HTN with ACEI
• dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
• may require nephrectomy for symptomatic relief of pain or due to recurrent infections

Autosomal Recessive Polycystic Kidney Disease

• 1:20,000 incidence
• prenatal diagnosis by enlarged kidneys
• perinatal death from respiratory failure
• patients who survive perinatal period develop CHF, HTN, CKD
• treated with dialysis, kidney and/or liver transplant

Medullary Sponge Kidney

• common, autosomal dominant, usually diagnosed in 4th-5th decades
• multiple cystic dilatations in the collecting ducts of the medulla
• renal stones, hematuria, and recurrent UTIs are common features
• an estimated 10% of patients who present with renal stones have medullary sponge kidney
• nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
• diagnosis: contrast filled medullary cysts on IVP leading to characteristic radial pattern (“bouquet of flowers”), “Swiss cheese” appearance on histological cross-section
• treat UTIs and stone formation as indicated
• does not result in renal failure
End Stage Renal Disease

ESRD represents an irreversible decline in kidney function requiring renal replacement therapy

Presentation of End Stage Renal Disease

1. Volume Overload
   • due to increase in total body Na⁺ content
   • signs: weight gain, HTN, pulmonary or peripheral edema

2. Electrolyte Abnormalities
   • high
     • K⁺ (decreased renal excretion, increased tissue breakdown)
     • PO₄³⁻ (decreased renal excretion, increased tissue breakdown)
     • Ca²⁺ (rare; happens during recovery phase after rhabdomyolysis-induced AKI or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
     • uric acid
   • low
     • Na⁺ (failure to excrete excessive water intake)
     • Ca²⁺ (decreased Vitamin D activation, hyperphosphatemia, hypoalbuminemia)
     • HCO₃⁻ (especially with sepsis or severe heart failure)

3. Uremic Syndrome
   • manifestations result from retention of urea and other metabolites as well as hormone deficiencies

Figure 20. Signs and symptoms of end stage renal disease

Complications

• CNS: decreased LOC, stupor, seizure
• CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
• GI: peptic ulcer disease, gastroduodenitis, AVM
• hematologic: anemia, bleeding tendency (platelet dysfunction), infections
• endocrine
  • decreased testosterone, estrogen, progesterone
  • increased FSH, LH
• metabolic
  • renal osteodystrophy: secondary increased PTH due to decreased Ca²⁺, high PO₄³⁻, and low active vitamin D
  • osteitis fibrosa cystica
  • hypertriglyceridemia, accelerated atherogenesis
  • decreased insulin requirements, increased insulin resistance
• dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular Ca²⁺ deposition)
Renal Replacement Therapy

Indications for Dialysis in Chronic Kidney Disease

Table 16. Indications for Dialysis

<table>
<thead>
<tr>
<th>Absolute Indications</th>
<th>Relative Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume overload*</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Hyperkalemia*</td>
<td>Decreased cognitive functioning</td>
</tr>
<tr>
<td>Severe metabolic acidosis*</td>
<td>Profound fatigue and weakness</td>
</tr>
<tr>
<td>Neurologic signs or symptoms of uremia</td>
<td>Severe anemia unresponsive to erythropoietin</td>
</tr>
<tr>
<td>(encephalopathy, neuropathy, seizures)</td>
<td>Persistent severe pruritus</td>
</tr>
<tr>
<td>Uremic pericarditis</td>
<td>Restless leg syndrome</td>
</tr>
<tr>
<td>Refractory accelerated HTN</td>
<td></td>
</tr>
<tr>
<td>Clinically significant bleeding diathesis</td>
<td></td>
</tr>
<tr>
<td>Persistent severe N/V</td>
<td></td>
</tr>
</tbody>
</table>

*Unresponsive to medications

- hemodialysis: blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  - available as intermittent (e.g. 3-6x/wk) continuous (CVVHD) or sustained low efficiency (SLED)
  - can be delivered at home or in-centre, nocturnal
  - vascular access can be achieved through a central line, an artificial graft, or an AV fistula
- patients with CKD should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350 µmol/L, or within 1 yr of an anticipated need
- peritoneal dialysis: peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  - available as continuous ambulatory (CAPD; 4-5 exchanges per day) or cyclic (CCPD; machine carries out exchanges overnight)
  - refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)

Table 17. Peritoneal Dialysis vs. Hemodialysis

<table>
<thead>
<tr>
<th></th>
<th>Peritoneal Dialysis</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Location</td>
<td>Home (usually)</td>
<td>Hospital</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Osmotic pressure via dextrose dialysate</td>
<td>Hydrostatic pressure</td>
</tr>
<tr>
<td>Solute Removal</td>
<td>Concentration gradient and convection</td>
<td>Concentration gradient and convection</td>
</tr>
<tr>
<td>Membrane</td>
<td>Peritoneum</td>
<td>Semi-permeable art ficial membrane</td>
</tr>
<tr>
<td>Method</td>
<td>Indwelling catheter in peritoneal cavity</td>
<td>Line from vessel to artificial kidney</td>
</tr>
<tr>
<td>Complications</td>
<td>Infection at catheter site</td>
<td>Vascular access (clots, collapse)</td>
</tr>
<tr>
<td></td>
<td>Bacterial peritonitis</td>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Metabolic effects of glucose</td>
<td>Bleeding due to heparin</td>
</tr>
<tr>
<td></td>
<td>Difficult to achieve adequate clearance in patients with large body mass</td>
<td>Hemodynamic stress of extracorporeal circuit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated syndrome (headache, cerebral edema)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension, nausea, muscle cramps related to solute/water flux over short time)</td>
</tr>
<tr>
<td>Preferred When</td>
<td>Residual renal function</td>
<td>Comorbidities, no renal function</td>
</tr>
<tr>
<td></td>
<td>Success depends on presence of residual renal function</td>
<td>Residual renal function not as important</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic instability</td>
<td>History of abdominal surgery</td>
</tr>
</tbody>
</table>

MUST BE INDIVIDUALIZED

How to Write Dialysis Orders

- Filter Type (e.g. F80)
- Length (e.g. 4 h 3x/wk or 2 h daily)
- Q Blood Flow (max 500 cc/min)
- Ultrafiltration (e.g. 2 L or to target dry weight)
- Na+ (~140 can be adjusted by starting at 155 and “ramping” down to minimize cramping)
- K+ (based on serum K+’)
  - Serum K+: Dialysate
    - 4.6: 1.5
    - 3.5-4: 2.5
    - <3.5: 3.5
- Ca2+: 1.25
- HCO3–: 40
- Heparin (none, tight [500 U/h] or full [1000 U/h])
- N fluid to support BP (e.g. NS)

When to Initiate Dialysis

- Ccr < 20 mL/min
- Educate patient regarding dialysis; if not a candidate for peritoneal dialysis, make arrangements for AV fistula
- Ccr < 15 mL/min
- Weigh risk and benefits for initiating dialysis
- Ccr < 10 mL/min
- Dialysis should be initiated

NOTE
- Cockcroft-Gault equation (or MDRD equation) should be used to measure kidney function
- Monitor for uremic complications
- Significant benefits in quality of life can occur if dialysis started before Ccr < 15 mL/min
- It is unclear whether patients who start dialysis early have increased survival
- A preemptive transplant can be considered if patient is stable, in order to avoid dialysis

Commonly Used Immunosuppressive Drugs

- Calcineurin inhibitors
  - Cy Isoporne
  - Tacrolimus
- Anti-proliferative medications
  - Mycophenolate mofetil
  - Azathioprine
- Other agents
  - Sirolimus
  - Prednisone
- Anti-lymphocyte antibodies
  - Thymoglobulin
  - Basiliximab

Indications for Dialysis

- (refractory to medical therapy)
  - Acute Kidney Injury
    - Acute tubular necrosis
    - Prerenal azotemia
  - Chronic Kidney Disease
    - Anemia
    - Hypertension
    - Uremia
    - Uremic pericarditis
    - Pruritus
Renal Transplantation

- provides maximum replacement of GFR
- preferred modality of RRT in CKD, not AKI
  - best way to reverse uremic signs and symptoms
- renal transplantation has been shown to have improved long-term patient survival and greater quality of life over dialysis
- native kidneys usually left in situ
- 2 types: deceased donor, living donor (related or unrelated)
- living donor transplants have been shown to have better outcomes than deceased donor transplants
- kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- 1 yr renal allograft survival rates ≥90%

Complications

- #1 cause of mortality in transplanted patients is cardiovascular disease
- de novo GN (usually membranous)
- new-onset DM (often due to prednisone and calcineurin inhibitors, especially tacrolimus)
- graft rejection
- acute rejection: graft site tenderness, rise in Cr, oliguria, ± fever, although symptoms are uncommon
- early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
- transplant glomerulopathy from antibody injury causes nephrotic proteinuria
- cyclosporine or tacrolimus nephrotoxicity (see Small Vessel Disease, NP29)
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss
- leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
- depends on immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset DM)
- infections (CMV, PJP and other opportunistic infections usually occur between 1 and 6 mo post-transplant)
- malignancy (skin cancer, Kaposi’s sarcoma, non-Hodgkin’s lymphoma)

Table 18. Common Medications in Nephrology

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
<th>Site of Action</th>
<th>Mechanism of Action (Secondary Effect)</th>
<th>Indication</th>
<th>Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop Diuretics</td>
<td>furosemide (Lasix®)</td>
<td>Thick ascending limb of Loop of Henle</td>
<td>↓ Na+/K+ (AC2) transport: renal and peripheral vasoconstrictors effects (K+ loss; ↑ H+ secretion; ↑ Ca2+ excretion)</td>
<td>Management of edema secondary to CHF, nephrotic syndrome, cirrhotic ascites; ↑ free water clearance (e.g. in SIADH-induced hypothermia), ↓ BP (less effective due to short action)</td>
<td>furosemide: edema: 20-60 mg IV/IM/PO q8-12h (max 600 mg/d) until desired response HTN: 20-80 mg PO/OD/ bid dosing</td>
<td>Allergy in sulfon-sensitive individuals Electrolyte abnormalities; hypocalcemia, hypoproteinemia, hypocalcemia, hypercalciuria (with stone formation) Volume depletion with metabolic alkalosis Precipitates gouty attacks</td>
</tr>
<tr>
<td></td>
<td>bumetamide (Bumex®, Buena®)</td>
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<td></td>
<td>ethacrynate (Edecrin®, Edecrin®)</td>
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<td>torsemide (Demadex®, Diuril®)</td>
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<tr>
<td>Thiazide Diuretics</td>
<td>hydrochlorothiazide (HCTZ)</td>
<td>Distal convoluted tubule</td>
<td>Inhibit Na+/Cl transporter (K+ loss; ↑ H+ secretion; ↑ Ca2+ excretion)</td>
<td>1st line for essential HTN Treatment of edema idiopathic/hypercalcemia and stones Diabetes insipidus (neprogenic)</td>
<td>HCTZ: edema: 25-100 mg PO/OD HTN: 12.5-25 mg PO/OD (max 50 mg) nophrothiasis/hypercalciuria: 25-100 mg PO/OD</td>
<td>Hypokalemia Increased serum urate levels Precipitates gouty attacks, hypercalciuria Elevated lipids Glucose intolerance</td>
</tr>
<tr>
<td></td>
<td>chlorothiazide (Gliuril®, Gliuril®)</td>
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<td>indapamide (Cordarone®, Lopid®)</td>
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<td></td>
<td>metolazone (Zaroxolyn®, Zaroxolyn®)</td>
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<td></td>
<td>chlorothalidone (Hygroton®, Hycroton®)</td>
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<tr>
<td>Potassium-Sparing Diuretics</td>
<td>spironolactone (Aldactone®, Aldactone®)</td>
<td>Cortical collecting duct (↓ Na+ reabsorption)</td>
<td>Aldosterone antagonist (spironolactone) Block Na+ channels (triamterene and amiloride)</td>
<td>Reduces K+ loss caused by other diuretics Edema/hypertension Severe CHF, ascites (spironolactone), cystic fibrosis (amiloride) ↓ viscosity of secretions</td>
<td>spironolactone: 25-200 mg/d OD/bid dosing HTN: 50-200 mg/d OD/bid dosing Hyperparathyroidism: 100-400 mg/d OD/ bid dosing amiloride: edema/HTN: 5-10 mg PO/OD</td>
<td>Hyperkalemia (caution with ACEI) Trameterene can be nephrotoxic (rare) Nephrotaxis (Glycosaminoglycan effect of spironolactone)</td>
</tr>
<tr>
<td></td>
<td>triamterene (Dyazide®, Dyazide®)</td>
<td></td>
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<tr>
<td></td>
<td>(spironolactone + HCTZ)</td>
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<tr>
<td></td>
<td>amiloride (Midamor®, Moduretic®)</td>
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<td></td>
<td>(amiloride + HCTZ)</td>
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<tr>
<td></td>
<td>Vaseretic® (enalapril + HCTZ)</td>
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<tr>
<td></td>
<td>Zeetron® (lisinopril + HCTZ)</td>
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<tr>
<td>Combination Agents</td>
<td>Dyazide® (triamterene + HCTZ)</td>
<td></td>
<td>Combination of ACEI and thiazide have a synergistic effect</td>
<td>Combine K+-sparring drug with thiazide to reduce hyperkalemia</td>
<td>Combine K+-sparring drug with thiazide to reduce hyperkalemia</td>
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<td></td>
<td>Aldactase® (spironolactone + HCTZ)</td>
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<td>Moduretic® (amiloride + HCTZ)</td>
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<td></td>
<td>Vaseretic® (enalapril + HCTZ)</td>
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<td></td>
<td>Zeetron® (lisinopril + HCTZ)</td>
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<tr>
<td>Osmotic Diuretics</td>
<td>mannitol (Osmolite®, Osmolyte®)</td>
<td>Renal tubules (proximal and collecting duct)</td>
<td>Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate – inhibits reabsorption of water and ↑ urinary excretion of toxic materials</td>
<td>To ↓ intracranial or intracerebral pressure Mobilization of excess fluid in renal failure or edematous states</td>
<td>mannitol: ≤ 25 g/kg IV over 30-60 min</td>
<td>Transient volume expansion Electrolyte abnormalities (↓ Na+, ↓ K+)</td>
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<tr>
<td></td>
<td>glycerol ura</td>
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Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors

NEJM 2016;374:940-950

Purpose: To assess whether there is a survival advantage to receiving a kidney from HLA-incompatible donors compared to remaining on the waiting list for a possible matched deceased donor kidney.

Study: Retrospective, multi-centre analysis

Population: 10,205 individuals who received HLA-incompatible live donor kidneys compared to two different controls: individuals waiting and possibly receiving a deceased donor kidney (N=5125), or individuals ultimate y no receiving a kidney transplant (N=5125).

Outcome: Survival, tracked for up to 8 years.

Results: Individuals who received HLA-incompatible kidneys had increased survival compared to either control group for time points at 1 year, 5 years, and 8 years post-transplant (p<0.001). After 8 years non-matched kidney recipients had 76.5% survival compared to 43.9% for individuals who ultimately did not receive a kidney transplant. Survival advantage was significant regardless of how the recipient anti-HLA antibodies were detected.

Conclusions: Individuals who received HLA-incompatible kidneys had significantly improved long-term survival compared to individuals who waited for compatible deceased donor kidneys.

Common Medications

- Osmotic Diuretics
  - mannitol (Osmolite®, Osmolyte®)
  - glycerol ura
  - provides maximum replacement of GFR
  - preferred modality of RRT in CKD, not AKI
  - best way to reverse uremic signs and symptoms
  - renal transplantation has been shown to have improved long-term patient survival and greater quality of life over dialysis
  - native kidneys usually left in situ
  - 2 types: deceased donor, living donor (related or unrelated)
  - living donor transplants have been shown to have better outcomes than deceased donor transplants
  - kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
  - 1 yr renal allograft survival rates ≥90%

Complications

- #1 cause of mortality in transplanted patients is cardiovascular disease
- de novo GN (usually membranous)
- new-onset DM (often due to prednisone and calcineurin inhibitors, especially tacrolimus)
- graft rejection
  - acute rejection: graft site tenderness, rise in Cr, oliguria, ± fever, although symptoms are uncommon
  - early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
  - transplant glomerulopathy from antibody injury causes nephrotic proteinuria
  - cyclosporine or tacrolimus nephrotoxicity (see Small Vessel Disease, NP29)
  - BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss
  - leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
  - depends on immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset DM)
  - infections (CMV, PJP and other opportunistic infections usually occur between 1 and 6 mo post-transplant)
  - malignancy (skin cancer, Kaposi’s sarcoma, non-Hodgkin’s lymphoma)
### Table 18. Common Medications in Nephrology (continued)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
<th>Site of Action</th>
<th>Mechanism of Action (Secondary Effect)</th>
<th>Indication</th>
<th>Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>ramipril (Altace®)</td>
<td>Lungs</td>
<td>Inhibits angiotensin converting enzyme, preventing formation of angiotensin II</td>
<td>HTN</td>
<td>Ramipril: HTN 2.5-20 mg PO OD/bid dosing renoprotective use; 10 mg PO OD</td>
<td>Cough, Angioedema, Hyperkalemia, Agranulocytosis (captopril) AKI, Teratogenic</td>
</tr>
<tr>
<td></td>
<td>enalapril (Vasotec®)</td>
<td>Tissues diffusely</td>
<td>Prevents angiotensin II vasoconstricting vascular smooth muscle → net vasoconstriction → ↑ BP</td>
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<tr>
<td></td>
<td>lisinopril (Prinivil®)</td>
<td></td>
<td>Reduces fibrosis and arteriogenesis</td>
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<tr>
<td></td>
<td>trandolapril (Mavik®)</td>
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<tr>
<td></td>
<td>captopril (Capoten®)</td>
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<tr>
<td>ARB</td>
<td>losartan (Cozaar®)</td>
<td>Vascular smooth muscle, adrenal cortex, proximal tubules</td>
<td>Competitive inhibitor at the angiotensin II receptor; prevents angiotensin II vasoconstricting action on vascular smooth muscle → ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↓ Na+ and H2O excretion</td>
<td>HTN</td>
<td>Losartan 25 100 mg PO OD, candesartan 8-32 mg PO OD, valsartan 80-320 mg PO OD, telmisartan 20-80 mg PO OD, eprosartan 400-800 mg PO OD, olmesartan 20-40 mg PO OD</td>
<td>Hyperkalemia, Cough – reduce dose in hepatic impairment AKI, Teratogenic</td>
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<tr>
<td></td>
<td>valsartan (Diovan®)</td>
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<td></td>
<td>eprosartan (Teveten®)</td>
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<td></td>
<td>irbesartan (Avapro®)</td>
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<td></td>
<td>olmesartan (Olmetec®)</td>
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<td></td>
<td>ramipril (Altace®)</td>
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<td>lisinopril (Prinivil®)</td>
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<td></td>
<td>telmisartan (Micardis®)</td>
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<td>eprosartan (Teveten®)</td>
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<td>irbesartan (Avapro®)</td>
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<tr>
<td></td>
<td>olmesartan (Olmetec®)</td>
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</tbody>
</table>

### Landmark Nephrology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D</td>
<td>NEJM 2005;353:238-48</td>
<td>Patients with type 2 DM receiving maintenance hemodialysis were randomized to 20 mg of atorvastatin per day or matching placebo; no difference in composite index of death from cardiac causes, nonfatal myocardial infarction, and stroke</td>
</tr>
<tr>
<td>AASK</td>
<td>JAMA 2001;285:2719-28</td>
<td>Ramipril, compared with amloidipine, slows progression of hypertensive renal disease and proteinuria and may benefit patients without proteinuria as well</td>
</tr>
<tr>
<td>ACCOMPLISH</td>
<td>NEJM 2008;359:2417-20</td>
<td>Combination treatment with an ACEI and a CCB (benazepril-amlodipine) was more successful than a combination of ACEI and a thiazide diuretic (benzapril-HCTZ) in reducing cardiovascular events in patients with HTN who were at risk for such events</td>
</tr>
<tr>
<td>ACEI and Diabetic</td>
<td>NEJM 1993;329:1456-62</td>
<td>Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood pressure control alone</td>
</tr>
<tr>
<td>ALERT</td>
<td>Lancet 2003;361:2024-31</td>
<td>The use of fluvastatin in renal transplant recipients did not significantly decrease the risk of the occurrence of a major adverse cardiac event (defined as cardiac death, non-fatal MI, or coronary intervention procedure) compared with placebo; however, there was a significant reduction in cardiac deaths or non-fatal MI</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>Early Termination (Unpublished Results;protocol – NDT 2009;24:166-71)</td>
<td>Combining Aliskiren with ACEI or ARB in high-risk patients with type 2 DM leads to increased incidence of nonfatal stroke, hyperkalemia, and hypertension</td>
</tr>
<tr>
<td>ASTRAL</td>
<td>NEJM 2009;361:1956-62</td>
<td>Renal artery recanalization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality, and carries significant operative risks</td>
</tr>
<tr>
<td>AURORA</td>
<td>NEJM 2009;360:1395-407</td>
<td>Patients receiving maintenance hemodialysis randomized to rosuvastatin 10 mg daily or placebo; rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
</tr>
<tr>
<td>BENEDICT</td>
<td>NEJM 2004;351:1941-51</td>
<td>Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 DM and HTN with normoalbuminuria</td>
</tr>
<tr>
<td>CHOIR</td>
<td>NEJM 2006;355:2085-98</td>
<td>Patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 135 g/L or 113 g/L; the higher target group had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), or stroke</td>
</tr>
<tr>
<td>CORAL</td>
<td>NEJM 2014; 370:1-22</td>
<td>Renal-artery stenting did not confer a significant benefit with respect to the prevention of renal or cardiac events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease</td>
</tr>
<tr>
<td>CREATE</td>
<td>NEJM 2006;355:2071-84</td>
<td>Patients with CKD (15 35 mL/min) and mild to moderate anemia (110-125 g/L) were randomized to normal (130-150 g/L) or subnormal (105-115 g/L) hemoglobin levels; early and complete correction of hemoglobin did not reduce the risk of cardiovascular events</td>
</tr>
<tr>
<td>Trial</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>DETAIL</td>
<td>NEJM 2004;351:1952-61</td>
<td>The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 DM with mild to moderate HTN and early nephropathy</td>
</tr>
<tr>
<td>ELITE SYMPHONY</td>
<td>NEJM 2007;357:2562-75</td>
<td>Daclizumab induction, MMF, steroids, and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNI regimens</td>
</tr>
<tr>
<td>FHN</td>
<td>NEJM 2010;363:2297-300</td>
<td>Patients were randomized to dialysis 6x/wk (frequent) or 3x/wk (conventional); frequent hemodialysis was associated with improvement in composite outcomes of death, or change in left ventricular mass and death, or change in a physical-health composite score; frequent hemodialysis caused more frequent interventions related to vascular access</td>
</tr>
<tr>
<td>HEM0</td>
<td>NEJM 2002;347:2010-19</td>
<td>Use of high dose dialysis or high flux membranes versus standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes; possible benefit in cardiac-related outcomes with high flux membranes</td>
</tr>
<tr>
<td>IDEAL</td>
<td>NEJM 2010;363:609-19</td>
<td>Patients with progressive CKD and GFR between 10 and 15 mL/min randomized to initiate dialysis at GFR of 10-14 mL/min (early) or 5.7 mL/min (late); early initiation of dialysis in patients with stage G5 CKD was not associated with an improvement in survival or clinical outcomes</td>
</tr>
<tr>
<td>IDNT</td>
<td>NEJM 2001;345:851-60</td>
<td>Treatment with irbesartan reduced the risk of developing end-stage renal disease and worsening renal function in patients with type 2 DM and diabetic nephropathy</td>
</tr>
<tr>
<td>IRMA</td>
<td>NEJM 2001;345:670-8</td>
<td>Irbesartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 DM and microalbuminuria</td>
</tr>
<tr>
<td>MDRD</td>
<td>Ann Intern Med 1995;123:75-62</td>
<td>Patients with proteinuria of more than 1 g/d should have a target BP &lt;125/75 mmHg; patients with proteinuria of 0.25 to 1.0 g/d should have a target BP &lt;130/80 mmHg</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Lancet 2008;372:547-53</td>
<td>Telmisartan and ramipril monotherapy reduced proteinuria and rise in Cr in patients with high vascular risk; combination of the two agents led to increased acute renal failure episodes, syncope, and hypotension</td>
</tr>
<tr>
<td>REIN</td>
<td>Lancet 1999;354:359-64</td>
<td>In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria</td>
</tr>
<tr>
<td>REIN2</td>
<td>Lancet 2005;365:399-406</td>
<td>In non-diabetic nephropathy already on ACEI, no further benefit from intensified BP control (sBP/dBP&lt;130/80 mmHg) by adding a CCB versus conventional BP control (dBP&lt;90 mmHg) on ACEI alone</td>
</tr>
<tr>
<td>RENAAAL</td>
<td>NEJM 2001;345:861-9</td>
<td>Losartan conferred significant renal benefits in patients with type 2 DM and nephropathy and was generally well tolerated</td>
</tr>
<tr>
<td>RENAL</td>
<td>NEJM 2009;361:1627-38</td>
<td>High intensity continuous renal-replacement therapy in AKI does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia</td>
</tr>
<tr>
<td>Rituximab in Children with Steroid-Dependent Nephrotic Syndrome</td>
<td>JASN 2015;26 DO:ASN.201406799</td>
<td>Rituximab is non-inferior to steroids in maintaining remission in juvenile steroid dependent nephrotic syndrome</td>
</tr>
<tr>
<td>ROAD</td>
<td>JASN 2007;18:1899-98</td>
<td>Uptitrations of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without DM who had proteinuria and renal insufficiency</td>
</tr>
<tr>
<td>ROADMAP</td>
<td>NEJM 2011;364:907-17</td>
<td>The use of the ARB olmesartan was more effective than placebo in delaying the onset of microalbuminuria in patients with type 2 DM, normoalbuminuria, and good blood pressure control; however, a higher rate of fatal cardiovascular events was found amongst patients with preexisting coronary heart disease in the olmesartan group</td>
</tr>
<tr>
<td>SHARP</td>
<td>Lancet 2011;377:2181-92</td>
<td>Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization took simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo; simvastatin 20 mg plus ezetimibe 10 mg daily resulted in reduction of LDL cholesterol with associated reduction of major atherosclerotic events in patients with CKD</td>
</tr>
<tr>
<td>SPRINT</td>
<td>NEJM 2015;373:2102-2116</td>
<td>A lower blood pressure target of 120/80 reduced the risk of composite cardiovascular events in a hypertensive patient population</td>
</tr>
<tr>
<td>TREAT</td>
<td>NEJM 2009;361:2019-32</td>
<td>Patients with type 2 DM, CKD, and anemia were randomized to darbepoetin targeting a hemoglobin of 13 g/dL or placebo; darbepoetin did not reduce the risk of death, a cardiovascular event, or a renal event, and was associated with an increased risk of stroke</td>
</tr>
<tr>
<td>Tolvaptan in ADPKD</td>
<td>NEJM 2012;367:2407-18</td>
<td>Tolvaptan (vs. placebo) slowed the increase in total kidney volume and decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, due to adverse events</td>
</tr>
<tr>
<td>SGLT 2 inhibitor use and diabetic</td>
<td>J Am Soc Nephrol 2017;28:388-375</td>
<td>Canagliflozin a sodium-glucose cotransporter 2 inhibitor, slowed the progress on of renal disease over 2 years in patients with type 2 diabetes, and may confer renoprotective effects independently of glycemic control</td>
</tr>
</tbody>
</table>
Approach to the Neurological Complaint .......................... 2
Lesion Localization
The Neurological Exam .............................................. 3
General Exam and Mental Status
Cranial Nerve Exam
Motor Exam
Sensory Exam
Coordination Exam and Gait
Basic Anatomy Review ............................................. 6
Lumbar Puncture ....................................................... 9
Approach to Common Presentations ......................... 9
Weakness
Numbness/Altered Sensation
Gait Disturbance
Cranial Nerve Deficits ............................................. 11
CN I  CN IV  CN VII  CN X
CN II  CN V  CN VIII  CN XI
CN III  CN VI  CN IX  CN XII
Neuro-Ophthalmology ............................................... 14
Optic Neuritis
Anterior Ischemic Optic Neuropathy (AION)
Amaurosis Fugax
Optic Disc Edema
Optic Disc Atrophy
Abnormalities of Visual Field ................................. 15
Disorders of Gaze
Internuclear Ophthalmoplegia
Diplopia
Nystagmus
Abnormalities of Pupils
Nutritional Deficiencies and Toxic Injuries .......... 17
Seizure Disorders and Epilepsy .......................... 18
Seizure
Status Epilepticus
Behavioural Neurology .......................................... 20
Acute Confusional State/Delirium
Mild Neurocognitive Disorder
Major Neurocognitive Disorder
Major or Mild NCD due to Alzheimer’s Disease
Major or Mild NCD with Lewy Bodies
Major or Mild Frontotemporal NCD
Major or Mild Vascular NCD
Creutzfeldt-Jakob Disease
Aphasia
Apraxia
Agnosia
Mild Traumatic Brain Injury ................................. 28
Neuro-Oncology ..................................................... 29
Paraneoplastic Syndromes
Tumours of the Nervous System
Movement Disorders ............................................. 29
Function of the Basal Ganglia
Overview of Movement Disorders
Parkinson’s Disease
Other Parkinsonian Disorders
Huntington’s Disease
Dystonia
Tic Disorders
Tourette’s Syndrome
Cerebellar Disorders .............................................. 34
Wernicke-Korsakoff Syndrome
Cerebellar Ataxias
Vertigo ................................................................. 35
Motor Neuron Disease ............................................. 35
Amyotrophic Lateral Sclerosis
Other Motor Neuron Diseases
Peripheral Neuropathies ...................................... 36
Neuromuscular Junction Diseases ..................... 38
Myasthenia Gravis
Lambert-Eaton Myasthenic Syndrome
Botulism
Myopathies .......................................................... 40
Clinical Approach to Muscle Diseases
Myotonic Dystrophy
Pain Syndromes .................................................... 41
Approach to Pain Syndromes
Neuropathic Pain
Trigeminal Neuralgia
Postherpetic Neuralgia
Painful Diabetic Neuropathy
Complex Regional Pain Syndromes
Headache ............................................................... 44
Migraine Headaches
Sleep Disorders ....................................................... 46
Overview of Sleep
Disturbances of Alertness and Sleep
CNS Infections ...................................................... ID18
Spinal Cord Syndromes ....................................... NS29
Stroke ................................................................. 48
Terminology
Pathophysiology
Assessment and Treatment of Ischemic Stroke
Primary and Secondary Prevention of Ischemic Stroke
Cerebral Hemorrhage
Neurocutaneous Syndromes ................................ P79
Multiple Sclerosis ................................................. 52
Common Medications .......................................... 54
Landmark Neurology Trials ................................ 55
References ............................................................ 55
### Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>anterior cerebral artery</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>ADL</td>
<td>activities of daily living</td>
</tr>
<tr>
<td>AED</td>
<td>anti-epileptic drugs</td>
</tr>
<tr>
<td>AREN</td>
<td>acute ischemic optic neuropathy</td>
</tr>
<tr>
<td>ALS</td>
<td>amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>AVM</td>
<td>arteriovenous malformation</td>
</tr>
<tr>
<td>AVPU</td>
<td>alert, verbal, pain, unresponsive</td>
</tr>
<tr>
<td>CJD</td>
<td>Creutzfeldt-Jakob disease</td>
</tr>
<tr>
<td>CN</td>
<td>cranial nerve</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CRVO</td>
<td>central retinal vein occlusion</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CVJ</td>
<td>cerebrovascular disease</td>
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<tr>
<td>DBS</td>
<td>deep brain stimulation</td>
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<tr>
<td>DLB</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>EMD</td>
<td>extracorpuscular movement</td>
</tr>
<tr>
<td>EOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>EED</td>
<td>ethanol equivalent dose</td>
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<tr>
<td>FEF</td>
<td>frontal eye field</td>
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<tr>
<td>FTD</td>
<td>frontotemporal dementia</td>
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<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
</tr>
<tr>
<td>GCA</td>
<td>giant cell arteritis</td>
</tr>
<tr>
<td>GpV</td>
<td>Globus pallidus pars externa</td>
</tr>
<tr>
<td>GpP</td>
<td>Globus pallidus pars interna</td>
</tr>
<tr>
<td>HD</td>
<td>Huntington's disease</td>
</tr>
<tr>
<td>IAAD</td>
<td>instrumental activities of daily living</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
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<td>intracranial hemorrage</td>
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<td>intracranial venous pressure</td>
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<tr>
<td>IIV</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>JCV</td>
<td>John Cunningham virus</td>
</tr>
<tr>
<td>LEMS</td>
<td>Lambert-Eaton myasthenic syndrome</td>
</tr>
<tr>
<td>LGB</td>
<td>lateral geniculate body</td>
</tr>
<tr>
<td>LMN</td>
<td>lower motor neuron</td>
</tr>
<tr>
<td>LOC</td>
<td>level of consciousness</td>
</tr>
<tr>
<td>LP</td>
<td>lumbar puncture</td>
</tr>
<tr>
<td>MCA</td>
<td>middle cerebral artery</td>
</tr>
<tr>
<td>MG</td>
<td>myasthenia gravis</td>
</tr>
<tr>
<td>MLF</td>
<td>medial longitudinal fasciculus</td>
</tr>
<tr>
<td>MMSE</td>
<td>mini mental status examination</td>
</tr>
<tr>
<td>NC</td>
<td>nerve conduction studies</td>
</tr>
<tr>
<td>NCS</td>
<td>nerve conduction studies</td>
</tr>
<tr>
<td>NMJ</td>
<td>neuromuscular junction</td>
</tr>
<tr>
<td>NPH</td>
<td>normal pressure hydrocephalus</td>
</tr>
<tr>
<td>PComn</td>
<td>posterior communicating artery</td>
</tr>
<tr>
<td>PCA</td>
<td>posterior cerebral artery</td>
</tr>
<tr>
<td>PIC</td>
<td>posterior inferior cerebellar artery</td>
</tr>
<tr>
<td>PLMS</td>
<td>periodic limb movement in sleep</td>
</tr>
<tr>
<td>PPA</td>
<td>primary progressive aphasia</td>
</tr>
<tr>
<td>PPRF</td>
<td>paramedian pontine reticular formation</td>
</tr>
<tr>
<td>PSP</td>
<td>progressive supranuclear palsy</td>
</tr>
<tr>
<td>RADO</td>
<td>relative afferent pupillary defect</td>
</tr>
<tr>
<td>REM</td>
<td>rapid eye movement</td>
</tr>
<tr>
<td>RLS</td>
<td>restless legs syndrome</td>
</tr>
<tr>
<td>ROM</td>
<td>range of motion</td>
</tr>
<tr>
<td>SAD</td>
<td>subarachnoid hemorrhage</td>
</tr>
<tr>
<td>SDH</td>
<td>subdural hemorrhage</td>
</tr>
<tr>
<td>SNC</td>
<td>substantia nigra pars compacta</td>
</tr>
<tr>
<td>SNr</td>
<td>substantia nigra pars reticulata</td>
</tr>
<tr>
<td>STN</td>
<td>subthalamic nucleus</td>
</tr>
<tr>
<td>TBI</td>
<td>traumatic brain injury</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>UMN</td>
<td>upper motor neuron</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>VZV</td>
<td>varicella zoster virus</td>
</tr>
</tbody>
</table>

### Approach to the Neurological Complaint

**Lesion Localization**

- **cortical**
  - contralateral paresis (with differential effect on face and arm vs. leg)
  - UMN injury (hyperreflexia, Babinski sign, spasticity, no atrophy, pyramidal pattern of weakness)
  - cortical sensory loss (hemisensory loss, position sense, two-point discrimination, graphesthesia, stereognosis)
  - dominant hemisphere (aphasia, alexia, agraphia, acalculia, left-right disorientation)
  - non-dominant hemisphere (hemineglect, dysprosody, anosmia, constructional apraxia)
  - homonymous hemianopia, quadrantanopia
  - gaze deviation
  - seizure
  - agnosia (visual, auditory)
  - apraxia
  - alien hand syndrome

- **subcortical**
  - internal capsule: contralateral paresis with equal face, arm, leg involvement without sensory/cortical deficits; contralateral dysmetria/clumsiness and leg paresis
  - basal ganglia: pill-rolling tremor, bradykinesia, festinating gait, hemiballismus, chorea, dystonic posture
  - thalamus: dense sensory loss, contralateral severe pain

- **brainstem (bulbar)**
  - crossed hemiplegia or sensory loss (i.e. ipsilateral face, contralateral body)
  - ipsilateral cerebellar (dysmetria, rapid alternating movements, tandem gait)
  - nystagmus toward lesion, diplopia, INO (impaired adduction on contralateral gaze)
  - dysphagia, dysarthria
  - hearing loss, vertigo

- **cerebellum**
  - ipsilateral ataxia (unsteadiness, incoordination)
  - dysmetria, intention tremor
  - dysdiadochokinesis
  - wide-based gait, truncal titubation (staggering, reeling, lurching)
  - scanning speech (explosive speech with noticeable pauses and accentuated syllables)
  - nystagmus, distorted smooth pursuit, oscillopsia

- **spinal cord**
  - bilateral motor and/or sensory deficits below the lesion without facial involvement
  - ataxia, sensory level (sharp line below which there is decreased sensation); suspended "cape-like" sensory level
  - LMN signs (flaccid paresis, hypotonia, hyporeflexia, atrophy, fasciculations) at level of lesion; UMN signs below lesion (marked spasticity and Babinski)
  - bowel, bladder, sexual dysfunction
  - saddle anesthesia
  - ataxia

- **nerve root**
  - multiple peripheral nerve involvement
  - myotomal/dermatomal deficits
  - back/neck pain radiating to leg/arm
• peripheral nerve
  ■ distal “stocking-glove distribution” sensory loss
  ■ LMN signs (hypotonia, hyporeflexia, fasciculations, atrophy)
• neuromuscular junction
  ■ fluctuating/fatiguable symptoms
  ■ facial and limb weakness
  ■ dysphonia, dysarthria
  ■ ophthalmoparesis (diplopia), ptosis
• muscle
  ■ symmetric proximal weakness (climbing stairs, getting up from chair) without sensory deficits
  ■ muscle tenderness
  ■ muscle atrophy

The Neurological Exam

General Exam and Mental Status

• vitals: pulse (especially rhythm), BP, RR, temperature
• H&N: meningismus, head injury/bruises (signs of basal skull fracture: Battle’s sign, raccoon eyes, hemotympanum, CSF rhinorrhea/otorrhea), tongue biting
• CVS: carotid bruits, heart murmurs
• mental status: orientation (person, place, time), LOC (GCS) (see Emergency Medicine, ER4)
  ■ GCS/15 – Motor/6, Verbal/5 (T= intubated), Eyes/4
• cognition
  ■ Folstein MMSE – /30 (note: dementia is a clinical diagnosis and is not diagnosed by cognitive testing)
  ■ MoCA – /30 (≥26 is considered normal)
  ■ frontal lobe testing (for perseveration – i.e. go/no-go test)
  ■ clock drawing

Screening Neurologic Exam

• Mental status: orientation (person, place, time), obeys commands, GCS
• Head and neck: examine for lacerations, contusions, deformities, signs of basal skull fracture, flex neck for meningismus if c-spine injury has been ruled out
• Cranial nerve exam: visual fields ± fundoscopy, pupil size and reactivity, extraocular movements, facial strength, hearing to finger rub
• Motor: tone, power in deltoids, triceps, wrist extensors, hand interossei, hamstrings, ankle dorsiflexors, pronator drift
• Coordination: finger tapping, finger-to-nose, heel knee shin
• Gait: tandem gait, heel walking
• Reflexes: plantar, biceps, triceps, patellar
• Sensation: all 4 limbs, including double simultaneous stimulation, vibration sense

Cranial Nerve Exam

Table 1. Cranial Nerve Examination and Associated Deficits

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Recommended Physical Exams</th>
<th>Signs/Symptoms of Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory (CN I)</td>
<td>Odour sensation: test each nostril separately</td>
<td>Anosmia (can be associated with loss of taste)</td>
</tr>
<tr>
<td>Optic (CN II)</td>
<td>Visual acuity: test each eye individually; best corrected vision</td>
<td>Blindness Absence of light reflexes, RAPD</td>
</tr>
<tr>
<td></td>
<td>Test visual fields</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assess pupils: direct and consensual pupillary reaction (afferent), swinging flashlight test (for RAPD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fundoscopy: optic disc edema and pallor, venous pulsations, hemorrhages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colour vision testing (Ishihara plates)</td>
<td></td>
</tr>
<tr>
<td>Oculomotor (CN III)</td>
<td>Assess extraocular movements and nystagmus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test efferent limb of pupillary light response</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assess size and shape of pupils; accommodation and saccadic eye movements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for ptosis (levator palpebrae superioris)</td>
<td>Eyes deviated down and out; can demonstrate mydriasis</td>
</tr>
<tr>
<td>Trochlear (CN IV)</td>
<td>Test movement of superior oblique</td>
<td>Vertical diplopia; may tilt head towards unaffected side; affected eye cannot turn inward and downward</td>
</tr>
<tr>
<td>Trigeminal (CN V)</td>
<td>Test sensation above supraorbital ridge (V1), buccal area (V2), mandible (V3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test corneal reflex (afferent limb)</td>
<td>Loss of facial sensations and corneal reflex on stimulation ipsilaterally, weakness and wasting of muscles of mastication, deviation of open jaw to ipsilateral side; trigeminal neuralgia</td>
</tr>
<tr>
<td></td>
<td>Assess motor function: temporalis, masseter, pterygoids, jaw jerk reflex</td>
<td></td>
</tr>
<tr>
<td>Abducens (CN VI)</td>
<td>Test movement of lateral rectus</td>
<td>Horizontal diplopia, esotropia (convergent strabismus) and abductor paralysis of ipsilateral eye</td>
</tr>
<tr>
<td>Facial (CN VII)</td>
<td>Test sensorimotor nerve function with muscles of facial expression</td>
<td>Paralysis of ipsilateral upper and lower facial muscles</td>
</tr>
<tr>
<td></td>
<td>Test efferent limb of corneal reflex</td>
<td>Loss of lacrimation</td>
</tr>
<tr>
<td></td>
<td>Visceral sensory nerve function: to anterior 2/3 of the tongue</td>
<td>Decreased salivation, dry mouth</td>
</tr>
<tr>
<td></td>
<td>Visceral motor nerve function: to salivary and lacrimal glands</td>
<td>Loss of taste to anterior 2/3 of the tongue ipsilaterally</td>
</tr>
<tr>
<td></td>
<td>LMN lesion = ipsilateral facial weakness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UMN lesion = contralateral facial weakness, sparing the brow bilaterally</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. Cranial Nerve Examination and Associated Deficits (continued)

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Recommended Physical Exams</th>
<th>Signs/Symptoms of Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibulocochlear (CN V II)</td>
<td>Vestibular function - nystagmus, caloric reflexes</td>
<td>Vertigo, disequilibrium, and nystagmus Sensorineural hearing loss</td>
</tr>
<tr>
<td></td>
<td>Cochlear function - whisper test, Rinne, Weber</td>
<td></td>
</tr>
<tr>
<td>Glossopharyngeal (CN IX)</td>
<td>Assess vocal cord function and gag reflex</td>
<td>Loss of taste in posterior third of ipsilateral tongue Unilateral lesion is rare</td>
</tr>
<tr>
<td></td>
<td>Assess taste to posterior third of the tongue (bitter and sour taste)</td>
<td>Loss of gag reflex and dysphasia</td>
</tr>
<tr>
<td>Vagus (CN X)</td>
<td>Assess vocal cord function and gag reflex</td>
<td>Paralysis of soft palate (failed elevation)</td>
</tr>
<tr>
<td></td>
<td>Observe uvula deviation and palatal elevation</td>
<td>Deviation of uvula to contralateral side of lesion; anesthesia of pharynx and larynx ipsilaterally</td>
</tr>
<tr>
<td>Accessory (CN XI)</td>
<td>Assess strength of trapezius (shoulder shrug) and sternocleidomastoid muscles (head turn)</td>
<td>Ipsilateral shoulder weakness and turning head to opposite side</td>
</tr>
<tr>
<td>Hypoglossal (CN XII)</td>
<td>Inspect tongue for signs of lateral deviation, atrophy, fasciculations, asymmetry of movement and strength</td>
<td>Wasting of ipsilateral tongue muscles and deviation to ipsilateral side on protrusion</td>
</tr>
</tbody>
</table>

### Table 2. Localization of Motor Deficits

<table>
<thead>
<tr>
<th>LMN</th>
<th>UMN</th>
<th>Extrapyramidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Tone</td>
<td>Flaccid</td>
<td>Spastic</td>
</tr>
<tr>
<td>Involuntary Movements</td>
<td>Fasciculations</td>
<td>None</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Plantar Reflex</td>
<td>Down-going (flexor)</td>
<td>Up-going (extensor, i.e. Babinski sign)</td>
</tr>
<tr>
<td>Pattern of Muscle Weakness</td>
<td>Proximal, distal, or focal</td>
<td>Pyramidal pattern: look for hemiparetic gait (flexed arm, extended legs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper extremities: extensors weaker than flexors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower extremities: flexors weaker than extensors</td>
</tr>
</tbody>
</table>

### Table 3. Overview of Neuromuscular Diseases

<table>
<thead>
<tr>
<th>Motor Neuron Disease (i.e. ALS)</th>
<th>Peripheral Neuropathy</th>
<th>Neuromuscular Junction</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and Symptoms</td>
<td>Weakness: Segmental and asymmetrical, distal → proximal</td>
<td>Distal (except GBS) but may be asymmetrical</td>
<td>Proximal and fatigable (e.g. MG), or weak then recovers (e.g. LEMS)</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Increased</td>
<td>Decreased/absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Sensory</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Autonomic*</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Tests

- **EMG**: Denervated and reinnervated, signs of demyelination ≤ anomalous loss, decremental response, jitter on single fibre EMG, small, short motor potentials
- **NCS**: Normal
- **Muscle Enzyme**: Normal

* *e.g. orthostatic hypotension, anhidrosis, visual blurring, urinary hesitancy or incontinence, constipation, erectile dysfunction*
Table 4. Approach to Strength Testing of Radiculopathies vs. Peripheral Neuropathies

How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, all associated peripheral nerves (and their movements) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerve. Particularly useful peripheral nerve “pairs” are bolded for emphasis.

<table>
<thead>
<tr>
<th>Root</th>
<th>Peripheral Nerve</th>
<th>Movement</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Axillary</td>
<td>Shoulder abd.</td>
<td>Deltoid</td>
</tr>
<tr>
<td>C6</td>
<td>Musculocutaneous (C5/6) Radial (C6)</td>
<td>Elbow flexion</td>
<td>Biceps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elbow flexion</td>
<td>Brachioradialis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wrist ext.</td>
<td>Extensor carpi radialis longus</td>
</tr>
<tr>
<td>C7</td>
<td>Radial</td>
<td>Elbow ext.</td>
<td>Triceps</td>
</tr>
<tr>
<td></td>
<td>Posterior interosseus</td>
<td>Finger ext.</td>
<td>Extensor digitorum communis</td>
</tr>
<tr>
<td>C8, T1</td>
<td>Median</td>
<td>Thumb flexion</td>
<td>Flexor pollicis brevis (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thumb abd. mover</td>
<td>Abductor pollicis brevis (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opposition</td>
<td>Opponens pollicis (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td>Ulnar</td>
<td>Finger abd.</td>
<td>First dorsal interosseus (look for wasting in first dorsal webbed space)</td>
</tr>
<tr>
<td>L2, 3, 4</td>
<td>Femoral</td>
<td>Hip ext.</td>
<td>Iliopsoas</td>
</tr>
<tr>
<td></td>
<td>Obturator</td>
<td>Hip add.</td>
<td>Adductor muscles</td>
</tr>
<tr>
<td>L3, 4</td>
<td>Femoral (L2/4)</td>
<td>Knee ext.</td>
<td>Quadriceps</td>
</tr>
<tr>
<td></td>
<td>Deep peroneal (L4/5)</td>
<td>Dorsiflexion</td>
<td>Tibialis anter or</td>
</tr>
<tr>
<td>L5</td>
<td>Sciatic (L5, S1)</td>
<td>Hip ext.</td>
<td>Gluteus maximus</td>
</tr>
<tr>
<td></td>
<td>Tibial Superficial peroneal</td>
<td>Ankle ext.</td>
<td>Peroneal muscles</td>
</tr>
<tr>
<td></td>
<td>Deep peroneal</td>
<td>Ankle ev.</td>
<td>Extensor hallucis longus</td>
</tr>
<tr>
<td>S1</td>
<td>Sciatic</td>
<td>Knee ext.</td>
<td>Hamstring muscles</td>
</tr>
<tr>
<td></td>
<td>Tibial</td>
<td>Plantar ext.</td>
<td>Gastrocnemius and soleus</td>
</tr>
</tbody>
</table>

Sensory Exam

- primary sensation
  - spinothalamic tract: crude touch, pain, temperature
  - dorsal column-medial lemniscus pathway: fine touch, vibration, proprioception
- cortical sensation
  - graphesthesia, stereognosis, extinction, 2 point discrimination

Coordination Exam and Gait

- coordination exam
  - finger-to-nose, heel-to-shin, knee taps, rapid alternating movements
- stance and gait
  - Romberg test
  - pull test or push and release test for postural instability
  - gait: antalgic, hemiplegic, ataxic, apraxic (or apraxia-like – not necessarily true apraxia), Parkinsonian gait, foot drop, broad-based
  - tandem gait (heel-to-toe test)
Basic Anatomy Review

Figure 1. Brainstem (axial view)

Figure 2. Brainstem (posterior view)
Figure 3. Discriminative touch pathway (dorsal column) from body

Figure 4. Spinothalamic tract from body

Figure 5. Discriminative touch pathway (dorsal column) from face

Figure 6. Spinothalamic tract pathway from face

Figure 7. Corticospinal motor pathway
Figure 8. Sympathetic and parasympathetic pathway

Sympathetic
- Pupil (Dilation, Constriction)
- Lacrimal and salivary glands (Modulate secretion)
- Submaxillary g. (salivation)
- Otic g. (parotid secretion)
- Superior cervical ganglion
- Bronchodilation
- Coronary arteries and heart rate (Vasodilation, acceleration)
- Glycogen utilization
- Adrenal medulla
- Bladder (Inhibit constriction)
- Reproductive system
- Piloerector
- Skin
- Vasoconstriction

Parasympathetic
- Pupil (Dilation, Constriction)
- Lacrimal and salivary glands (Modulate secretion)
- Pterygopalatine g. (lacrimation)
- Modulate secretion
- Otic g. (parotid secretion)
- Bronchodilation
- Coronary arteries and heart rate (Vasoconstriction, deceleration)
- Glycogen utilization
- Liver
- Bile secretion
- Gl tract
- GI tract
- Inhibit motility and enzyme secretion
- Stimulate motility and enzyme secretion
- Reproductive system
- Ejaculation
- Erection

Figure 9 Dermatome map

Myotomes
- C5 – Shoulder abduction/elbow flexion
- C6 – Wrist extenders
- C7 – Elbow extension
- C8 – Finger flexion
- T1 – Finger abduction
- T2–9 – Intercostal (abdominal reflexes)
- T9-10 – Upper abdominals
- T11–12 – Lower abdominals
- L1 – Hip flexion
- L2 – Hip adduction
- L4 – Knee extension and ankle dorsiflexion
- L5 – Ankle dorsiflexion and big toe extension
- S1 – Plantarflexion
Lumbar Puncture

**Indications**
- diagnostic: CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barré, vasculitis), subarachnoid hemorrhage (if CT negative), CNS neoplasm (neoplastic meningitis)
- therapeutic: to administer anesthesia, chemotherapy, contrast media; to decrease ICP (pseudotumour cerebri, NPH)

**Contraindications**
- mass lesion causing increased ICP, could lead to cerebral herniation; CT first if suspect mass lesion
- infection over LP site/suspected epidural abscess
- low platelets (<50,000) or treatment with anticoagulation (high INR or aPTT)
- uncooperative patient

**Complications**
- tonsillar herniation (rare)
- SDH (rare)
- transient 6th nerve palsy (rare)
- post-LP headache (5-40%): worse when upright, better sitting; generally onset within 24 h
  - prevention: smaller gauge (i.e. 22) needle, reinsert stylet prior to needle removal, blunt-ended needle
  - symptomatic treatment: caffeine and sodium benzoate injection
  - corrective treatment: blood patch (autologous)

**LP Tubes**
- **tube #1**: cell count and differential: RBCs, WBCs, and differential
  - xanthochromia (yellow bilirubin pigmentation implies recent bleed into CSF, diagnostic of SAH)
- **tube #2**: chemistry: glucose (compare to serum glucose) and protein
- **tube #3**: microbiology: Gram stain and C&S
  - specific tests depending on clinical situation/suspicion
    - viral: PCR for herpes simplex virus (HSV) and other viruses
    - bacterial: polysaccharide antigens of *H. influenzae*, *N. meningitidis*, *S. pneumoniae*
    - fungal: cryptococcal antigen, culture
    - TB: acid-fast stain, TB culture, TB PCR
- **tube #4**: cytology: for evidence of malignant cells
- **tube #5**: cell count: compare RBC count to that of tube #1
  - note: tube 4 or 5 can be sent for repeat cell count

**Table 5. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colour</th>
<th>Protein</th>
<th>Glucose</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL</strong></td>
<td>Clear</td>
<td>&lt;0.45 g/L</td>
<td>60% of serum glucose or &gt;3.0 mmol/L</td>
<td>0.5 x 10^6/L</td>
</tr>
<tr>
<td><strong>Viral Infection</strong></td>
<td>Clear or opalescent</td>
<td>Normal or slightly increased &lt;0.45-1 g/L</td>
<td>Normal</td>
<td>&lt;1,000 x 10^6/L</td>
</tr>
<tr>
<td><strong>Bacterial Infection</strong></td>
<td>Opalescent yellow, may clot</td>
<td>&gt;1 g/L</td>
<td>Decreased (&lt;25% serum glucose or &lt;2.0 mmol/L)</td>
<td>&gt;1,000 x 10^6/L PMNs</td>
</tr>
<tr>
<td><strong>Granulomatous Infection</strong> (tuberculosis, fungal)</td>
<td>Clear or opalescent</td>
<td>Increased but usually &lt;5 g/L</td>
<td>Decreased (usually &lt;2.0-4.0 mmol/L)</td>
<td>&lt;1,000 x 10^6/L Lymphocytes</td>
</tr>
</tbody>
</table>

**Approach to Common Presentations**

**Weakness**

**Approach**
- **mode of onset**: abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (hereditary, degenerative, endocrine, neoplastic)
- **course**: worse at onset (vascular), progressive (neoplastic, degenerative, infective), episodic (vascular, inflammatory), activity dependent (NMJ, muscular)
- **pattern**: objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
- **associated symptoms**: sensory, cortical, autonomic, spinal (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
- **history**: family history, developmental history, medications, risk factors, recent/preceding exposures
- **investigations for LMN**: NCS/EMG
- **investigations for UMN**: imaging (brain and/or spinal cord)
Differential Diagnosis
• objective muscle weakness; also, differentiate between true muscle weakness vs. fatigue
  • generalized
    • myopathy (proximal > distal weakness)
      – endocrine: hypothyroidism, hyperthyroidism, Cushing's syndrome
      – rheumatologic: polymyositis, vasculitis
      – infectious: HIV, CMV, influenza
      – other: collagen vascular disorders, steroids, statins, alcohol, electrolyte disorders
    • NMJ (MG, botulism, LEMS, organophosphate poisoning)
    • cachexia
  • localized
    • UMN (vasculitis, abscess, brain tumour, vitamin B12 deficiency, MS, stroke)
    • radicular pain (i.e. nerve root)
    • anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic, lead toxicity)
    • peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
• no objective muscle weakness
  • chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  • depression, deconditioning

Numbness/Altered Sensation
Approach
• positive sensory symptoms: paresthesia/dysesthesia = tingling, pins and needles, prickling, burning, stabbing
• negative sensory symptoms: hypoesthesia/anesthesia = numbness, reduction/absence of feeling
• determine distribution of sensory loss:
  • nerve root vs. peripheral nerve
  • symmetric stocking-glove pattern (indicative of distal symmetric polyneuropathy)
  • dissociated sensory loss: dorsal column (fine touch, proprioception, vibration) vs. spinothalamic tract (pain and temperature)
• investigations: NCS, blood glucose, vitamin B12 levels, imaging based on associated findings

Differentia Diagnosis
• cerebral: stroke, demyelination, tumour
  • associated symptoms: hemiplegia, aphasia, apraxia
• brainstem: stroke, demyelination, tumour
  • associated symptoms: diplopia, vertigo, dysarthria, dysphagia
• spinal cord/radiculopathy: cord infarction, tumour, MS, syringomyelia, vitamin B12 deficiency, disc lesion
  • associated symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern)
• neuropathy: focal compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, vitamin B12 deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid

Gait Disturbance
Approach
1. Characterization of the gait disturbance
  • posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, difficulty turning, tremor, elaborate/inconsistent movements, standing from sitting
2. Identification of accompanying neurologic signs
  • full neurological exam required (diagnosis often can be made by P/E alone)
3. Identify red flags
  • sudden onset, cerebellar ataxia, paresis (hemiparesis, para- or quadri-), bowel/bladder incontinence
4. Workup
  • based on etiology – requires blood work, neuroimaging, and urgent neurologist referral
### Cranial Nerve Deficits

#### CN I: Olfactory Nerve

**Clinical Features**
- anosmia associated with a loss of taste

**Differential Diagnosis**
- **nasal**: physical obstruction
  - heavy smoking, chronic rhinitis, sinusitis, neoplasms, septal deformity, choanal atresia, vestibular stenosis, foreign body
- **olfactory neuroepithelial**: destruction of receptors or their axon filaments
  - influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
- **central**: lesion of olfactory pathway
  - Kallmann syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeal inflammation, meningoïd, aneurysm, PD, stroke, MS
- **endocrine/metabolic**
  - DM, adrenal hypo/hyperfunction, pseudohypoparathyroidism, hypothyroidism, renal/liver failure, vitamin deficiency

If anosmia is not associated with loss of taste, consider malingering.

#### CN II: Optic Nerve

- see *Neuro-Ophthalmology*, N14

#### CN III: Oculomotor Nerve

**Clinical Features**
- ptosis, resting eye position is “down and out” (depressed and abducted), pupil dilated (mydriasis)
- vertical and horizontal diplopia; paralysis of adduction, elevation, and depression

**Differential Diagnosis**
- **PComm aneurysm**: early mydriasis, then CN III palsy
- **cavernous sinus** (internal carotid aneurysm, meningoïd, sinus thrombosis): associated with deficits in other CNs near the cavernous sinus
- **midbrain lesion**: complete unilateral CN III palsy with bilateral weakness of the superior rectus and ptosis with contralateral pyramidal signs ± mydriasis
- **orbital lesion**: associated with optic neuropathy, chemosis, proptosis
- **other** inflammatory, infection, neoplasia, uncal herniation, trauma

Lesions involving the cavernous sinus can lead to cranial nerve palsies of III, IV, VI, V1, and V2 as well as orbital pain and proptosis.

Lesion-isolating vs. pupil-sparing approach: mydriasis may be caused by ischemia or compression.”

Pupillary constrictor fibres run along outside of nerve, whereas vasculature is contained within nerve. For CN III palsy with a reactive pupil, always think ischemic cause (“pupil sparing”). For CN III palsy with mydriasis, think compressive lesion.

Kallmann syndrome is a congenital disorder of anosmia and hypogonadotropic hypogonadism.
**CN IV: Trochlear Nerve**

**Clinical Features**
- vertical and torsional diplopia; defect of intorsion and depression
- patient may complain of difficulty going down stairs or reading

**Differential Diagnosis**
- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, superior orbital fissure (tumour, granuloma)

**CN V: Trigeminal Nerve**

**Clinical Features**
- ipsilateral loss of facial sensation and corneal reflex, weakness of muscles of mastication (V3 only) with pterygoid deviation towards the side of the lesion

**Differential Diagnosis**
- brainstem: ischemia, tumour, syringobulbia, demyelination
- peripheral: tumour, aneurysm, chronic meningitis, me atastic infiltration of nerve
- trigeminal ganglion: acoustic neuroma, meningioma, fracture of middle fossa
- cavernous sinus: carotid aneurysm, meningioma, sinus thrombosis
- trauma
- note: other CN V lesions that cause facial pain = trigeminal neuralgia, herpes zoster

**CN VI: Abducens Nerve**

**Clinical Features**
- resting inward deviation (esotropia)
- horizontal diplopia; defect of lateral gaze

**Differential Diagnosis**
- pons (infarction, hemorrhage, demyelination, tumour): associated with facial weakness and contralateral pyramidal signs
- tentorial orifice (compression, meningioma, trauma): false localizing sign of increased ICP
- cavernous sinus: carotid aneurysm, meningioma, sinus thrombosis
- ischemia of CN VI: DM, temporal arteritis, HTN, atherosclerosis
- congenital: Duane's syndrome

**CN VII: Facial Nerve**

**Clinical Features**
- LMN lesion: ipsilateral facial weakness (facial droop, flattening of forehead, inability to close eyes, flattening of nasolabial fold)
- UMN lesion: contralateral facial weakness with forehead sparing (due to bilateral frontalis innervation)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

**Differential Diagnosis**
- idiopathic = Bell's palsy, 80-90% of cases (see Otolaryngology, OT22)
- most often related to HSV, but other viruses may be implicated (CMV, herpes zoster, EBV)
- other: temporal bone fracture, EBV, Ramsay Hunt (VZV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease, Lyme meningitis, HIV

![Figure 11. Cavernous sinus (coronal view)](image-url)
**CN VIII: Vestibulocochlear Nerve**

- see Otolaryngology, OT14

**CN IX: Glossopharyngeal Nerve**

**Clinical Features**
- unilateral lesion is rare
- taste dysfunction in posterior 1/3 of tongue
- absent gag reflex and dysphagia

**Disorders**
- glossopharyngeal neuralgia: sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
  - treated with carbamazepine or surgical ablation of CN IX

**CN X: Vagus Nerve**

**Clinical Features**
- oropharyngeal dysphagia (transfer dysphagia) due to palatal and pharyngeal weakness
  - neuromuscular causes of dysphagia
    - CNS: stroke, cerebral palsy, tumour, trauma, PD, AD, MS
    - CN: DM, laryngeal nerve palsy, polio, ALS
    - myopathic/NMJ: dermatomyositis, polymyositis, MG, sarcoidosis
  - other causes of dysphagia: see Gastroenterology G8
- dysarthria: inability to produce understandable speech due to impaired phonation and/or resonance

**CN XI: Accessory Nerve**

**Clinical Features**
- LMN lesion: paralysis of ipsilateral trapezius and sternocleidomastoid (ipsilateral shoulder drop, weakness on turning head to contralateral side)
- UMN lesion: paralysis of ipsilateral sternocleidomastoid and contralateral trapezius

**CN XII: Hypoglossal Nerve**

**Clinical Features**
- LMN lesion: tongue deviation towards lesion; ipsilateral tongue atrophy and fasciculations (if chronic)
- UMN lesion: tongue deviation away from lesion; absence of atrophy and fasciculations
**Neuro-Ophthalmology**

**Optic Neuritis**
- See Optic Disc Edema, Multiple Sclerosis, N52

**Anterior Ischemic Optic Neuropathy (AION)**
- See Optic Disc Edema
- Non-arteritic (NAION): due to atherosclerosis
- Arteritic (AAION): due to giant cell arteritis (see Rheumatology, RH20)

**Amaurosis Fugax**
- See Ophthalmology, OP35 and Stroke, N48

**Optic Disc Edema**

<table>
<thead>
<tr>
<th></th>
<th>Optic Neuritis</th>
<th>Papilledema</th>
<th>AION</th>
<th>CRVO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&lt; 50 yr</td>
<td>Any</td>
<td>&gt; 50 yr but usually &gt; 70 yr</td>
<td>&gt; 50 yr</td>
</tr>
<tr>
<td><strong>Vision</strong></td>
<td>Rapidly progressive monocular central vision loss (+ acuity and colour vision) with recovery</td>
<td>Late visual loss</td>
<td>Painless unilateral acute field defect over hours to days with ↓ colour vision</td>
<td>Painless unilateral variable vision loss</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Pain (especially with eye movement)</td>
<td>H/A, N/V, local neurological deficits</td>
<td>If GCA: H/A, scalp tenderness, jaw claudication, weight loss, fatigue</td>
<td>Cardiovascular risk factors</td>
</tr>
<tr>
<td><strong>Pupil</strong></td>
<td>RAPD</td>
<td>No RAPD</td>
<td>RAPD</td>
<td>± RAPD</td>
</tr>
<tr>
<td><strong>Fundus</strong></td>
<td>Disc swelling if anterior Normal disc if retrobulbar</td>
<td>Bilateral disc swelling, retinal hemorrhage, no venous pulsations</td>
<td>Pale segmental disc edema, retinal dot, flame hemorrhages</td>
<td>Swollen disc, venous engorgement, retinal hemorrhage</td>
</tr>
<tr>
<td><strong>Etiologies</strong></td>
<td>MS, viral</td>
<td>Increased ICP</td>
<td>Giant cell arteritis</td>
<td>Associated with vasculopathy thrombus</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>MRI with gadolinium</td>
<td>Emergent CT; LP if CT is normal to measure opening pressure</td>
<td>CBC, ESR, CRP, temporal artery biopsy</td>
<td>Fluorescein angiogram and coherence tomography</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>IV methylprednisolone</td>
<td>Treat cause</td>
<td>Consider ASA if non-arteritic; steroids if arteritic</td>
<td>Optimize risk factors, reduce IOP ± laser, ± VEGF inhibitors</td>
</tr>
</tbody>
</table>

**Optic Disc Atrophy**
- **Etiologies**: glaucoma, AION, compressive tumour, optic neuritis, Leber’s hereditary optic neuropathy, congenital
- **Presentation**: disc pallor, low visual acuity, peripheral vision defect, decreased colour vision
- **Treatment**: none (irreversible), aim to prevent

NAION can be caused by use of sildenafil (Viagra®) in rare cases.
If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results, begin treatment immediately.

NAION can be caused by use of sildenafil (Viagra®) in rare cases.
Abnormalities of Visual Field

Figure 13 Characteristic visual field defects with lesions along the visual pathway

Abnormalities of Eye Movements

Disorders of Gaze

Pathophysiology
- horizontal gaze: FEF → contralateral PPRF (midbrain/pons) → eyes saccade away from FEF
- vertical gaze: cortex → rostral interstitial nucleus in the MLF (midbrain)

Clinical Features
- unilateral lesion in one FEF → eyes deviate toward the side of the lesion
  - can be overcome with doll’s eye maneuver
- unilateral lesion in the PPRF → eyes deviate away from the lesion
  - cannot be overcome with doll’s eye maneuver if CN VI nucleus lesion as well
- seizure involving a FEF: eyes deviate away from the focus

Etiology
- common: infarcts (frontal or brainstem), MS, tumours

Internuclear Ophthalmoplegia

Pathophysiology
- results from a lesion in MLF which disrupts coordination between CN VI nucleus in pons and the contralateral CN III nucleus in midbrain → disrupts conjugate horizontal gaze

Clinical Features
- horizontal diplopia on lateral gaze, oscillopsia
- gaze away from the side of the lesion: ipsilateral adduction defect and contralateral abduction nystagmus
- cannot be overcome by caloric testing
- accommodation reflex intact
- may be bilateral (especially in MS)

Etiology
- common: MS, brainstem infarct

Investigations
- MRI

Figure 14. Internuclear ophthalmoplegia
## Abnormalities of Eye Movements

### Diplopia

**Etiology – Monocular**
- mostly due to relatively benign optical problems (refractive error, cataract) or functional

**Etiology – Binocular (due to ocular misalignment)**
- muscle: Graves' ophthalmopathy, EOM restriction/entrapment
- neuromuscular junction: MG (see Myasthenia Gravis, N38)
- cranial nerve palsy (see Cranial Nerve Deficits, N11)
- INO (see Internuclear Ophthalmoplegia, N15)
- other
  - orbital trauma (orbital floor fracture), tumour, infection, inflammation
  - Miller-Fisher variant of GBS
  - Wernicke's encephalopathy
  - leptomeningeal disease

### Approach to Diplopia
- monocular (diplopia when one eye open) vs. binocular (diplopia when both eyes open)
- horizontal vs. vertical vs. oblique diplopia
- direction of gaze that exacerbates diplopia
- corrective head movements

**Workup**
- may observe isolated 4th or 6th nerve palsy for a few weeks, but workup if persistent or other symptoms develop
- indications for neuroimaging
  - bilateral or multiple nerve involvement
  - severe sudden onset headache (rule out aneurysm)

### Nystagmus

**Definition**: rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
- direction of nystagmus is labelled by the rapid component of the eye movement
- can be categorized by movement type (pendular, jerking, rotatory, coarse) or as physiological vs. pathological

### Table 8. Nystagmus Features

<table>
<thead>
<tr>
<th></th>
<th>Peripheral (Vestibular)</th>
<th>Central (Brainstem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction</td>
<td>Unidirectional, fast phase away from the lesion</td>
<td>May be bilateral/unidirectional</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Usually horizontal</td>
<td>Usually vertical</td>
</tr>
<tr>
<td>Gaze Fixation</td>
<td>Relieves nystagmus</td>
<td>Does not relieve nystagmus</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Auditory Symptoms</td>
<td>Common</td>
<td>Extremely rare</td>
</tr>
<tr>
<td>Other Neurological Signs</td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td>DDx</td>
<td>Benign paroxysmal positional vertigo, vestibular neuritis, Ménière’s disease, toxicity, trauma, Ramsay Hunt syndrome</td>
<td>MS, vascular (brainstem/cerebellar), neoplastic/paraneoplastic</td>
</tr>
</tbody>
</table>

### Abnormalities of Pupils

- see Ophthalmology, OP28
Nutritional Deficiencies and Toxic Injuries

- Sufficient nutritional intake is required for optimal nervous system functioning; deficiencies in the following key nutrients, among others, may impair central and peripheral nervous system function (potential neurological symptoms are provided).

<table>
<thead>
<tr>
<th>Table 9. Nutritional Deficiency Features and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin Deficiency</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Vitamin B12</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Folate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Copper</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
</tr>
<tr>
<td>Thiamine</td>
</tr>
<tr>
<td>Pyridoxine (Vitamin B6)</td>
</tr>
<tr>
<td>Niacin (Vitamin B3)</td>
</tr>
</tbody>
</table>

*IM = intramuscular; IV = intravenous

- It is also important to consider occupational neurotoxic syndromes secondary to exposure to pesticides, solvents, and metals. Encephalopathy, extrapyramidal features, neurodegenerative diseases, and peripheral neuropathy are commonly encountered. Onset and progression of neurological diseases should be temporally related to neurotoxin exposure. Main toxins associated with neurotoxicity are listed below.

<table>
<thead>
<tr>
<th>Table 10. Selected Occupational Neurotoxic Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxin</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Organic Solvents</td>
</tr>
<tr>
<td>Pesticides (e.g. insecticides, fungicides, rodenticides, fumigants, herbicides)</td>
</tr>
<tr>
<td>Heavy Metals (e.g. lead, mercury, manganese, aluminum, arsenic)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Gases (e.g. carbon dioxide, nitrous oxide formaldehyde)</td>
</tr>
</tbody>
</table>

Neurologic Complications due to Toxic Injuries Related to Bariatric Surgery

- Deficiencies of both fat- and water-soluble vitamins may occur following malabsorptive bariatric surgery.
- Patients who have undergone malabsorptive surgery should be monitored for late metabolic complications and neurological manifestations.
Seizure Disorders and Epilepsy

Definitions

**Seizure**: transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal brain activity

- can be symptom of acute insult to the brain such as: alcohol and illicit drug use/withdrawal, brain injury/abnormality (tumour, trauma, vascular), CNS infection, fever (children), metabolic (hypoglycemia, electrolyte abnormalities, liver/renal failure), medications, or be a manifestation of epilepsy

**Epilepsy**: disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and, by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure

- etiologies: genetic, structural (e.g. prior stroke, tumour, meningoencephalitis, perinatal insult, vascular malformation, malformation of cortical development neurodegenerative), or unknown

Classification

**Clinical Features**

- **focal (partial) seizures**
  - focal can secondarily generalize, or focal (simple) → focal with impaired awareness (complex) → generalized seizures
  - focal with intact awareness (simple partial)
    - motor: postural, phonatory, forceful turning of eyes and/or head, focal muscle rigidity/jerking ± Jacksonian march (spreading to adjacent muscle groups)
    - sensory: unusual sensations affecting vision, hearing, smell, taste, or touch
    - autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
    - psychiatric: symptoms rarely occur without impairment of consciousness and are more commonly complex partial
  - focal with impaired awareness (complex partial)
    - patient may appear to be awake but with impairment of awareness
    - classic complex seizure is characterized by automatisms such as chewing, swallowing, lip smacking, scratching, fumbling, running, disrobing, and other stereotypic movements
    - other forms: dysphasic, dysemic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness

- **generalized seizures**
  - absence (petit mal): usually seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - clonic: repetitive rhythmic jerking movements
  - tonic: muscle rigidity in flexion or extension
  - tonic-clonic (grand mal)
    - may have prodrome of unease or irritability hours to days before the episode (aura)
    - tonic ictal phase: muscle rigidity
    - clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence
    - post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours; may have focal paralysis (Todd's paralysis)
  - myoclonic: sporadic contractions localized to muscle groups of one or more extremities
  - atonic: loss of muscle tone leading to drop attack

Stroke is the most common cause of late-onset (>50 yr) seizures, accounting for 50-80% of cases

Seizures and Dementia

Neurodegenerative diseases can underlie seizures; conversely, seizures can be a cause of dementia

Temporal lobe epilepsy is suggested by an aura of fear, olfactory or gustatory hallucinations, and visceral or déjà vu sensations

Frontoparietal cortex seizures are suggested by contralateral focal sensory or motor phenomena
**Table 11. Classic Factors Differentiating Seizure, Syncope and Pseudoseizure**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Syncope</th>
<th>Pseudoseizure* (Psychogenic non-epileptic seizure)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Day or night</td>
<td>Day</td>
<td>Day; other people present</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Sudden, in any position</td>
<td>Gradual; Upright position (not recumbent)</td>
<td>Provoked by emotional disturbance or suggestion</td>
</tr>
<tr>
<td><strong>Prodrome</strong></td>
<td>Possible specific aura</td>
<td>Lightheadedness, pallor, diaphoresis</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Brief or prolonged</td>
<td>Brief</td>
<td>Often prolonged</td>
</tr>
<tr>
<td><strong>Incontinence</strong></td>
<td>Common</td>
<td>Possible but rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Post-Ictal</strong></td>
<td>Occurs in tonic-clonic or complex partial</td>
<td>No</td>
<td>Rare; often none</td>
</tr>
<tr>
<td><strong>Motor Activity</strong></td>
<td>Synchronous, stereotypic, automatisms (common in absence and complex partial, lateral tongue biting, eyes rolled back)</td>
<td>Occasional brief jerks</td>
<td>Opisthotonos, rigidity, eye closure, irregular extremity movements, shaking head, pelvic thrust, crying, geotopic eye movements, tongue biting at the tip</td>
</tr>
<tr>
<td><strong>Injury</strong></td>
<td>Common</td>
<td>Rare unless from fall</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>Usually abnormal; ± interictal discharges</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Pseudoseizures do not rule out seizures (not uncommon to have both)*

- alcoholic withdrawal seizures may occur up to 2 days from the last exposure to alcohol (see Emergency Medicine, ER54)

**Investigations**
- CBC, electrolytes, fasting blood glucose, Ca²⁺, Mg²⁺, ESR, Cr, liver enzymes, CK, prolactin
- also consider toxicology screening, EtOH level, AED level (if applicable)
- CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
- LP (if fever or meningismus)
- EEG

**Treatment**
- avoid precipitating factors
- indications for antiepileptic drugs (AED): EEG with epileptiform activity, remote symptomatic cause (organic brain disease, prior head injury or CNS infection), abnormal neurologic examination or findings on neuroimaging, nocturnal seizure
- psychosocial issues: stigma of seizures, education of patient and family, status of driver’s license, pregnancy issues
- safety issues: driving, operating heavy machinery, bathing, swimming alone
- refer for evaluation for possible surgical treatment if focal and refractory

**Status Epilepticus**
- definition: unremitting seizure or successive seizures without return to a baseline state of greater than 5 min
- complications: anoxia, cerebral ischemia and cerebral edema, MI, arrhythmias, cardiac arrest, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)
- initial measures: ABCs, vitals, monitors, capillary glucose (STAT), ECG, nasal O₂, IV NS, IV glucose, IV thiamine, ABGs (if respiratory distress/cyanotic)
- blood work: electrolytes, Ca²⁺, Mg²⁺, PO₄³⁻, glucose, CBC, toxicology screen, EtOH level, AED levels
- focused history: onset, past history of seizures, drug and alcohol ingestion, past medical history, associated symptoms, witnesses/collateral history
- physical exam (once seizures controlled): LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurometabolic disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (rule out injuries)
- post-treatment stabilization: CT head, EEG, Foley catheter to monitor urine output, urine toxicology screen, monitor for rhabdomyolysis, and IV fluids to maintain normal cerebral perfusion pressure

**Antiepileptic Drugs**
- focal and more generalized seizures
  - valproate (Depakene®), lamotrigine (Lamictal®), levetiracetam (Keppra®), topiramate (Topamax®), phenobarbital (Phenobarb®), primidone, zonisamide, rufinamide (Ranzel®), felbamate, benzodiazepines
- primarily focal seizures (± 2° generalization)
  - carbamazepine (Tegretol®), phenytoin (Dilantin®), gabapentin (Neurontin®), lacosamide (Vimpat®), oxcarbazepine (Trileptal®), eslicarbazepine acetate (Aptiom®), pregabalin (Lyrica®), tiagabine (Gabitril®), vigabatrin (Sabril®)
- absence seizure: ethosuximide (Zarontin®)

**DDx of Convulsions**
- Syncope, pseudoseizure, hyperventilation, panic disorder, TIA, hypoglycemia, movement disorder, alcoholic blackouts, migraines (confusional, vertebrobasilar), narcolepsy (cataplexy)

Note that frontal seizures (rare) can look like a pseudoseizure due to odd motor activity that may occur

By law, the Ministry of Transportation in most provinces must be contacted for all patients who have had a seizure; patients will have their license suspended until seizure free for 6 mo; commercial drivers face a longer wait

EEG findings suggestive of epilepsy: abnormal spikes, polyspike discharges, spike-wave complexes

20-59% of first EEG are positive in epilepsy; 59-92% of epilepsy is picked up with repeated EEGs; normal interictal EEGs do not rule out epilepsy

**Medical Emergency: Status epilepticus**
- can cause irreversible brain damage without treatment

The most common causes of status epilepticus are failure to take AEDs and first presentation of epilepsy
- Status epilepticus as a result of EtOH withdrawal is rare, despite it being a very common cause of seizures

Rule out non-convulsive status epilepticus in any patient who is ≤ unconscious >20 min post-ictal; order a stat EEG if unsure

Complex partial status epilepticus can resemble schizophrenia or psychotic depression
**Behavioural Neurology**

- see Psychiatry, PS19

### Acute Confusional State/Delirium

#### Table 12. Selected Intracranial Causes of Acute Confusion

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Thunderclap H/A, increased ICP, meningismus</td>
<td>CT, LP Angiography if CT and LP negative</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>Focal neurological signs</td>
<td>CT</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>Fever, H/A, nausea, photophobia, meningismus</td>
<td>CT, LP</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Fever, H/A, ± seizure, Focal neurological signs</td>
<td>CT, LP, MRI</td>
</tr>
<tr>
<td>Abscess</td>
<td>Increased ICP, Focal neurological signs</td>
<td>CT with contrast (often ring enhancing lesion)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Diffuse axonal shear, epidural hematoma, SDH</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>Trauma Hx, Increased ICP, Focal neurological signs</td>
<td>CT, MRI</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Acute CNS vasculitis, Skin rash, active joints</td>
<td>ANA, ANCA, RF MRI Angiography</td>
</tr>
<tr>
<td>Paraneoplastic encephalitis (anti-NMDA-R)</td>
<td>Onset: Psychiatric features, memory loss, seizures Delayed: Movement disorder, and changes in BP, HR, and temperature</td>
<td>CSF (test for presence of antibodies)</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Mass effect/edema, hemorrhage, seizure, Increased CP, Focal neurological signs Papilledema</td>
<td>CT, MRI</td>
</tr>
<tr>
<td>Seizure</td>
<td>Status epilepticus</td>
<td>See Seizure Disorders and Epilepsy, N18 EEG</td>
</tr>
<tr>
<td>Primary Psychiatric</td>
<td>Psychotic disorder, mood disorder, anxiety disorder</td>
<td>No specific tests</td>
</tr>
<tr>
<td>Other</td>
<td>Drugs (e.g. cocaine)</td>
<td>Vital signs, Serum chemistry and electrolyte analysis</td>
</tr>
<tr>
<td></td>
<td>Medications (with anticholinergic side effects)</td>
<td>Serum chemistry and electrolyte analysis</td>
</tr>
<tr>
<td></td>
<td>Neuroleptic Malignant Syndrome</td>
<td>Serum chemistry and electrolyte analysis</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic medication use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle rigidity, Hyperthermia, Autonomic instability</td>
<td></td>
</tr>
</tbody>
</table>
**Mild Neurocognitive Disorder (Mild Cognitive Impairment)**

**Definition**
- cognitive impairment not meeting criteria of Major Neurocognitive Disorder
- measurable deficit in at least one cognitive domain reported by patient or others without impairment in ADLs
- amnestic (precursor to AD) vs. non-amnestic

**Epidemiology**
- mild NCD: 2-10% at age 65 yr and 5-25% by age 85 yr

**Risk Factors**
- vascular: hypertension, diabetes mellitus, obesity, cardiac disease, apolipoprotein E epsilon 4 genotype

**Clinical Features**
- cognitive impairment
  - particularly in amnestic subtype
  - important to ascertain that memory complaints represent change from baseline
  - patients with mild NCD are often troubled by memory symptoms in comparison to patients with dementia
- neuropsychiatric symptoms
  - depression (50%), irritability, anxiety, aggression, and apathy

**Investigations**
- establish a baseline for follow-up
- clinical interview with patient and caregivers is the cornerstone of mild NCD evaluation
- neuropsychological testing
  - MMSE or MoCA; should not be used in isolation
  - if abnormal, follow-up in one year to monitor cognitive and functional decline
- neuroimaging
  - role uncertain
  - most advocate for a non-contrast brain CT to evaluate for structural abnormalities (CVD, SDH, NPH, or mass lesion)
- other testing
  - exclude treatable conditions and underlying psychiatric conditions

**Treatment**
- watch and wait
- no evidence for cholinesterase inhibitors, anti-inflammatory agents, vascular risk factor modification, exercise, cognitive interventions

**Prognosis**
- 10% progress to major NCD per yr
- typically progress to major NCD over a period of 2-3 yr

**Major Neurocognitive Disorder (formerly Dementia)**

- see Psychiatry, PS20 and Geriatric Medicine, GM4

**Definition**
- an acquired, generalized, and (usually) progressive impairment of cognitive function associated with impairments in ADLs/iADLs (i.e. shopping, food preparation, finances, medication management)
- diagnosis of major NCD requires presence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  A) concern of the individual or a knowledgeable informant AND
  B) a substantial impairment in cognitive performance either documented by standardized neuropsychological testing, or quantified clinical assessment
- see Psychiatry, PS20 for DSM-5 diagnostic criteria
- in comparison, mild NCD does not affect ADLs
  - mild NCD represents an intermediate stage between major NCD and normal aging

**Epidemiology**
- major NCD: 1-2% at age 65 yr and reaching as high as 30% by age 85 yr
- note
  - major NCD due to Alzheimer’s disease is uncommon before age 60 yr
  - major NCD due to frontotemporal lobar degeneration has an earlier onset and represents a progressively smaller fraction of all NCDs with increasing age
Etiology
- see Table 13 for selected causes of major NCD
- reversible causes: alcohol (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metal toxicity, hepatic or renal failure, B12 deficiency, glucose, cortisol, thyroid dysfunction, normal pressure hydrocephalus (NPH), depression (pseudodementia), intracranial tumour, SDH, hypercalcemia (secondary to elevated PTH)
- must rule out delirium

History
- "geriatric giants"
  - confusion/incontinence/falls
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects, driving)
  - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
  - polypharmacy and compliance (sedative hypnotics, antipsychotics, antidepressants, anticholinergics)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS, head trauma history
- alcohol, smoking
- collateral history

Physical Exam
- blood pressure
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings
- general physical exam with focus on CVD, patient-specific risk factors and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

Investigations
- rule out reversible causes
  - CBC (note MCV for evidence of alcohol use and B12 deficiency), glucose, TSH, B12, RBC folate
electrolytes, LFTs, renal function, lipids, serum calcium
- CT head, MRI as indicated, SPECT (optional)
- as clinically indicated: VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
  - failure to cope, fitness to drive, caregiver capacity and wellbeing, power of attorney, legal will, advanced medical directives, patient and caregiver safety

Table 3. Selected Causes of Major NCD (Dementia)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY DEGENERATIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>Memory impairment, Aphasia, apraxia, agnosia</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Visual hallucinations, Parkinsonism</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td>Frontotemporal dementia (e.g. Pick's disease)</td>
<td>Behavioural presentation: Disinhibition, perseveration, decreased social awareness, mental rigidity, memory, relatively spared Language presentation: Progressive non-fluent aphasia, semantic dementia</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>Chorea</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>VASCULAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular cognitive impairment (previously Multi-infarct dementia)</td>
<td>Bradyphrenia without features of parkinsonism (slow thinking, slow rate of learning, slow gait), Dysexecutive syndrome, May be abrupt onset, Stepwise deterioration is classic but progressive deterioration is most common</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>Systemic signs and symptoms of vasculitis</td>
<td>ANA; ANCA; RF, CT or MRI, Angiography</td>
</tr>
</tbody>
</table>

Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Tool</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>Clinical Judgment</td>
<td>85%</td>
<td>82%</td>
</tr>
<tr>
<td>DSM IV</td>
<td>76%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Vitamin B12 Deficiency Symptoms
- Macrocytic anemia, pallor, SOB, fatigue, chest pain, palpitations
- Confusion or change in mental status (if advanced)
- Decreased vibration sense
- Distal numbness and paresthesia
- Weakness with UMN findings
- Diarrhea, anorexia

Major NCD Considerations for Management

ACBDs
- Affective disorders, ADs
- Behavioural problems
- Caretaker, Cognitive medications and stimulation
- Directives, Driving
- Sensory enhancement (glasses/hearing aids)

Most common causes of rapidly progressive neurodegenerative dementia (less than 4 yr survival): CJD, frontal temporal lobar dementia, tauopathies, diffuse Lewy body disease, and AD
Arch Neurol 2009;66:201-207
Head turning sign: when patient looking at his/her caregiver for answers after being asked a question in clinical interviews
60% sensitivity, 98% specificity for diagnosis of cognitive Impairment

Early Signs of Major NCD

<table>
<thead>
<tr>
<th>Normal Aging</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgetting the names of close relations</td>
<td>Forgetting the names of acquaintances</td>
<td></td>
</tr>
<tr>
<td>Increased frequency of forgetting</td>
<td>Briefly forgetting part of an experience</td>
<td></td>
</tr>
<tr>
<td>Reporting phrases/stories in the same conversation</td>
<td>Not putting away things properly</td>
<td></td>
</tr>
<tr>
<td>Unpredictable mood changes</td>
<td>Mood changes in response to appropriate causes</td>
<td></td>
</tr>
<tr>
<td>Decreased interest in activities and difficulty making choices</td>
<td>Changes in usual interests</td>
<td></td>
</tr>
</tbody>
</table>
Table 13. Selected Causes of Major NCD (Dementia) (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic meningitis</td>
<td>Fever, H/A, nausea</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Meningism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Localizing neurological deficits</td>
<td></td>
</tr>
<tr>
<td>Chronic encephalitis</td>
<td>Fever, headache</td>
<td>CT or MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic abscess</td>
<td>Increased ICP</td>
<td>CT with contrast</td>
</tr>
<tr>
<td></td>
<td>Localizing neurological deficits</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>See Infectious Diseases, ID27</td>
<td>HIV serology</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Rapidly progressive, myoclonus</td>
<td>EEG, CT or MRI, LP</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Ataxia, myoclonus, tabes dorsalis</td>
<td>LP, CT, or MRI VDRL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAUMATIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse axonal shear, epidural hematoma, subdural hematoma, SDH</td>
<td>Trauma Hx, Increased ICP, papilledema Localizing neurological signs</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHEUMATOLOGIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>See Rheumatology, RH11</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ANA, anti-dsDNA</td>
</tr>
<tr>
<td>NEOPLASTIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass effect/edema, hemorrhage, seizure Paraneoplastic encephalitis</td>
<td>Increased ICP Systemic symptoms of cancer</td>
<td>CT with contrast MRI Anti-Hu antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTHER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>Gait disturbances Urinary incontinence See Neurosurgery, NS8</td>
<td>CT or MRI</td>
</tr>
</tbody>
</table>

Major or Mild NCD due to Alzheimer’s Disease

- see Psychiatry, PS20

Definition
- beyond criterion for NCD, the core features of Alzheimer’s disease include an insidious onset and gradual progression of cognitive and behavioural symptoms
- typical presentation: amnestic
  - mild phase: impairment in memory and learning sometimes accompanied with deficits in executive function
  - moderate-severe phase visuoconstructional/perceptual-motor ability and language may also be impaired
  - social cognition tends to be preserved until late in the course of the disease
- atypical nonamnestic presentation (one of the following):
  1. aphasia: language disturbance
  2. apraxia: impaired ability to carry out motor activities despite intact motor function
  3. agnosia: failure to recognize or identify objects despite intact sensory function

Pathophysiology
- genetic factors
  - minority (<7%) of AD cases are familial (autosomal dominant)
  - 3 major genes for autosomal dominant AD have been identified:
    - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
    - the E4 polymorphism of apolipoprotein E (APOE) is a susceptibility genotype (E2 is protective)
    - note: APOE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
  - pathology (although not necessarily specific for AD)
    - gross pathology
      - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
microscopic pathology
- senile plaques (extracellular deposits of amyloid in the grey matter of the brain)
- loss of synapses
- neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated Tau protein)
- loss of cholinergic neurons in nucleus basalis of Meynert that project diffusely throughout the cortex

biochemical pathology
- 50-90% reduction in action of choline acetyltransferase

Epidemiology
- 1/12 of population 65-75 yr of age
- up to 1/3 population >85 yr of age
- very rare <65 yr of age
- accounts for 60-90% of all dementias (depending on setting and diagnostic criteria)

Risk Factors
- age is the largest risk factor
- genetic susceptibility polymorphism: apolipoprotein E4 increases risk and decreases age of onset
- other factors include: traumatic brain injury, family history; Down syndrome, low education, and vascular risk factors (e.g. smoking, HTN, hypercholesterolemia, DM)

Clinical Features
- cognitive impairment
  - memory impairment for newly acquired information (early)
  - deficits in language, abstract reasoning, and executive function
- behavioural and psychiatric manifestations (80% of those with major NCD)
  - mild NCD: major depressive disorder and/or apathy
  - major NCD: psychosis, irritability, agitation, combative ness, and wandering
- motor manifestations (late)
  - gait disturbance, dysphagia, incontinence, myoclonus, and seizures

Investigations
- perform investigations to rule out other potentially reversible causes of dementia
- EEG: usually normal, may observe generalized slowing (nonspecific)
- MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
- SPECT: hypoperfusion in temporal and parietal lobes
- PET imaging using Pittsburgh compound B (PIB) as a tracer enables imaging of beta-amyloid plaque in neuronal tissue

Treatment
- acetylcholinesterase inhibitors have been shown to slow decline in cognitive function
  - Do not prolong life expectancy but improve morbidity
  - donepezil, rivastigmine, galantamine
  - relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers, or risk factors for ulcers and/or GI bleeding
  - galantamine is contraindicated in patients with hepatic/renal impairment
- memantine is an NMDA-receptor antagonist that has some benefits in later stage AD (i.e. when MMSE <17)
- symptomatic management
  1. pharmacologic
    - low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
    - trazodone for sleep disturbance
    - antidepressants (SSRIs)
  2. non-pharmacologic
    - redirection
    - explore inciting factors for behaviour and modify behaviour of patient or caregiver
    - family support and day care facilities

Prognosis
- mean duration of survival after diagnosis is approximately 10 yr, reflecting the advanced age of the majority of individuals rather than the course of the disease
- death commonly results from aspiration

Cognitive Effects of Atypical Antipsychotic Medications in Patients with Alzheimer’s Disease: Outcomes from CATIE-AD
Am J Psychiatry 2011;168:831-839

Study: 421 outpatients with Alzheimer’s disease and psychosis or agitation/dissease behaviour were randomized to receive olanzapine, quetiapine, risperidone, or placebo in a multicentre double-blind RCT. MMSE and Alzheimer’s Disease Assessment Scale (ADAS) scores were measured at 36 wk.

Results: Patients receiving atypical antipsychotics exhibited a faster rate of cognitive decline as measured by MMSE scores (-0.067/wk vs. -0.007/wk). They also had a significantly faster decline compared to placebo on a composite measure of ADAS, MMSE, and various other cognitive tests (-0.011/wk vs. -0.010/wk).

Conclusions: Long-term use of atypical antipsychotics for behavioural symptoms and psychosis in dementia patients is associated with greater rates of cognitive decline.
Major or Mild NCD with Lewy Bodies
(formerly Dementia with Lewy Bodies)

Definition
• A NCD characterized by progressive cognitive impairment (with early changes in complex attention and executive function) and recurrent complex visual hallucinations
• core diagnostic features
  ■ fluctuating cognition with pronounced variations in attention and alertness
  ■ recurrent visual hallucinations that are well formed and detailed
  ■ spontaneous features of parkinsonism, with onset subsequent to development of cognitive decline (rest tremor may be absent in DLB, but otherwise same classic features of Parkinson's disease)
• suggestive/supportive features
  ■ rapid eye movement (REM) sleep behaviour disorder
  ■ severe sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms)
  ■ repeated falls, syncope, or transient episodes of unexplained loss of consciousness
  ■ auditory or other nonvisual hallucinations, systematic delusions, and depression

Etiology and Pathogenesis
• Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
• mixed DLB and AD pathology is common

Diagnostically Suggestive Markers
• low striatal dopamine transporter uptake on SPECT or PET
• relative preservation of medial temporal structures on CT/MRI

Epidemiology
• 0.1-5% of the general elderly population
• Lewy bodies are present in 20-35% of all dementia cases (more common in males)

Treatment
• acetylcholinesterase inhibitors (e.g. donepezil)

Prognosis
• average duration of survival 5-7 yr

Major or Mild Frontotemporal NCD
(formerly Frontotemporal Dementia)

Definition
• refers to a group of disorders caused by progressive cell degeneration in the brain's frontal or temporal lobes
  ■ deficits in executive function (e.g. poor mental flexibility, abstract reasoning, response inhibition, planning/organization, increased distractibility) with relative sparing of learning, memory and perceptual–motor function
• “probable” is distinguished from “possible” frontotemporal NCD by:
  ■ evidence of causative frontotemporal NCD genetic mutation, from either family history or genetic testing
  ■ evidence of disproportionate frontal and/or anterior temporal atrophy on MRI or CT
  ■ evidence of frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

Behavioural Variant FTD
• most common variant
• insidious onset: must show progressive deterioration of behaviour and/or cognition by observation or history
• typically early symptom presentation (i.e. within the first 3 yr)
• three out of the following symptoms must be present and persistent/recurrent:
  ■ behavioural disinhibition (socially inappropriate behaviour, impulsive, careless)
  ■ apathy or inertia (decreased initiation or continuation of behaviour, requiring cues/prompts, less likely to initiate or sustain conversations)
  ■ loss of sympathy or empathy (diminished response to others' needs/feelings, social interest)
  ■ perseverative, stereotyped, or compulsive/ritualistic behaviour
  ■ hyperorality and dietary changes (binge eating, increased consumption of alcohol/cigarettes or inedible objects)
Language Variants (Primary Progressive Aphasia)

- prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension
- three subtypes
  - nonfluent/agrammatic variant PPA (NFAV-PPA) or progressive nonfluent aphasia (PNFA): non fluent, laboured articulation/speech, anomia, preserved single word comprehension, word-finding deficit, impaired repetition
  - semantic variant PPA (SV-PPA) or semantic dementia (SD): fluent, normal rate, anomia, impaired single word comprehension, intact repetition, use words of generalization ("thing") or suprordinate categories ("animal" for "dog")
  - logopenic progressive aphasia (LPA): naming difficulty and impaired repetition

FTD Movement Disorders

- corticobasal degeneration (CBD) (see Parkinsonism)
- progressive supranuclear palsy (PSP) (see Parkinsonism)

Etiology and Pathogenesis

- unknown, however there is likely a genetic/familial component (40% have family history of early onset NCD)
- genetic variants: MAPT gene (Tau), PGRN gene (progranulin), VCP gene, TARDBP gene (TDP-43), CHMP2D gene
- unlike AD, FTD does not show amyloid plaques or neurofibrillary tangles, instead it is characterized by severe atrophy and specific neuronal inclusion bodies
- gross changes: atrophy in the frontal and anterior temporal lobes; cortical thinning; possible ventricular enlargement
- histological changes: gliosis, swollen neurons, microvacuolation, inclusion bodies in neurons/glia (Tau or TDP-43)

Epidemiology

- fourth most common cause of dementia (5% of all dementia cases)
- common cause of early-onset NCD in individuals younger than 65 yr

Prognosis

- median survival being 6-11 yr after symptoms onset and 3-4 yr after diagnosis
- survival is shorter and decline is faster than in typical Alzheimer’s disease

Major or Mild Vascular NCD

Definition

- diagnosis of major or mild NCD with determination of CVD as the dominant if not exclusive pathology that accounts for the cognitive deficits
- vascular etiology suggested by one of the following:
  - onset of cognitive deficits is temporally related to one or more cerebrovascular events
  - evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function
- neuroimaging evidence of cerebrovascular disease comprises one or more of the following:
  - one or more large vessel infarct or hemorrhage
  - a strategically placed single infarct or hemorrhage (e.g. angular gyrus, thalamus, basal forebrain)
  - two or more lacunar infarcts outside the brainstem
  - extensive and confluent white matter lesions
- for mild vascular NCD: history of a single stroke or extensive white matter disease is sufficient
- for major vascular NCD: history of two or more strokes, a strategically placed stroke, or a combination of white matter disease and one or more lacunae is generally necessary
- associated features supporting diagnosis: personality and mood changes, abulia, depression, emotional lability, and psychomotor slowing

Etiology and Pathogenesis

- major risk factors are the same as those for CVD (i.e. HTN, DM, smoking, obesity, high cholesterol levels, high homocysteine levels, other risk factors for atherosclerosis, atrial fibrillation, and conditions increasing risk of cerebral emboli)
- major or mild vascular NCD with gradual onset and slow progression is generally due to small vessel disease leading to lesions in white matter, basal ganglia, and/or thalamus
- cognitive deficits can be attributed to disruption of cortical-subcortical circuits

Epidemiology

- second most common cause of NCD
- prevalence estimates for vascular dementia/NCD range from 0.2 13% (by age 70), 16% (ages 80+) to 44.6% (ages 90+)
- higher prevalence in African Americans compared to Caucasians and East Asians
- prevalence higher in males than in females
Creutzfeldt-Jakob Disease

- rare degenerative fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
- most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)
- investigations: CSF analysis, MRI brain (cortical and/or subcortical FLAIR changes), EEG (periodic complexes)
- definitive diagnosis is by brain biopsy
- no treatments currently exist

Aphasia

Definition
- an acquired disturbance of language characterized by errors in language production, writing, comprehension, or reading

Neuroanatomy of Aphasia
- Broca's area (posterior inferior frontal lobe) involved in language production (expressive)
- Wernicke's area (posterior superior temporal lobe) involved in comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke's area for reading comprehension
- arcuate fasciculus association bundle connects Wernicke's and Broca's areas

Assessment of Language
- assessment of context
  • handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
- assessment of aphasia
  • spontaneous speech (fluency, paraphasias, repetition, naming, comprehension – auditory and reading, writing, neologisms)

Figure 19. Aphasia classification

Prion proteins have a normal form and an infectious form, which results from conversion of the protein from α-helix (normal) to β-pleated sheet (abnormal); these abnormally folded proteins aggregate leading to neuronal loss

>99% of right-handed people have left hemisphere language representation

70% of left-handed people have left hemisphere language representation, 15% have right hemisphere representation, and 15% have bilateral representation

Types of Paraphasias
Semantic (“chair” for “table”)
Phonemic (“clable” for “table”)

Aphasia localizes the lesion on to the dominant cerebral hemisphere

Types of Transcortical Aphasia

- Broca's Motor TCA* (posterior inferior frontal lobe)
- Motor TCA* (frontal lobe watershed between MCA & ACA territories)
- Wernicke's Sensory TCA* (posterior superior temporal lobe, temporal lobe watershed between MCA & PCA territories)
- Conduction Anomic (arcuate fasciculus)
- Mixed TCA*
- Global

* Transcortical aphasia are typically associated with cerebral anoxia (e.g. post-MI, CO poisoning, hypotension)
Mild Traumatic Brain Injury

Definition
- mild TBI = concussion
- trauma induced transient alteration in mental status that may involve loss of consciousness
- hallmarks of concussion: confusion and amnesia which may occur within minutes
- loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h

Epidemiology
- 75% of TBIs are estimated to be mild; remainder are moderate or severe (see Neurosurgery, NS30 and Emergency Medicine, ER8)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features
- impairments following mild TBI
  - somatic: headache, sleep disturbance, nausea, vomiting, blurred vision
  - cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
  - emotion and behaviour: impulsivity, irritability, depression
  - severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
  - associated conditions: brain contusion, diffuse axonal injury, C-spine injury

Apraxia

Definition
- inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension, or inattention

Clinicopathological Correlations

Table 14. Apraxia

<table>
<thead>
<tr>
<th>Description</th>
<th>Tests</th>
<th>Hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideomotor</td>
<td>Inability to perform skilled learned motor sequences</td>
<td>Blowing out a match; combing one’s hair</td>
</tr>
<tr>
<td>Ideational</td>
<td>Inability to sequence actions</td>
<td>Preparing and mailing an envelope</td>
</tr>
<tr>
<td>Constructional*</td>
<td>Inability to draw or construct</td>
<td>Copying a figure</td>
</tr>
<tr>
<td>Dressing*</td>
<td>Inability to dress</td>
<td>Dressing</td>
</tr>
</tbody>
</table>

*Refers specifically to the inability to carry out the learned movements involved in constructing, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks.

Agnosia

Definition
- disorder in the recognition of the significance of sensory stimuli in the presence of intact sensation and naming

Clinicopathological Correlations

Table 15. Agnosias

<table>
<thead>
<tr>
<th>Description</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apperceptive Visual Agnosia</td>
<td>Inability to name or demonstrate the use of an object presented visually 2° to distorted visual perception Bilateral temporo-occipital cortex</td>
</tr>
<tr>
<td>Associative Visual Agnosia</td>
<td>Inability to name an object presented visually 2° to disconnect between visual cortex and language areas Visual perception is intact as demonstrated by visual matching Bilateral inferior temporo-occipital junction</td>
</tr>
<tr>
<td>Prosopagnosia</td>
<td>Inability to recognize familiar faces in the presence of intact visual perception and intact auditory recognition Bilateral temporo-occipital areas or right inferior temporo-occipital region</td>
</tr>
<tr>
<td>Colour Agnosia</td>
<td>Inability to perceive colour Bilateral inferior temporo-occipital lesions</td>
</tr>
<tr>
<td>Impaired Stereognosis</td>
<td>Inability to identify objects by touch Anterior parietal lobe in the hemisphere opposite the affected hand</td>
</tr>
<tr>
<td>Finger Agnosia</td>
<td>Inability to recognize, name, and point to individual fingers Dominant hemisphere parietal-occipital lesions</td>
</tr>
</tbody>
</table>

Parietal Lobe Lesions
- Lesions of the dominant parietal lobe are characterized by Gerstmann’s syndrome: acalculia, agraphia, finger agnosia, and left-right disorientation
- Lesions of the non-dominant parietal lobe are characterized by neglect, anosognosia, and asomatognosia
- Cortical sensory loss (graphesthesia, astereognosia, impaired 2 point discrimination and extinction) can be seen with left or right parietal lesions

Mild Traumatic Brain Injury

Definition
- mild TBI = concussion
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- hallmarks of concussion: confusion and amnesia which may occur within minutes
- loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h

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  - severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
  - associated conditions: brain contusion, diffuse axonal injury, C-spine injury

Extent of retrograde amnesia correlates with severity of injury
- Regained from most distant to recent memories
Investigations

- neurological exam to identify focal neurologic deficits
- neurocognitive assessment
  - simple orientation questions are inadequate to detect cognitive changes
  - initial assessment of severity is determined by
    - Glasgow Coma Scale: mild: 13-15, moderate: 9-12, severe: 3-8
    - sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool
- neuroimaging
  - x-ray of skull: not indicated for routine evaluation of MTBI
  - CT head as indicated by Canadian CT Head Rules (see Emergency Medicine, ER8)
  - MRI not indicated in initial evaluation – indicated in presence of continued or worsening symptoms despite normal CT

Treatment

- observation for first 24 h after mild TBI in all patients because of risk of intracranial complications
- emergency department for assessment if any loss of consciousness or persistent symptoms
- hospitalization with normal CT if GCS <15, seizures, or bleeding diathesis; or abnormal CT scan
- early rehabilitation to maximize outcomes
  - OT, PT, SLP, vestibular therapy, driving, therapeutic recreation
  - pharmacological management of headaches, pain, depression
  - CBT, relaxation therapy
- follow Return to Play guidelines (www.thinkfirst.ca)

Prognosis

- most recover from mild TBI with minimal treatment, but some experience long-term consequences
- Patients with a previous concussion are at increased risk of subsequent concussion and cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
- sequela include
  - post-concussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within weeks to months)
  - post-traumatic headaches: begin within 7 d of injury
  - post-traumatic epilepsy: approximately 2% risk of epilepsy post-mild TBI, prophylactic anticonvulsants not effective
  - post traumatic vertigo

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**Neuro-Oncology**

**Paraneoplastic Syndromes**

- see Endocrinology, E48

**Tumours of the Nervous System**

- see Neurosurgery, NS39

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**Movement Disorders**

**Function of the Basal Ganglia**

- the cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, which then activate two pathways: direct and indirect
- direct: cortex activates the thalamus allowing movement
- indirect: inhibits the thalamus and ultimately prevents movement
Figure 20. Neural connections of the basal ganglia

Figure 21. Horizontal section of basal ganglia
Overview of Movement Disorders

Table 16. Movement Disorder Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>Subjective generalized restlessness relieved by voluntary stereotypic movements (e.g. squirming)</td>
</tr>
<tr>
<td>Asterixis</td>
<td>Transient loss of muscle tone (negative myoclonus)</td>
</tr>
<tr>
<td>Athetosis</td>
<td>Slow writhing movements, especially distally</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Slow and/or small amplitude of movements</td>
</tr>
<tr>
<td>Chorea</td>
<td>Brief, flowing, irregular movements; can appear purposeful in milder forms</td>
</tr>
<tr>
<td>Dysdiadochokinesia</td>
<td>Inability to smoothly perform rapidly alternating movements</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>Any involuntary movement, but the term is often used to describe the stereotypical movements that come with long-term neuroleptic use (tardive dyskinesia)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Co-contraction of agonist and antagonist muscles causing sustained twisting movements which can be tonic (dystonic postures) or phasic (dystonic movements)</td>
</tr>
<tr>
<td>Freezing</td>
<td>Episodes of halted motor action, especially during repetitive actions (e.g. walking)</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>Unilateral violent flinging movement</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Brief muscle group contraction that is either focal, segmental, or generalized</td>
</tr>
<tr>
<td>Myokymia</td>
<td>Spontaneous, fine, fascicular contraction of muscle</td>
</tr>
<tr>
<td>Torsades de Pointes</td>
<td>Stereotyped and brief repetitive actions due to inner urge; can be suppressed; can be phonic (vocal) or motor</td>
</tr>
<tr>
<td>Tremor</td>
<td>Rhythmic and involuntarily alternating muscle contractions</td>
</tr>
</tbody>
</table>

Movement Disorders

Differential Diagnoses

1. Tremor

Table 17. Approach to Tremors

<table>
<thead>
<tr>
<th>Body Part</th>
<th>Resting Action</th>
<th>Action-Postural</th>
<th>Action-Intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Worse with Associated Sx</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DDx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Chorea: Huntington’s disease (HD), HD-like syndromes, neuroacanthocytosis, SLE, APLA syndrome, Wilson’s disease, CVD, tardive dyskinesia, senile chorea, Sydenham’s chorea, pregnancy chorea (chorea gravidarum)

3. Dystonia
   - primary dystonia: familial, sporadic (torticollis, blepharospasm, writer’s cramp)
   - dystonia-plus syndromes: dopa-responsive dystonia, myoclonus-dystonia
   - secondary dystonia: thalamotomy, stroke, CNS tumour, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
   - heredodegenerative dystonias: Parkinsonian disorders, Wilson’s disease, Huntington’s disease

4. Myoclonus
   - physiologic myoclonus: hiccups, nocturnal myoclonus
   - essential myoclonus: myoclonus-dystonia with minimal or no occurrence of dystonia
   - epileptic myoclonus
   - symptomatic myoclonus
   - degenerative disorders: Wilson’s disease, Huntington’s disease, Corticobasal degeneration
   - infectious disorders: CJD, viral encephalitis, AIDS-dementia complex
   - metabolic disorders: drug intoxication/withdrawal, hypoglycemia, hyponatremia, HHS, hepatic encephalopathy, uremia, hypoxia
   - focal brain damage: head injury, stroke, mass

In some cases, dystonias may only occur during voluntary movement and sometimes only during specific activities such as writing, chewing, or speaking (task-specific dystonia).

Hemiballismus is most often due to a vascular lesion of the contralateral subthalamic nucleus.

Myoclonus is often stimulus-sensitive as it can be induced by sudden noise, movement light, visual threat, or pinprick.

In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson’s disease), and CT/MRI (cerebellar disease) as indicated by type of tremor.

The majority of essential tremor does not need treatment.

Alcohol
   - Dampens essential tremor
   - Potentiates intention tremor during abstinence (delirium tremens)
   - Does not improve resting tremor of PD

Most common cause of chorea is drug therapy for PD (L-dopa induced dyskinesias).

Palatal myoclonus can result from lesion to the Dentato-Rubro-Olivary tract, and is associated with an audible clicking and tremor of other facial muscles.
### Parkinson’s Disease

**Etiology**
- sporadic: combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- familial (10%): autosomal dominant α-synuclein or LRRK2 mutations, autosomal recessive parkin, PINK1 or DJ-1 mutation (juvenile onset)
- MPTP (neurotoxin)

**Epidemiology**
- prevalence of 0.3% in industrialized countries, but rises with increased age
- second most common neurodegenerative disorder, after Alzheimer’s
- mean age of onset is 60 yr

**Associated Factors**
- risk: family history, male, head injury, rural living, exposure to certain neurotoxins
- protective: coffee drinking, smoking, NSAID use, estrogen replacement in post-menopausal women

**Pathophysiology**
- loss of dopaminergic neurons in pars compacta of substantia nigra → decreased opamine in striatum → 1. disinhibition of the indirect pathway & 2. decreased activation of the direct pathway → increased inhibition of cortical motor areas
- α-synucleinopathy: α-synuclein accumulates in Lewy bodies and causes neurotoxicity in substantia nigra

**Clinical Features**
- positive motor
  - resting tremor: asymmetric 4-5 Hz “pill-rolling” tremor, especially in hands
  - rigidity: lead-pipe rigidity with cogwheeling due to superimposed tremor
- negative motor
  - bradykinesia: slow, small amplitude movements, fatiguing of rapid alternating movements, difficulty initiating movement
- related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
- freezing of gait: occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds
- postural instability: late finding presenting as falls
- cognition: bradyphrenia (slow to think/respond), dementia (late finding)
- behavioural: decreased spontaneous speech, depression, sleep disturbances, anxiety
- autonomic: constipation, urinary retention, sexual dysfunction, orthostatic hypotension, clonicogenic hypertension

**Treatment**
- pharmacologic
  - mainstay of treatment: levodopa/carbidopa (Sinemet®) or levodopa/benserazide (Prolopa®).
  - Levodopa is a dopamine precursor; carbidopa and benserazide decreases peripheral metabolism of levodopa, decreasing side effects and increasing half-life of levodopa
  - levodopa-related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration (“wearing-off”), random oscillations of on-off symptoms
  - major complication of levodopa is dyskinesia
  - treatment of early PD: dopamine agonists, amantadine, MAOI
  - adjuncts: dopamine agonists, MAOI, anticholinergics (especially if prominent tremors), COMT inhibitors
- surgical
  - thalamotomy
  - pallidotomy
  - DBS (thalamic, pallidal, subthalamic)
- psychiatric
  - SSRIs first line
  - TCAs (beware fall risk, cognitive impairment, and worsening symptoms of Parkinson’s disease)

### Other Parkinsonian Disorders

- NCD with Lewy bodies (see *Behavioural Neurology, N25*)
- progressive supranuclear palsy: tauopathy with limited gaze (downgaze more specific), early falls, axial rigidity and akinesia, dysarthria, and dysphagia
- corticobasal syndrome: tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia ± “alien limbs” phenomenon; may also present as progressive non-fluent aphasia
- multiple system atrophy: synucleinopathy presenting as either cerebellar predominant (MSA-C, previously olivopontocerebellar atrophy) or parkinsonism predominant (MSA-P, previously nigrostriatal degeneration); both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- vascular parkinsonism: multi-infarct presentation with gait instability and lower body parkinsonism; less likely associated with tremor

---

**Key Parkinsonian Features**

<table>
<thead>
<tr>
<th>TRAP</th>
<th>Tremor (resting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity</td>
<td>Alpha or bradykinesia</td>
</tr>
<tr>
<td>Postural instability</td>
<td></td>
</tr>
</tbody>
</table>

**2015 MDS Clinical Diagnostic Criteria for PD**

- “Clinically Established PD” requires:
  - Cardinal Parkinsonism Manifestations: Bradykinesia with either rest tremor or rigidity
  - 2 or more supportive criteria (clear and dramatic beneficial response to dopaminergic therapy, levodopa-induced dyskinesia, rest tremor of a limb, olfactory loss/cardiac sympathetic denervation on MBG scintigraphy)
  - No absolute exclusion criteria and no red flags (see full diagnostic criteria - Postuma et al (2015). Mov Disord.)

**Consider an Alternative Diagnosis if Atypical Parkinsonism**

- Poor response to levodopa
- Abrupt onset of symptoms
- Rapid progression
- Early falls
- Early autonomic dysfunction
- Symmetric symptoms at onset
- Early age of onset (<50 yr)
- Early cognitive impairment
- FHs of psychiatric/dementing disorders
- Recent diagnosis of psychiatric disease
- History of encephalitis
- Unusual toxin exposure
- Extensive travel history

**Dopamine Agonist Therapy in Early Parkinson’s Disease**

*Cochrane DB Syst Rev 2009;2:CD006664*

**Study:** Meta-analysis of trials of dopamine agonists in early Parkinson’s disease.

**Results:** Twenty-nine trials were included (n=5,247). Dopamine agonists were found to have decreased motor effects (dyshkinesia [OR 0.51], dyskinesia [IR 0.64], motor fluctuations [OR 0.75]) compared to levodopa, but provided poorer symptom control compared to levodopa. Also, other side effects were increased (constipation [IR 1.59], hallucinations [IR 1.88], diziness [IR 1.45]).

**Conclusion:** Dopamine agonists have fewer motor side effects than levodopa, but provide worse symptom control and increased rate of other side effects.
Huntington’s Disease

**Etiology and Pathogenesis**
- genetics: autosomal dominant CAG repeats (with anticipation) in Huntington’s gene on Chromosome 4, which leads to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway, and decreased activity of the indirect pathway

**Epidemiology**
- North American prevalence 4-8/100,000
- mean age of onset 35-44 yr; but varies with degree of anticipation from 5-70 yr

**Clinical Features**
- typical progression: insidious onset with clumsiness, fidgetiness, and irritability, progressing over 15 yr to major NCD, psychosis, and chorea
  - major NCD: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudo-purposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence
- Juvenile onset HD (Westphal variant) characterized by Parkinsonism and dystonia

**Investigations**
- MRI: enlarged ventricles, atrophy of cerebral cortex and caudate nucleus
- genetic testing
  - expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene
  - CAG repeats on chromosome 4p16.3 that encodes the protein huntingtin

**Treatment**
- no disease altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin

Dystonia

**Epidemiology**
- third most common movement disorder after Parkinson’s disease and essential tremor

**Clinical Features**
- sustained twitching movements caused by co-contraction of agonist and antagonist muscles
- symptoms exacerbated by fatigue, stress, emotions; relieved by sleep or specific tactile/proprioceptive stimuli (‘geste antagoniste’, e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalize if younger onset or leg dystonia

**Treatment**
- local medical: botulinum toxin
- systemic medical: anticholinergics (benztropine), muscle relaxants (baclofen), benzodiazepines, dopamine depleters (tetrabenazine); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotactic thalamotomy (unilateral dystonia), posteroventral pallidotomy, or DBS

Tic Disorders

**Definition**
- a tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
- common criteria
  - tics may wax and wane in frequency but have persisted for an extended period of time
  - onset before age 18 yr
  - disturbance is not attributable to the physiological effects of a substance or another medical condition

**Clinical Classification**
- **Tourette’s Syndrome**: multiple motor and one or more vocal tics that have persisted for more than 1 yr since onset
- **persistent (chronic) motor or vocal tic disorder**: single or multiple motor or vocal tics (but not both motor and vocal) that have persisted for more than 1 yr since onset
- **provisional tic disorder**: single or multiple motor and/or vocal tics present for <1 yr since first tic onset
- other specified or unspecified tic disorder: symptoms characteristic of a tic disorder but do not meet full criteria
- **secondary tic disorders**: encephalitis, CJD, Sydenham’s chorea, head trauma, drugs, mental retardation syndromes
Tic Types
- simple tics: short duration (milliseconds)
- complex tics: longer (seconds), more purposeful and often include a combination of simple tics
- motor tics:
  - simple: blinking, head jerking, shoulder shrugging, extension of the extremities
  - complex: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- vocal tics:
  - simple: blowing, coughing, grunting, throat clearing
  - complex: coprolalia (shout obscenities), echolalia (repeat others' phrases), palilalia (repeat own phrases)

Treatment
- dopamine blockers, dopamine depletors (tetrabenazine), clonidine, clonazepam, DBS

**Tourette’s Syndrome (Gilles de la Tourette Syndrome)**

**Definition According to DSM V**
1. presence of both multiple motor and one or more vocal tics at some point during the illness, although not necessarily concurrently
2. tics may wax and wane in frequency but have persisted for more than 1 yr since first tic onset (with no tic-free periods greater than 3 mo)
3. onset is before age 18 yr
4. not due to effect of a substance or another medical condition

**Epidemiology**
- estimated prevalence among adolescents 3-8 per 1,000 school-age children; M:F = 2:1 to 4:1

**Signs and Symptoms**
- tics: wide variety that wax and wane in type and severity; can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
  - can be worsened by anxiety, excitement, and exhaustion; better during calm focused activities
- psychiatric: compulsive behaviour (associated with OCD and ADHD), hyperactive behaviour, ‘rages’, sleep-wake disturbances, learning disabilities

Treatment
- same as tics (dopamine blockers, dopamine depletors, clonidine, clonazepam, DBS)

**Prognosis**
- typically begins between ages 4-6
- peak severity occurs between ages 10-12, with a decline in severity during adolescence (50% are tic-free by 18 yr of age)
- tic symptoms, however, can manifest similarly in all age groups and across the lifespan

**Cerebellar Disorders**

**Clinico-Anatomic Correlations**
- vermis: trunk/gait ataxia
- cerebellar lobe (i.e. lateral): rebound phenomenon, scanning dysarthria, dysdiadochokinesia, dysmetria, nystagmus

**Symptoms and Signs of Cerebellar Dysfunction**
- nystagmus: observe during extraocular movement testing (most common is gaze-evoked nystagmus)
- dysarthria (ataxic): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/shurred speech on spontaneous speech
- ataxia: broad-based, uncoordinated, lurching gait
- dysmetria: irregular placement during voluntary movement of limb or eye
- dysdiadochokinesia: impairment of rapid alternating movements (e.g. pronation – supination task)
- postural instability: truncal ataxia on sitting, titubation (rhythmic rocking of trunk and head), difficulty with tandem and broad-based gait
- intention tremor: typically orthogonal to intended movement, and increases as target is approached
- hypotonia: decreased resistance to passive muscular extension (occurs shortly after injury to lateral cerebellum)
- pendular patellar reflex: knee reflex causes pendular motion of leg (occurs after injury to cerebellar hemispheres); pendular reflexes at triceps
- rebound phenomenon: overcorrection after displacement of a limb
- hypometric and hypermetric saccades
**Wernicke-Korsakoff Syndrome**

- see Psychiatry: PS24
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy

**Cerebellar Ataxias**

**Congenital Ataxias**
- early onset non-progressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

**Hereditary Ataxias**
- autosomal recessive: includes Friedrich’s ataxia, ataxia with oculomotor apraxia, ataxia telangiectasia, vitamin E deficiency
  - Friedrich’s ataxia: prevalence 2/100,000; typical onset between 8 and 15 yr
    - signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration, dysarthria
    - death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- autosomal dominant: most commonly spinocerebellar ataxias (SCAs) (over 30 types, most common SCAs due to CAG repeats)
  - signs: ataxia and dysarthria, chorea, polyneuropathy, pyramidal and/or extrapyramidal features, dementia

**Acquired Ataxias**
- neurodegeneration: e.g. multiple system atrophy
- systemic: alcohol, celiac sprue, hypothyroidism, Wilson’s, thiamine deficiency
- toxins: carbon monoxide, heavy metals, lithium, anticonvulsants, solvents
- vascular: infarct, bleed, basilar migraine
- autoimmune: MS, Miller-Fischer (GBS)

**Vertigo**

- see Otolaryngology: OT12

**Motor Neuron Disease**

**Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease)**

**Definition**
- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal

**Etiology**
- idiopathic (most), genetic (5-10% familial, especially SOD1 mutation, other: C9orf72, TARDBP)

**Pathology**
- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

**Epidemiology**
- 5/100,000; incidence increases with age

**Clinical Features**
- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms
- bulbar findings: dysarthria (flaccid or spastic), dysphagia, tongue atrophy and fasciculations, facial weakness and atrophy
- pseudobulbar affect, frontotemporal dementia (up to 10%)
- sparing of sensation, ocular muscles, bowel, bladder, sphincters

**Investigations**
- EMG: chronic denervation and reinnervation, fasciculations
- NCS: to rule out peripheral neuropathy (i.e. multifocal motor neuropathy with conduction block)
- CT/MRI: to rule out cord disease/compression

---

Red Flags Inconsistent with ALS
- Sensory Sx, predominant pain, bowel or bladder incontinence, cognitive impairment, ocular muscle weakness

Denervation on EMG
- Fibrillations, positive sharp waves, complex repetitive discharges; reinnervation — increased amplitude and duration of motor units

The only interventions that have been shown to extend survival in ALS are riluzole and use of BiPAP
**Peripheral Neuropathies**

### Treatment
- *riluzole* (modestly slows disease progression)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine (Zanaflex®), regular exercise, and physical therapy
  - sialorrhea: TCA (i.e. amitriptyline), sublingual atropine drops, parotid/submandibular Botox® (rare)
  - pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
- non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (i.e. PEG tube), rehabilitation (PT, OT, SLP), psychosocial support

### Prognosis
- median survival 3 yr; death due to respiratory failure

### Other Motor Neuron Diseases
- degenerative
  - *progressive muscular atrophy* (progressive bulbar palsy): only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centres
  - *primary lateral sclerosis* (progressive pseudobulbar palsy): UMN symptoms, later onset, not fatal, variable disability; 5-10% of patients in ALS centres
  - *spinal muscular atrophy*: pediatric disease with symmetric LMN symptoms
- infectious
  - post-polio syndrome, West Nile infection: residual asymmetric muscle weakness, atrophy

### Diagnostic Approach to Peripheral Neuropathies
1. differentiate: motor vs. sensory vs. autonomic vs. mixed
2. pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; cranial nerve involvement
3. temporal pattern: acute vs. chronic; relapsing/remitting vs. constant vs. progressive
4. history: PMH, detailed FHx, exposures (e.g. insects, toxins, sexual, travel), systemic symptoms
5. detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status

**Figure 22. Pattern of distribution for peripheral neuropathies**

#### Classification
- **monoradiculopathy**: dermatomal deficit due to single nerve root lesion
  - due to disc herniation or root compression causing radicular pain
  - little tactile anesthesia, as dermatomes overlap
- **polyradiculopathy**: multiple dermatome deficits due to multiple nerve root lesions
  - one type is cauda equina syndrome (lumbosacral roots)
- **plexopathy**: deficit matching distribution of a nerve plexus
  - **brachial plexopathy**
    - upper (C5-C7): LMN Sx of shoulder and upper arm muscles (Erbs palsy)
    - lower (C8-T1): LMN Sx and sensory Sx of forearm and hand (Klumpke's palsy)
    - **DDx**: trauma, idiopathic neuritis, tumour infiltration, radiation, thoracic outlet syndrome (i.e. cervical rib)
  - **lumbosacral plexopathy** (rare, especially unilateral)
    - **DDx**: idiopathic neuritis, infarction (i.e. DM), compression

**Diabetic Neuropathies**
- Peripheral neuropathy: pain or loss of sensation in a glove and stocking distribution (hands and feet affected before arms and legs)
- Autonomic: anhidrosis, orthostatic hypotension, impotence, gastroparesis, bowel and bladder dysfunction
- Mononeuropathy multiplex: nerve infarct or compression
- Cranial neuropathy: CN III (pupil sparing) > IV > VI
- Lumbosacral plexopathy

**Tinel’s Sign**
Tap lightly over the median nerve at the wrist, the patient’s symptoms of carpal tunnel will be elicited in a positive test

**Phalen’s Test**
Hold both wrists in forced flexion (with the dorsal surfaces of the hands pressed against each other) for 30-60 s; test is positive if symptoms of carpal tunnel are elicited

**DDx of Demyelinating Neuropathy**
GBS, CIDP, paraproteinemia, diphtheria, amyloidosis, Charcot-Marie-Tooth, storage diseases, pressure palsy predisposition, paraneoplastic
• **mononeuropathy**: single nerve deficit
  • **carpal tunnel syndrome** (most common): compression of median nerve at wrist
    • symptoms: wrist pain, paresthesia first 3 ½ digits, ± radiation to elbow, worse at night
    • signs: Tinel’s sign, Phalen’s test, thenar muscle wasting, sensory deficit
    • etiology: entrapment, pregnancy, DM, gammopathy, rheumatoid arthritis, thyroid disease
  • **Bell’s palsy** (most common cranial neuropathy): see Otolaryngology, OT22
  • **Entrapment/compression**: ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)
• **mononeuropathy multiplex**: deficit affecting multiple discrete nerves (asymmetric)
  • must rule out vasculitis or collagen vascular disease; consider MMN (multifocal motor neuropathy) or MADSAM (multifocal acquired demyelinating sensory and motor neuropathy)
• **polyneuropathy**: symmetrical distal stocking-glove pattern
  • symmetrical distal sensorimotor deficit affecting longest fibres first (stocking-glove distribution), hypotonia; progression of dysesthesia early and weakness later
  • etiology: DM (most common), renal disease, substances, toxins; genetics, SLE, HIV, leprosy, alcohol, B12 deficiency, uremia
• **chronic inflammatory demyelinating polyneuropathy (CIDP)**
  • chronic relapsing sensorimotor polyneuropathy with increase protein in CSF and demyelination (shown on EMG/NCS)
  • course is fluctuating, in contrast with the acute onset of GBS
  • treatment: first-line is prednisone; alternatives are plasmapheresis, IVIG, and azathioprine

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Table 18. Differential Diagnosis of Symmetric Polyneuropathy

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Mechanism</th>
<th>Course</th>
<th>Modalities</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAN</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>See Rheumatology, RH19</td>
</tr>
<tr>
<td>SLE</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>See Rheumatology, RH11</td>
</tr>
<tr>
<td>RA</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>See Rheumatology, RH8</td>
</tr>
<tr>
<td>Infectious</td>
<td>HIV</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/A</td>
</tr>
<tr>
<td></td>
<td>Leprosy</td>
<td>Infiltrative</td>
<td>Acute</td>
<td>S/A</td>
</tr>
<tr>
<td></td>
<td>Lyme</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>M</td>
</tr>
<tr>
<td>Immune</td>
<td>GBS</td>
<td>Demyelination</td>
<td>Acute</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>CIDP</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
</tr>
<tr>
<td>Hereditary</td>
<td>HMSN</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Paraneoplastic</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
</tr>
<tr>
<td></td>
<td>Myeloma</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>Axonal</td>
<td>Chronic</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Monoclonal gammopathy</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
</tr>
<tr>
<td>Toxin</td>
<td>EtOH</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
</tr>
<tr>
<td></td>
<td>Heavy metals</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
</tr>
<tr>
<td>Metabolic</td>
<td>DM</td>
<td>Ischemic/axonal</td>
<td>Chronic</td>
<td>S/A</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/M</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/A</td>
</tr>
<tr>
<td>Nutritional</td>
<td>B12 deficiency</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
</tr>
<tr>
<td>Other</td>
<td>Porphyria</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Amyloid</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S</td>
</tr>
</tbody>
</table>

A = autonomic; CDP = chronic inflammatory demyelinating polyneuropathy; GGT = gamma-glutamyl transferase; HMSN = hereditary motor sensory neuropathy; M = motor; OGGTT = oral glucose tolerance test; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; S = sensory; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis.

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Axonal neuropathies have decreased amplitude on NCS; demyelinating neuropathies have decreased velocity on NCS

Ototoxic drugs (e.g. aminoglycosides) should not be given to diabetics

Sensory neuropathy of the feet prevent them from adequately compensating for loss of vestibular function

IV G and plasmapheresis lead to more rapid improvement, less intensive care and less ventilation, but do not change mortality or relapse rate


Genetic Testing: Indicated for cryptogenic polyneuropathy exhibiting classic hereditary neuropathy phenotype. Screen for CMT1A duplication/deletion and Cx32 mutations.

A = autonomic; CDP = chronic inflammatory demyelinating polyneuropathy; GGT = gamma-glutamyl transferase; HMSN = hereditary motor sensory neuropathy; M = motor; OGGTT = oral glucose tolerance test; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; S = sensory; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis.
Guillain-Barré Syndrome
- **definition**: acute rapidly evolving demyelinating inflammatory polyradiculoneuropathy that often starts in the distal lower limbs and ascends
- **etiology**
  - autoimmune attack and damage to peripheral nerve myelin
  - sometimes preceded by viral/bacterial infections
- **signs and symptoms**
  - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
  - motor: weakness starting distally in legs, areflexia
  - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- **investigations**
  - CSF: albuminocytologic dissociation (high protein, normal WBC)
  - EMG/NCS: conduction block, differential or focal (motor > sensory) slowing, decreased F-wave, sural sparing
- **treatment**
  - IVIG or plasmapheresis, ± pain management, monitor vitals and vital capacity
- **prognosis**
  - peak of symptoms at 2-3 wk, resolution at 4-6 wk
  - 5% mortality (higher if require ICU); up to 15% have permanent deficits

Clinical Approach to Disorders of the Neuromuscular Junction

### Table 19. Common Disorders of the Neuromuscular Junction

<table>
<thead>
<tr>
<th></th>
<th>Myasthenia Gravis</th>
<th>Lambert-Eaton</th>
<th>Botulism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular/Bulbar Paresis</td>
<td>+</td>
<td>–</td>
<td>+ + (early)</td>
</tr>
<tr>
<td>Limb Weakness</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fatigability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Post-Exercise Enhancement</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reflexes</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Anticholinergic Sx</td>
<td>–</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Sensory Sx</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Associated Conditions</td>
<td>Thymoma</td>
<td>Small cell carcinoma</td>
<td>GI S&amp;S</td>
</tr>
<tr>
<td>Repetitive EMG Stimulation</td>
<td>Decremental response</td>
<td>Incremental response</td>
<td>↑ (rapid stimulation) ↓ (slow stimulation)</td>
</tr>
</tbody>
</table>

**Myasthenia Gravis**

**Etiology and Pathophysiology**
- progressive autoimmune disorder due to anti-AChR or anti-MuSK antibodies, resulting in early saturation at the NMJ and inadequate muscle activation with increasing nerve stimulation
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia

**Epidemiology**
- bimodal age of onset – 20s (mostly women) and 60s (mostly men)

**Clinical Features**
- fatigable, symmetric or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
- ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
- symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
- respiratory muscle weakness may lead to respiratory failure

**Investigations**
- edrophonium (Tensilon®) test - assess for improvement over 2 min following edrophonium injection
- EMG
  - repetitive stimulation → decremental response
  - single fibre electromyography shows increased jitter (80-100% sensitivity)
- spirometry – forced vital capacity may be used to monitor adequacy of respiratory effort over time
- anti-AChR antibody assay (70-80% sensitivity); anti-MuSK antibody may be used if seronegative for anti-AChR antibody
- CT/MRI to screen for thymoma/thymic hyperplasia

**Neuromuscular Junction Disease**

*Neuromuscular Junction Disease*

Diseases of the neuromuscular junction typically feature prominent fatigability

Fatigability can be tested by holding the arms out or by holding the gaze in the upward position (especially in MG)

Muscle weakness due to fatigability will improve with rest or ice

**Miller-Fisher Variant of GBS – Triad**
- Ophthalmoplegia
- Ataxia
- Areflexia

**GBS** is a neurological emergency due to risk of imminent respiratory failure

The most common antecedent infection in GBS is *Campylobacter jejuni*

**Neuromuscular Junction Diseases**
Neuromuscular Junction Diseases

Treatment
- thymectomy 85% of patients show improvement or remission
- symptomatic relief
- acetylcholinesterase inhibitors (e.g. pyridostigmine) - does not affect primary pathologic process so rarely results in control of disease when used alone
- immunosuppression
- steroids are mainstay of treatment (70-80% remission rate) - azathioprine, cyclophosphamide, and mycophenolate as adjuncts or as steroid sparing therapy
- short-term immunomodulation (for crises) – IVIG and plasmapheresis

Prognosis
- 30% eventual spontaneous remission
- with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

Lambert-Eaton Myasthenic Syndrome

Etiology and Pathophysiology
- autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased ACh release at the NMJ
- 50-66% are associated with small cell carcino ma of the lung

Clinical Features
- weakness of skeletal muscles without sensory or coordination abnormalities, proximal and lower muscles more affected
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and ocular muscles affected in 25% (vs. 90% in MG)
- prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

Investigations
- edrophonium test → no response
- EMG
  - rapid (>10 Hz) repetitive stimulation → incremental response
  - post-exercise facilitation → an incremental response with exercise
- screen for malignancy, especially small cell lung cancer

Treatment
- tumour removal
- acetylcholine modulation
  - increased acetylcholine release (3,4-diaminopyridine)
  - decreased acetylcholine degradation (pyridostigmine)
- immunomodulation - steroids, plasmapheresis, IVIG

Botulism

Etiology and Pathophysiology
- caused by a toxin produced by spores of Clostridium botulinum bacteria, which can enter through wounds or by ingestion
- infantile botulism is the most common form, and is usually from ingestion of honey or corn syrup

Clinical Features
- occur 6-48 h after ingestion
- CN paralysis: ptosis, extraocular muscle weakness, dilated poorly reactive pupils, dysarthria, jaw weakness, dysphagia
- autonomic dysfunction: nausea, orthostatic hypotension, constipation (paralytic ileus), bladder distension
- anticholinergic symptoms: dry mouth, constipation, urinary retention
- spreads to trunk and limbs: symmetric weakness with paralysis and absent/decreased deep tendon reflexes
- pattern of paresis often starts with GI symptoms, then extraocular muscle weakness, then dysphagia, then limbs and respiratory involvement; all associated with dry mouth.
- rarely respiratory distress, potentially advancing to respiratory failure

Investigations
- blood test for toxin, stool culture
- CT/MRI to rule out stroke, lesion (normal in botulism)

Treatment
- botulinum anti-toxin – good prognosis with prompt treatment
- supportive therapy as required

Tensilon® is a drug that inhibits acetylcholinesterase. It improves muscle function immediately in myasthenia gravis, but not in a cholinergic crisis. This test is infrequently used; when performed, a crash cart should be nearby as respiratory difficulty and/or bradycardia may occur.

Figure 24. Lambert-Eaton myasthenic syndrome (LEMS)
## Myopathies

### Clinical Approach to Muscle Diseases

#### Table 20. Myopathies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Key Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyositis (see Rheumatology, RH15)</td>
<td>Myalgias</td>
<td>↑ CK Biopsy: endomysial infiltrates; necrosis</td>
</tr>
<tr>
<td>Dermatomyositis (see Rheumatology, RH15)</td>
<td>Myalgias Characteristic rashes Can be paraneoplastic</td>
<td>↑ CK Biopsy: perifascicular atrophy</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>See Respiratory, R14</td>
<td>Biopsy: granulomas</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Weak quadriceps and deep finger flexors</td>
<td>↑ CK Biopsy: inclusion bodies</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid († or ‡) Cushing’s syndrome Parathyroid († or ‡)</td>
<td>See Endocrinology, E32</td>
<td>TSH, serum cortisol, calcium panel</td>
</tr>
<tr>
<td><strong>Toxic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Medication or toxin history</td>
<td>Toxicology screen</td>
</tr>
<tr>
<td>Critical illness myopathy</td>
<td>ICU patient Hx steroids and nondepolarizing paralyzing agents Failure to wean from ventilation</td>
<td>Biopsy: selective loss of thick myosin filaments</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasitic, bacterial, or viral</td>
<td>Myalgias Inflammatory myopathy</td>
<td>↑ myoglobin</td>
</tr>
<tr>
<td><strong>Hereditary Dystrophy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duchenne (see Medical Genetics, MG1)</td>
<td>Early onset (Duchenne and Becker)</td>
<td>Dystrophin analysis: absent</td>
</tr>
<tr>
<td>Becker</td>
<td>Progressive proximal muscle weakness Calf pseudohypertrophy</td>
<td>Dystrophin analysis: abnormal</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Distal myopathy Myo onia Genetic anticipation</td>
<td>Genetic testing</td>
</tr>
<tr>
<td><strong>Hereditary Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McArdle’s</td>
<td>Exercise-related myalgias, cramping, and myoglobinuria</td>
<td>↑ lactate ↑ serum/urinary myoglobin post-exercise</td>
</tr>
<tr>
<td><strong>Hereditary Periodic Paralysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Channelopathy”</td>
<td>Episodic weakness Normal between attacks</td>
<td>Normal, ↑ or ↓ K</td>
</tr>
<tr>
<td><strong>Hereditary Mitochondrial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERFF</td>
<td>Myoclonus, generalized seizures, dementia, myopathy</td>
<td>Biopsy: ragged red fibres</td>
</tr>
<tr>
<td>MELAS</td>
<td>Pediatric onset, stroke-like symptoms, episodic vomiting, dementia</td>
<td>Increased lactate</td>
</tr>
<tr>
<td>Kearns Sayre</td>
<td>Progressive ophthalmoplegia, retinal pigment degeneration, cardiac conduction abnormalities</td>
<td></td>
</tr>
</tbody>
</table>

*MERF = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MELAS = mitochondrial encephalomyopathy with ragged red fibres*
Myotonic Dystrophy

**Etiology and Pathophysiology**
- unstable trinucleotide (CTG) repeat in DMK gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms, autosomal dominant

**Epidemiology**
- most common adult muscular dystrophy, prevalence 3-5/100,000

**Clinical Features**
- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance
  - physical exam
    - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
    - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
    - cardiac: 90% have conduction defects (1º heart block; atrial arrhythmias)
    - respiratory: hypoventilation 2º to muscle weakness
    - ocular: subcapsular cataracts, retinal degeneration decreased intraocular pressure
    - other: DM, infertility, testicular atrophy
  - EMG: subclinical myotonia – long runs with declining frequency and amplitude

**Treatment and Prognosis**
- no cure, progressive, death usually around 50 yr
- management of myotonia: phenytoin

Pain Syndromes

**Approach to Pain Syndromes**

**Definitions**
- nociceptive pain: pain arising from normal activation of peripheral nociceptors
- neuropathic pain: pain arising from direct injury to neural tissue, bypassing nociceptive pathways
- spontaneous pain: unprovoked burning, shooting, or lancinating pain
- paresthesia: spontaneous abnormal non-painful sensation (e.g. tingling)
- dysesthesia: evoked pain with inappropriate quality or excessive quantity
- allodynia: a dyesthetic response to a non-noxious stimulus
- hyperalgesia: an exaggerated pain response to a noxious stimulus

**Non-Pharmacological Management**
- physical (PT, acupuncture, chiropractic manipulation, massage)
- psychoeducational (CBT, family therapy, education, psychotherapy)

**Medical Pain Control**
- combination multi-modal therapy is important
- primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches, and arthritis), opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympathectomies (phenoxybenzamine), α2-adrenergic agonists (clonidine)

**Surgical Pain Control**
- peripheral ablation: nerve blocks, facet joint denervation
- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy, or dorsal root entry lesion
- DBS or dorsal column stimulation

**Neuropathic Pain**

**Definition**
- pain resulting from a disturbance of the central or peripheral nervous system

**Epidemiology**
- affects up to 6% of people (2 million Canadians)
Symptoms and Signs
- hyperalgesia/allodynia
- subjectively described as burning, heat/cold, prickling, electric shock, perception of swelling, numbness
- can be spontaneous or stimulus evoked, distribution may not fall along classical neuro-anatomical lines
- associated issues: sleep difficulty, anxiety/stress/mood alteration

Causes of Neuropathic Pain
- sympathetic: complex regional pain syndrome
- non-sympathetic: damage to peripheral nerves
  - systemic disease: DM, thyroid disease, renal disease, rheumatoid arthritis, multiple sclerosis
  - nutritional/toxicity: alcoholism, pernicious anemia, chemotherapy
  - infectious: post-herpetic, HIV
  - trauma/compression: nerve entrapment, trigeminal neuralgia, post-surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy
- central: abnormal CNS activity
  - phantom limb, post spinal cord injury, post stroke, MS

Treatment
- identify/treat underlying cause
- pharmacotherapy
  - Stepwise approach (Canadian Pain Society, 2014)
    - 1st line: Gabapentinoids, TCA, SNRI
    - 2nd line: Tramadol, opioid analgesics
    - 3rd line: Cannabinoids
    - 4th line: topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin
- common non-pharmacologic therapies
  - neuropsychiatry: CBT, psychotherapy
  - rehabilitation: physiotherapy
- surgical therapies: dorsal column neurostimulator, DBS (thalamus)

Trigeminal Neuralgia

Clinical Features
- recurrent episodes of sudden onset, excruciating unilateral paroxysmal shooting “electric” pain in trigeminal root territory (V3>V2>V1)
- may have normal sensory exam
- pain lasts seconds/minutes over days/weeks; may remit for wk/mo
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up

Etiology
- classic TN: idiopathic
- secondary TN: compression by tortuous blood vessel (superior cerebellar artery), cerebellopontine angle tumour (5%), MS (5%)

Epidemiology
- F>M; usually middle-aged and elderly

Diagnosis
- clinical diagnosis
- investigate for secondary causes, which are more likely if bilateral TN or associated sensory loss
  - MRI to rule out structural lesion, MS, or vascular lesion

Treatment
- first line: carbamazepine or oxcarbazepine
- second line: baclofen or lamotrigine
- narcotics not generally recommended
- if medical treatment fails: trigeminal ganglion percutaneous technique, gamma knife, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression

Postherpetic Neuralgia

Clinical Features
- pain persisting in the region of a cutaneous outbreak of herpes zoster
- constant deep ache or burning, intermittent spontaneous lancinating pain, allodynia
- distribution: thoracic, trigeminal, cervical > lumbar > sacral
- associated impaired sleep, decreased appetite, decreased libido
Etiology and Pathogenesis
• destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

Epidemiology
• incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
• risk factors: older age, greater acute pain, greater rash severity

Prevention
• varicella zoster vaccine (Varivax®) in childhood reduces incidence of varicella zoster
• herpes zoster vaccine (Zostavax®) reduces incidences of shingles, PHN, and other herpetic sequelae (currently recommended in Canada for those >60 yr old)

Treatment
• medical: TCA (i.e. amitriptyline), anti-convulsants (i.e. pregabalin, gabapentin), analgesia (i.e. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  • early treatment of acute herpes zoster with antivirals (acyclovir; longer-acting famciclovir and valacyclovir more effective)
  • treatment of herpes zoster with corticosteroids DOES NOT decrease PHN
• surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus

Painful Diabetic Neuropathy
see Endocrinology, E13

Approach
• determine if pain is neuropathic or vascular
• more likely neuropathic if pain present at rest and improves with walking, pain is sharp/tingling, more in feet than calves

Treatment
• Level A: pregabalin
• Level B: venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, rarely opioids, capsaicin

Complex Regional Pain Syndromes

Clinical Features
• presence of an initiating noxious event (MI, stroke)
• continuing pain, allodynia, or hyperalgesia with pain disproportionate to inciting event evidence during the course of symptoms of edema, changes in skin blood flow or abnormal vasomotor activity
• absence of conditions that would otherwise account for degree of pain and dysfunction
• other features can include edema, osteoporosis, hyperhidrosis, hair loss, fascial thickening

Classification
• CRPS type I (reflex sympathetic dystrophy): minor injuries of limb or lesions in remote body areas precede onset of symptoms
• CRPS type II (causalgia): injury of peripheral nerves precedes the onset of symptoms

Investigations
• trial of differential neural blockade may be helpful in diagnosis
• autonomic testing (evidence of sympathetic dysfunction)
• bone scan, plain radiography, MRI

Prevention
• early mobilization after injury/infarction

Treatment
• goal of treatment: to facilitate function
• conservative treatment: education, support groups, PT/OT, smoking cessation
• medical: topical capsaicin, TCA, NSAIID, tender point injections with corticosteroid/lidocaine, gabapentin/pregabalin/lamotrigine, calcitonin or bisphosphonates, oral corticosteroids
• surgical: paravertebral sympathetic ganglion blockade
• refer to pain management clinic
Headache

Clinical Approach

- **History**
  - pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g., worse in AM, worse with bending/cough/Valsalva)
  - associated symptoms: visual changes, change in mental status, nausea/vomiting, fever, meningismus, photophobia, phonophobia, TMJ popping/clicking, jaw claudication, neurological symptoms
  - precipitating/alleviating factors (triggering factors, analgesics), medications (especially nitrates, CCBs, NSAIDs, anticoagulants), PMH, FFx
  - red flags (possible indications for CT scan/further investigation): new-onset headache (especially if age <5 or >50), quality worse/different than previous headaches, sudden and severe (‘thunderclap’), immunocompromised, fever, focal neurological deficits, trauma

- **Physical Exam**
  - vitals (including BP and temp), Kernig’s/Brudzinski’s, MSK examination of head and neck
  - HEENT: fundi (papilledema, disc swelling), vitals (including temp, BP, O2), cervical OA, TMJ syndrome
  - full neurological exam (including LOC, orientation, pupils (symmetry), and focal neurological deficits)
  - red flags: papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

Classification

- **Primary**
  - tension, migraine, cluster, other autonomic cephalgias, SUNCT
- **Secondary**
  - cervical OA, TMJ syndrome, SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN or pseudotumour cerebri), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-ecchymosis, post LP, drugs/toxins (e.g., nitroglycerin use and analgesia withdrawal); all can be associated with serious morbidity or mortality

Table 21. Headaches – Selected Primary Types

<table>
<thead>
<tr>
<th></th>
<th>Tension-Type</th>
<th>Migraine</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>70%</td>
<td>~10-20%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>15-40</td>
<td>10-30</td>
<td>20-40</td>
</tr>
<tr>
<td><strong>Sex Bias</strong></td>
<td>F&gt;M</td>
<td>F&gt;M</td>
<td>M&gt;F</td>
</tr>
<tr>
<td><strong>Family History</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Bilateral frontal</td>
<td>Unilateral &gt; bilateral</td>
<td>Retro-orbital</td>
</tr>
<tr>
<td></td>
<td>Nuchal-occipital</td>
<td>Fronto-temporal</td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Minutes – days</td>
<td>Hours – days</td>
<td>10 min-2 h</td>
</tr>
<tr>
<td><strong>Onset/Course</strong></td>
<td>Gradual; worse in PM</td>
<td>Gradual; worse in PM</td>
<td>Daily attacks for weeks to months; more common early AM or late PM</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Band-like; constant</td>
<td>Throbbing</td>
<td>Constant, aching, stabbing</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Mild-moderate</td>
<td>Moderate-severe</td>
<td>Severe (wakes from sleep)</td>
</tr>
<tr>
<td><strong>Triggers/Provoking</strong></td>
<td>Depression</td>
<td>Noise/light</td>
<td>Light</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Caffeine/alcohol</td>
<td>EtOH</td>
</tr>
<tr>
<td></td>
<td>Noise</td>
<td>Hunger</td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td>Hunger</td>
<td>Sleep deprivation</td>
<td>Sleep deprivation</td>
</tr>
<tr>
<td><strong>Palliating</strong></td>
<td>Rest</td>
<td>Rest</td>
<td>Walking around</td>
</tr>
<tr>
<td><strong>Associated Sx</strong></td>
<td>No vomiting</td>
<td>Nausea/vomiting</td>
<td>Red watery eye</td>
</tr>
<tr>
<td></td>
<td>No photophobia</td>
<td>Photo/phonophobia</td>
<td>Nasal congestion or rhinorrhoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aura</td>
<td>Unilateral Horner’s</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Non-pharmacological</td>
<td>Acute Rx</td>
<td>Acute Rx</td>
</tr>
<tr>
<td></td>
<td>Psychological counselling</td>
<td>ASA</td>
<td>O2</td>
</tr>
<tr>
<td></td>
<td>Physical modalities (e.g., heat, massage)</td>
<td>NSAIDs</td>
<td>Sumatriptan (nasal or injection)</td>
</tr>
<tr>
<td></td>
<td>Pharmacological</td>
<td>Ergotamine</td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td>Simple analgesics</td>
<td>Prophylaxis</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
<td>TCA</td>
<td>Methysgeride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticonvulsants</td>
<td>Prednisolone</td>
</tr>
</tbody>
</table>

Conclusions and Prophylaxis

**Antiepileptics in Migraine Prophylaxis: An Updated Cochrane Review**
Capovalva 2015;35:51-62

**Purpose:** To review the evidence for anticonvulsants in migraine prophylaxis.

**Study:** Systematic meta-analysis of 37 published and 3 unpublished prospective, controlled trials of regular use of anticonvulsants to prevent migraines and improve quality of life related to migraines.

**Results:** Sodium valproate and topiramate were associated with a reduction of 4 and 1 days of headache per month, respectively, and patients taking either drug were more than two times as likely to experience greater than 50% reduction in headache frequency, versus placebo. Neither drug was associated with undue rates of adverse events though higher doses of topiramate were associated with increased adverse events. There is insufficient evidence of efficacy of other antiepileptic drugs, including gabapentin, for migraine prophylaxis.

**Conclusions:** Daily sodium valproate 400 mg and topiramate 50 mg are well tolerated and effective in prophylactic treatment of migraine headache in adults.
### Table 22. Prophylactic Management of Migraine Headaches

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Evidence</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Propranolol</td>
<td>A</td>
<td>Asthma, DM (mask hypoglycemia) CHF</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Timolol</td>
<td>A</td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>B</td>
<td></td>
<td>Light-headedness</td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>A</td>
<td>Heart disease, glaucoma *Avoid in elderly</td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>C</td>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Light-headedness</td>
</tr>
<tr>
<td>CCBs</td>
<td>Flunarizine</td>
<td>A</td>
<td>Depression, obesity</td>
<td>Weight gain, depression, PD (rare)</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>B</td>
<td>Heart disease</td>
<td>Weight gain (4.5-9 kg), constipation</td>
</tr>
<tr>
<td>AED</td>
<td>Valproate</td>
<td>A</td>
<td>Liver, renal, pancreatic disease</td>
<td>Weight gain, tremor, alopecia, teratogenic: neural tube defect</td>
</tr>
<tr>
<td></td>
<td>Topiramate + folic acid supplement</td>
<td>A</td>
<td>Renal disease</td>
<td>Paresthesia, weight loss, cognitive: memory loss, difficulty concentrating, renal stone (rare)</td>
</tr>
</tbody>
</table>

### Table 23. Headaches – Selected Serious but Rare Secondary Types

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Meningeal Irritation</th>
<th>Increased ICP</th>
<th>Temporal Arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any age</td>
<td>Any age</td>
<td>&gt;60 yr</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Generalized</td>
<td>Any location</td>
<td>Temporal</td>
</tr>
<tr>
<td>Onset/Course</td>
<td>Meningitis: hours-days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAH: thunderclap onset</td>
<td>Gradual; worse in AM</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Severe</td>
<td>Severe</td>
<td>Variable; can be severe</td>
</tr>
<tr>
<td>Provoking</td>
<td>Head movement</td>
<td>Lying down</td>
<td>Jaw claudication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valsalva</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head low</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exertion</td>
<td></td>
</tr>
<tr>
<td>Associated Sx</td>
<td>Neck stiffness</td>
<td>N/V</td>
<td>Polymyalgia rheumatica</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
<td>Focal neuro symptoms</td>
<td>Visual loss</td>
</tr>
<tr>
<td></td>
<td>Focal deficits (e.g. CN palsies)</td>
<td>Decreased level of consciousness</td>
<td></td>
</tr>
<tr>
<td>Physical Signs</td>
<td>Kerning’s sign</td>
<td>Focal neuro symptoms</td>
<td>Temporal artery changes:</td>
</tr>
<tr>
<td></td>
<td>Brudzinski’s sign</td>
<td>Papilledema</td>
<td>Firm, nodular, incompressible</td>
</tr>
<tr>
<td></td>
<td>Meningismus</td>
<td></td>
<td>Tender</td>
</tr>
<tr>
<td>Management</td>
<td>CT/MRI with gadolinium LP, antibiotics for bacterial meningitis</td>
<td>CT/MRI and treatment to reduce pressure</td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td>CT/MRI and treatment to reduce pressure</td>
<td>See Neurosurgery, NS4</td>
<td>See Rheumatology, RH20</td>
</tr>
<tr>
<td>Etiology</td>
<td>Meningitis, SAH</td>
<td>Tumour, IIH, malignant HTN</td>
<td>Vasculitis (GCA)</td>
</tr>
</tbody>
</table>

IIH = idiopathic intracranial HTN

---

### Migraine Headaches

#### Definition (Common Migraine)
- ≥5 attacks fulfilling each of the following criteria
  - 4-72 h duration
  - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  - 1 of the following: nausea/vomiting, photophobia/phonophobia/osmophobia

#### Epidemiology
- 18% females, 6% males; frequency decreases with age (especially at menopause)

#### Etiology and Pathophysiology
- theories of migraine etiology
  - depolarizing wave of “cortical spreading depression” across the cerebral cortex that may cause an aura (e.g. visual symptoms due to wave through occipital cortex) and also activate trigeminal nerve afferent fibres
  - possible association with vasoconstriction/dilation
  - significant genetic contribution
- triggers: stress, sleep deprivation, drugs (estrogen nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrates (e.g. processed meats)

The oral contraceptive pill is contraindicated with complicated migraine due to risk of stroke.

Migraine auras can mimic other causes of transient neurological deficits (e.g. TIAs and seizures).

"Menstrual Migraine" Subtype
Migraine headache that is associated with the onset of menstruation – usually 2 d before to 3 d after the onset of menstrual bleeding.

If patient presents to ED with severe migraine and N/V – consider treating with IV antiemetics (chlorpromazine, prochlorperazine).
Signs and Symptoms
- stages of uncomplicated migraine
  1. prodrome (hours to days before headache onset)
  2. aura
  3. headache
  4. postdrome
- aura
  - fully reversible symptom of focal cerebral dysfunction lasting <60 min
  - examples: visual disturbance (fortification spectra – zigzags; scintillating scotoma – spots), unilateral paresthesia and numbness or weakness, aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
- classification of migraines
  - common migraine: no aura
  - classic migraine: with aura (headache follows reversible aura within 60 min)
  - complicated migraine: with severe/persistent sensorimotor deficits
    - examples: basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness), hemiplegic/hemisensory migraine, ophthalmoplegic migraine
  - acephalgic migraine (i.e. migraine equivalent): aura without headache

Treatment
- avoid triggers
- mild to moderate migraine
  - 1st line: NSAIDs (ibuprofen, naproxen)
- moderate to severe migraine
  - triptans (most effective), ergots (dihydroergotamine, DHE)
- migraine prophylaxis: anticonvulsants (divalproex, topiramate, gabapentin), TCA (amitriptyline, nortriptyline), propranolol, calcium channel blocker (verapamil)

Sleep Disorders

Overview of Sleep

Definition
- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many elderly have reduced sleep as a consequence of underlying sleep disorders

Sleep Architecture
- polysomnogram (PSG) measures: EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG

Table 24. Sleep Stage Characteristics

<table>
<thead>
<tr>
<th>EEG</th>
<th>EOG</th>
<th>Muscle Tone</th>
<th>Other Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waking State</td>
<td>Alpha waves: high frequency (8-12 Hz) low voltage</td>
<td>Rapid, blinking</td>
<td>High</td>
</tr>
<tr>
<td>Stage N1 (~5%)</td>
<td>Less than 50% Alpha waves (see above), mixed with slow wave activity</td>
<td>Slow, moving eye movements</td>
<td>High, but gradually dropping Marker for very light quality sleep or sleep disruption</td>
</tr>
<tr>
<td>Stage N2 (~50%)</td>
<td>K complexes (high voltage negative and positive discharges) with sleep spindles (11-16 Hz)</td>
<td>Still</td>
<td>High</td>
</tr>
<tr>
<td>Stage N3 (previously 3 and 4)/Slow Wave/Delta Sleep (~20%)</td>
<td>Delta waves: low frequency (&lt; 2 Hz), high voltage (&gt; 75 µV)</td>
<td>Still</td>
<td>Low</td>
</tr>
<tr>
<td>Rapid Eye Movement (REM) Sleep (~25%)</td>
<td>Sawtooth waves, mixed frequency, low voltage</td>
<td>Rapid eye movements</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Pharmacological Treatments for Acute Migraine

Study: Meta-analysis of 54 double-blind, placebo-controlled RCTs of pharmacologic treatment of acute migraine of moderate to severe intensity (21,022 patients in total).

Data Extraction: Number of patients, dosing regimens, details of study design, and timing or type of rescue medication. Outcomes include headache relief at 1 and 2 h, freedom from pain at 2 h, sustained relief for 24 h, and adverse effects within 24 h.

Main Results: Data were available for 9 oral medications, 2 intranasal medications, and subcutaneous sumatriptan. For H/A relief at 2 h, all interventions were effective except Cafergot®, with NNTs ranging from 2.0 for sumatriptan 6 mg SC to 5.4 for naratriptan 2.5 mg. The lowest NNT for oral medication was 2.6 for eletriptan 80 mg. For patients pain free at 2 h, the lowest NNT was 2.1 for sumatriptan 6 mg SC, with the lowest NNT for oral medication being 3.1 for rizatriptan 10 mg. For sustained relief over 24 h NNT ranged from 2.6 for eletriptan 80 mg to 8.3 for rizatriptan 5 mg. Side effects could not be analyzed systematically. There were no drug-to-drug comparisons.

Conclusion: Overall, most treatments were effective. Subcutaneous sumatriptan and ral triptans were most effective.

Elements of Sleep History
- Initiation of sleep
- Events prior to bed
- Lights
- Latency (estimated)
- Restless legs
- Hallucinations
- Maintaining sleep
- Number of wakeups/night
- Sleep walking/talking
- Snoring/gasping
- Dreams/nightmares
- Consequences of sleep
- Restorative
- Morning headache
- Falling asleep in inappropriate setting
Disturbances of Alertness and Sleep

Coma

- see Neurosurgery, NS35

Insomnia

- difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep

  - types
    - sleep state misperception, psychophysiologic insomnia (learned sleep-preventing associations – i.e. clock watching), fatal familial insomnia (rare prion protein mutation causing autonomic dysfunction), idiopathic (lifelong difficulty)
    - secondary causes
      - psychiatric disorders (80% of psychiatric patients): anxiety and depression (see Psychiatry, PS13)
      - neurologic disorders: neurodegenerative disease, epilepsy, neuromuscular disorders, many others
      - sleep disorders: restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
      - medical conditions: pregnancy, cardiopulmonary (COPD/HF), GERD, pain (arthritis, fibromyalgia, cancer)
      - drugs/toxins: caffeine, alcohol, stimulants, antidepressants, glucocorticoids, sedative withdrawal

  - treatment
    - sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, CBT

Sleep Apnea

- disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence (or drowsiness)

  - epidemiology
    - >2–4% of the population
    - correlated with obesity
    - significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)

  - types
    - obstructive sleep apnea
    - central sleep apnea: no effort to breath over 10 s
    - mixed apnea: starts as central, but eventually becomes obstructive

  - etiology of central apnea: heart failure, opiates, brainstem pathology, myotonic dystrophy

  - etiology of obstructive apnea: collapse of airway due to low muscle tone in deep and REM sleep

  - diagnosis: apnea hypopnea index (AHI) or respiratory disturbance index (RDI) should be <5 in the normal state

  - treatment: conservative measures, dental devices, CPAP (common), surgery (rare), ensure driving safety

Restless Leg Syndrome (RLS) and Periodic Limb Movement in Sleep (PLMS)

- urge to move accompanied by uncomfortable sensations that begin or worsen with rest, are partially or totally relieved with movement, and are worse in evening/night; these features cannot be accounted for by another medical/behavioural condition

  - RLS refers to sensation

  - PLMS refers to the manifestation

  - epidemiology: 10% North Americans, 90% of RLS have PLMS, 50% of patients with PLMS have RLS

  - etiology: central (spasticity), peripheral nervous system (radiculopathy, neuropathy), pregnancy, iron deficiency, alcohol use

  - treatment
    - underlying contributors (iron and B12 supplementation), dopaminergic agonists (first line), clonazepam (causes tachyphylaxis), opioids (only exceptional circumstances)
    - NOT recommended: levodopa/carbidopa (Sinemet®), causes augmentation

Narcolepsy

- definition/clinical features: excessive daytime sleepiness (all narcolepsy), cataplexy = loss of muscle tone with emotional stimuli (pathognomonic) sleep paralysis (unable to move upon wakening), hypnagogic hallucinations (vivid dreams or hallucinations at sleep onset)

  - prevalence 1:2,000, onset in adolescence/early adulthood; life-long disorder

  - etiology: presumed autoimmune attack on orexin/hypocretin system, post head injury, MS, hypothalamic tumours; rarely familial

  - diagnosis: based on clinical history + multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps

  - treatment
    - sleep hygiene and scheduled brief naps, restricted driving
    - alerting agents: modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
    - anticitaplectic: TCAs, SSRIs, sodium oxybate

Drug Effects on Wakefulness and Sleep

- Antihistamines associated with increased sleepiness
- Stimulants increase arousal
- Caffeine (an adenosine antagonist) increases wakefulness
- Benzodiazepines reduce slow wave sleep
- Antidepressants (TCA/MAOI/SSRI) reduce REM, prolong REM latency
- Alcohol may hasten sleep onset but associated with increased arousals

Avoid sleep medications (especially in elderly patients) due to increased risk of falls, pseudodepression, and memory loss
Parasomnias
- **definition/clinical features**: unusual behaviours in sleep with clinical features appropriate to stage of sleep
- **etiology**: in elderly, REM sleep behaviour disorder may be associated with PD; in children, slow wave sleep arousals (sleep walking) may be associated with sleep disordered breathing
- **diagnosis**: clinical history in children, polysomnography in adults to exclude nocturnal seizures
- **treatment**: behavioural management (safety, adequate sleep); clonazepam for REM sleep behaviour tonsillectomy if appropriate in children

Circadian Rhythm
- **definition/clinical features**: abnormalities based on time of day rather than sleep (i.e. jet lag, shift work)
- **diagnosis**: clinical history

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**CNS Infections**
- see Infectious Diseases, ID18

**Spinal Cord Syndromes**
- see Neurosurgery, NS29

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**Stroke**

**Terminology**
- **stroke**: sudden onset of neurological deficits of a vascular basis with infarction of CNS tissue
  - infarction is permanent tissue injury (confirmed by neuroimaging)
- **TIA**: sudden onset of neurological deficits of a vascular basis without infarction (i.e. no imaging evidence of stroke)
  - may present with amaurosis fugax (transient monocular painless vision loss)

**Pathophysiology**
- two major types: ischemic (~80%) and hemorrhagic (~20%)

1. ischemic
   - arterial thrombosis: thrombus formation in artery (local/in situ)
     - large vessel: stenosis or occlusion of the internal carotid artery, vertebral, or intracranial arteries
       - mechanism: insufficient blood flow beyond lesion (hemodynamic stroke)
       - underlying processes: atherosclerosis (most common cause), dissection, and vasculitis
     - small vessel/lacunar
       - mechanism: chronic HTN and DM cause vessel wall thickening and decreased luminal diameter
       - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule, and thalamus)
   - cardioembolic: blockage of cerebral arterial blood flow due to particles originating from a cardiac source
     - atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
   - systemic hypoperfusion (global cerebral ischemia)
     - inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest arrhythmia, or MI)
     - primarily affects watershed areas (between the major cerebral arterial territories)

2. hemorrhagic
   - intracerebral hemorrhage
     - mechanisms
       - hypertensive (most common); rupture of small microaneurysms (Charcot-Bouchard aneurysms) causing intraparenchymal hemorrhage; most common sites: putamen, thalamus, cerebellum, andpons
       - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, vasculitis, drug use (cocaíne or amphetamines)
   - subarachnoid hemorrhage see Neurosurgery, NS18

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**Hypertension Encephalopathy**
Acute severe HTN (typically dBP >130 or sBP >200) can cause hypertensive encephalopathy – abnormal fundoscopic exam (papilledema, hemorrhages, exudates, cotton-wool spots), focal neurologic symptoms, N/V, visual disturbances, and change in LOC

Consider transfer of acute stroke patient to a designated stroke centre for neuroprotective or thrombolytic therapy if the patient is seen in first few hours

Early seizure activity occurs in 5-25% of patients after ICH

Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can also have seizures, focal neurological deficits, or cranial nerve palsies. This is diagnosed with MRV or CTV. Treatment is typically anticoagulation with heparin initially, then transition to warfarin

20-40% of patients with ischemic stroke may develop hemorrhagic transformation within 1 wk after the initial infarction

Blood work should only delay treatment if: patient is on anticoagulants, low platelet count suspected, abnormal electrolytes suspected, or any bleeding abnormality suspected
**Stroke Syndromes According to Vascular Territory**

- **ACA**: contralateral leg paresis, sensory loss, cognitive deficits (e.g. apathy, confusion, and poor judgment)
- **MCA**: proximal occlusion involves
  1. contralateral weakness and sensory loss of face and arm
  2. cortical sensory loss
  3. may have contralateral homonymous hemianopia or quadrantanopia
  4. if dominant (usually left) hemisphere: aphasia
  5. if non-dominant (usually right) hemisphere: neglect
  6. eye deviation towards the side of the lesion and away from the weak side
- **PCA**
  1. contralateral hemianopia or quadrantanopia
  2. midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  3. thalamic findings: sensory loss, amnesia, decreased level of consciousness
  4. if bilateral: cortical blindness or prosopagnosia
  5. hemiballismus
- **basilar artery**
  - proximal (usually thrombosis): impaired EOM, vertical nystagmus, reactive miosis, hemi- or quadriplegia, dysarthria, locked-in syndrome, coma
  - distal (usually embolic, i.e. top of the basilar syndrome): somnolence, memory and behaviour abnormalities, oculomotor deficit
- **PICA (lateral medullary or Wallenberg syndrome)**: ipsilateral ataxia, ipsilateral Horner’s, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, nausea/vomiting, dysphagia, dysarthria, hicups
- **medial medullary infarct** (anterior spinal artery, which can be associated with anterior cord infarct): contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness
- **lacunar infarcts** (deep hemispheric white matter; involving deep penetrating arteries of MCA, circle of Willis, basilar, and vertebral arteries)
  - pure motor hemiparesis (posterior limb of internal capsule): contralateral arm, leg, and face
  - pure sensory loss (ventral thalamic): hemisensory loss
  - ataxic hemiparesis (ventral pons or internal capsule): ipsilateral ataxia and leg paresis
  - dysarthria-clumsy hand syndrome (ventral pons or genu of internal capsule): dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness

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**Cortical Vascular Territories: Left Hemisphere**

- Area of anterior cerebral artery
- Area of middle cerebral artery
- Area of posterior cerebral artery

**Cortical Vascular Territories: Ventral Surface**

- Area of anterior cerebral artery
- Area of middle cerebral artery
- Area of posterior cerebral artery

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Figure 25. Vascular territories
Assessment and Treatment of Ischemic Stroke

General Assessment
- ABCs, full vital sign monitoring, capillary glucose (Accu-Chek®), urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis)
- level of consciousness (knows age, month, obeys commands), dysarthria, dysnomia (cannot name objects)
- gaze preference, visual fields, facial palsy
- arm drift, leg weakness, ataxia
- sensation to pinprick, extinction/neglect
- history
  - onset: time when last known to be awake and symptom free
  - mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
- investigations
  - non-contrast CT head (STAT): to rule out hemorrhage and assess extent of infarct
  - ECG: to rule out atrial fibrillation (cardioembolic cause)
  - carotid dopplers, echocardiogram
  - CBC, electrolytes, creatinine, PT/INR, blood glucose, lipid profile
- imaging (i.e. CT ± MR or CT angiography) signs of stroke
  - loss of cortical white-grey differentiation
  - sulcal effacement (i.e. mass effect decreases visualization of sulci)
  - hypodensity of parenchyma
  - insular ribbon sign
  - hyperdense MCA sign

ACUTE STROKE MANAGEMENT

1. Thrombolysis
   - rtPA (recombinant tissue plasminogen activator)
   - given within 4.5 h of acute ischemic stroke onset provided there are clinical indications and no contraindications to use
   - indications and contraindications (see sidebar)

2. Anti-Platelet Therapy
   - give at presentation of TIA or stroke if rtPA not received
   - antiplatelet agents
     - ASA: recommended dose 81 mg chewed
     - if patient intolerant to ASA, use other antiplatelet agent (i.e. clopidogrel)

3. Acute Anti-Coagulant Therapy
   - for patients with TIA or stroke and atrial fibrillation, if rtPA not received:
     - recommend IV heparin (or ensuring INR between 2-3 if already anticoagulated on warfarin)
     - may delay initiation of oral anticoagulation depending on size of infarct and presence of petechial/frank hemorrhage

4. Intra-arterial Thrombectomy by Interventional Radiology
   - early thrombectomy improves outcomes in ischemic stroke with large artery occlusions of the proximal anterior circulation

Other Acute Management Issues
- avoid hyperglycemia which can increase the infarct size
- lower temperature if febrile (febrile stroke: think septic emboli from endocarditis)
- prevent complications
  - INO if dysphagia (to be reassessed by SLP)
  - DVT prophylaxis if bed-bound
  - initiate rehabilitation early

Blood Pressure Control
- do NOT lower the blood pressure unless the HTN is severe
- antihypertensive therapy is withheld for 48-72 hr (permissive hypertension) after thromboembolic stroke unless sBP >220 mmHg or dBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection (IV labetalol first-line if needed)
- acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
- most patients with an acute cerebral infarct are initially hypertensive and their BP will fall spontaneously within 1-2 d

Etiological Diagnosis
- further investigations
  - additional neuroimaging (MRI)
  - vascular imaging: CTA/MRA/carotid dopplers
  - cardiac tests: echocardiogram, Holter monitoring
  - correct etiological diagnosis is critical for appropriate secondary prevention strategies
Primary and Secondary Prevention of Ischemic Stroke

Anti-Platelet Therapy
- primary prevention
  - no firm evidence for a protective role for antiplatelet agents for low-risk patients without a prior stroke/TIA
- secondary prevention
  - initial choice: ASA
  - if cerebrovascular symptoms while on ASA or if unable to tolerate ASA: Aggrenox® (ESPRIT trial), clopidogrel (CAPRIE trial)

Carotid Stenosis
- primary prevention (asymptomatic)
  - carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per yr; carotid endarterectomy reduces the risk of stroke by 1% per yr (but 5% risk of complications)
- secondary prevention (previous stroke/TIA in carotid territory)
  - carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%), and is less beneficial for those with symptomatic moderate stenosis (50-69%) (NASCET trial), see Vascular Surgery VS6
  - according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI, and death; however, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI

Atrial Fibrillation
- primary and secondary prevention with anticoagulation
  - classical risk stratification used CHADS2 score (0-6), but Stroke 2014 guidelines recommend that virtually all patients with atrial fibrillation without contraindication be anticoagulated
  - 0 (low risk, 1.9% annual stroke risk): antplatelet
  - 1 (intermediate risk, 2.8% annual stroke risk): anticoagulant or antplatelet – patient specific decision
  - >2 (high risk, 4-18.2% annual stroke risk): anticoagulant
- anticoagulation therapy
  - warfarin (ti rate to INR 2-3)
  - dabigatran (110 or 150 mg PO bid), apixaban (2.5 or 5 mg PO bid) or rivaroxaban (15 or 20 mg PO daily) may be alternatives to warfarin, but should be used cautiously; Praxbind reversal agent for dabigatran if necessary

Hypertension
- primary prevention
  - targets: BP <140/90 (or <130/80 for diabetics or renal disease); high risk but without diabetes, target sBP < 120 (SPRINT trial)
  - ACEI: ramipril 10 mg PO OD is effective in patients at high risk for cardiovascular disease (HOPE trial)
- secondary prevention
  - ACEI and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

Hypercholesterolemia
- primary prevention
  - statins in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE trial)
- secondary prevention
  - statins – high dose atorvastatin (SPARCL trial) but lower doses may be more appropriate if patient cannot tolerate high dose

Diabetes
- ideal management: HbA1c <7%, fasting blood glucose between 4 and 7

Smoking
- primary prevention: smoking increases risk of stroke in a dose-dependent manner
- secondary prevention: after smoking cessation, the risk of stroke decreases to baseline within 2-5 yr

Physical Activity
- beneficial effect of regular physical activity has a dose-related response in terms of intensity and duration of activity

Stroke Rehabilitation
- individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

Conclusions
- The rate of periprocedural stroke, myocardial infarction, death, and subsequent ipsilateral stroke did not differ between carotid-artery stenosis patients treated with stenting or endarterectomy at 10 years of follow-up.
- There was no significant difference in outcomes of either primary composite endpoint (HR 1.10; 95% CI 0.83-1.44) or periprocedural event (HR 0.90; 95% CI 0.64-1.52) in patients treated with stenting or endarterectomy.
- Asymptomatic and symptomatic patients showed to significant between-group differences in other endpoint.
- The rates of periprocedural stroke, myocardial infarction, death, and subquent ipsilateral stroke did not differ between carotid-artery stenosis patients treated with stenting or endarterectomy at 10 years of follow-up.

Stroke risk stratification for patients with atrial fibrillation

CHADS2
- Stroke risk stratification for patients with atrial fibrillation
  - CHF (1 point)
  - HTN sBP >160 mmHg/treated HTN (1 point)
  - Age >75 yr (1 point)
  - DM (1 point)
- Prior Stroke or TIA (2 points)

ABCD2 Score
- To predict/identify individuals at high risk of stroke following TIA
  - Age: 1 point for age >60 yr
  - Blood pressure (at presentation): 1 point for HTN (>140/90 mmHg at initial evaluation)
  - Clinical features: 2 points for unilateral weakness, 1 point for speech disturbance without weakness
  - Duration of symptoms: 1 point for 10-59 min, 2 points for >60 min
  - DM: 1 point
  - Stroke risk: 0-3: low risk, 4-5: moderate risk, 6-7: high risk

Long-Term Results of Stenting vs. Endarterectomy for Carotid-Artery Stenosis

Purpose: To evaluate the evidence for endovascular intervention in the treatment of ischemic stroke.

Study: Systematic review and meta-analysis of 10 randomized-controlled trials of 2,925 patients testing the efficacy and safety of endovascular intervention in patients suffering acute, ischemic stroke in the anterior circulation versus medical therapy, including thrombolysis, alone.

Results: The 7 RCTs published or presented in 2015 were without significant heterogeneity and formed the basis for the analysis. The majority of patients (86%) received stent retrievers and experienced higher than expected rates of recanalization (>50%). Risk ratio for good functional outcomes was 1.56 (RR: 0.86-0.90) and 0.78 for mortality (RR: 0.89-0.90). There was a difference in symptomatic intracranial hemorrhage following therapy.

Conclusions: Endovascular therapy is safe and improves outcomes when added to medical care with thrombolysis when administered in the 6-6 hours of large vessel, anterior circulation occlusive stroke. A trend towards improved mortality exists with complete follow-up results of several key trials pending.
Cerebral Hemorrhage

- **Definition**: intracranial bleeding into brain tissue
- **Etiology**: head trauma, hemorrhagic stroke

**Investigations**
- general investigations: see Assessment and Treatment of Ischemic Stroke, N50
- further investigations
  - LP (if suspect subarachnoid hemorrhage despite negative CT)
  - may require cerebral angiogram if suspect aneurysm or AVM
  - if typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion

**Treatment**
- medical
  - anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2010 AHA/ASA guidelines suggest that reducing sBP to as low as 140 mmHg with IV anti-hypertensives is safe and appropriate management (target sBP 140-160 systolic)
  - ICP lowering medical management (if necessary): see Neurosurgery, NS22
- surgical: see Neurosurgery, NS4

Neurocutaneous Syndromes

- see Pediatrics, P79

Multiple Sclerosis

**Definition**
- a chronic inflammatory disease of the CNS characterized by relapsing remitting, or progressive neurologic symptoms due to inflammation, demyelination, and axonal degeneration

**Clinical Patterns of MS**
- relapsing remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- benign MS (BMS): retrospective diagnosis made after 15 years of mild disease, with no evidence of worsening (functional ability and MRI)
- most RRMS goes on to become SPMS

**MS Variants**
- Devic's = neuromyelitis optica (NMO): severe optic neuritis and extensive transverse myelitis extending >3 vertebral segments (antibody positive)
- clinically isolated syndrome (CIS): single MS-like episode, which may progress to MS
- tumeformactive MS: solitary lesion >2 cm mimicking neoplasms on MRI
- fulminant MS (Marburg): rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- pediatric MS: onset of MS before the age of 18
  - epidemiology: rare (1.35-2.5 per 100,000 children)
  - presentation: more likely to present with isolated optic neuritis, isolated brainstem syndrome or symptoms of encephalopathy compared to adults
  - course: 98% have RRMS
  - diagnosis and treatment similar to adult MS
  - differential diagnosis: in the setting of nonspecific CSF abnormalities and MRI evidence of white matter lesion, rule out ADEM, optic neuritis, transverse myelitis, neumyelitis optica, CNS malignancies, leukodystrophies, and mitochondrial disease
- acute disseminated encephalomyelitis (ADEM): monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children often following infection or vaccination

**Etiology**
- genetic
  - polygenetic: the HLA DRB1 gene has been demonstrated to be a genetically susceptible area
  - 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
- environmental
  - MS is more common in regions with less sun exposure and lower stores of vitamin D (Europe, Canada, US, New Zealand, SE Australia)
  - MS has also been linked to certain viruses (EBV is associated with MS)
Epidemiology
- onset 17-35 yr; F:M = 3:1
- PPMS occurs in an older population with F=M

Diagnosis for RRMS
- demonstration of both dissemination in time and space based on the revised McDonald criteria (2010)
  - dissemination in time: 2 or more attacks, simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing MRI lesions at any time, or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI
  - dissemination in space: ≥1 T2 lesions on MRI in at least 2 of the 4 CNS regions (periventricular, juxtacortical, infratentorial, or spinal cord) or developing a second attack that implicates a different CNS region

Clinical Features
- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. INO), impaired gag, vertigo, bladder dysfunction
- Lhermitte's sign: flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- Uthoff's phenomenon: worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically weakness of legs in pyramidal distribution paired with cerebellar findings of arms (i.e. intention tremor)
- symptoms not commonly found in MS: visual field defects, aphasia, apraxia, progressive hemiparesis
- relapse: acute/subacute onset of clinical dysfunction that peaks from days to weeks, followed by remission with variable symptom resolution (symptoms must last at least 24 h)
- in RRMS, average 0.4 to 0.6 relapses/yr, but higher disease activity in 1st yr of disease

Investigations
- MRI: demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
  - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxtacortical region, and dorsolateral spinal cord
  - Dawson's fingers: periventricular lesions extending into corpus callosum
  - cranial MRI is more sensitive than spinal MRI
- CSF: oligoclonal bands in 90%, increased IgG concentration
- evoked potentials (visual/auditory/somatosensory): delayed but well-preserved wave forms

Treatment
- acute treatment: methylprednisolone 1,000 mg IV daily x 3-7 d (no taper required); if poor response to corticosteroids may consider plasma exchange
- disease modifying therapy (DMT)
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: teriflunomide, interferon-β (injection: Betaseron®, Avonex®, Rebi®), glatiramer acetate (injection: Copaxone®), BG-12 (Tecfidera®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion), fingolimod (Gilenya®)
  - increased risk of progressive multifocal leukoencephalopathy (PML)
  - CIS: early treatment with interferons may delay potential second attack
  - RRMS: DMT reduces rate of relapse by about 30%
  - PPMS/SPMS: no proven efficacy of DMTs
- symptomatic treatment
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantadine, modafinil, methylphenidate
  - depression: antidepressant, lithium
  - constipation: high fibre intake, stool softener, laxatives
  - sexual dysfunction: sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®)
- education and counselling: MS Society, support groups, psychosocial issues

Prognosis
- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy
## Common Medications

### Parkinson's Disease
- **Mechanism of Action/Class:** Dopamine precursor
- **Generic Name:** levodopa + carbidopa
- **Trade Name:** Sinemet®
- **Dosing:** Carbidopa 25 mg/levodopa 100 mg PO tid
  - Maximum 200 mg carbidopa and 2,000 mg levodopa per day
- **Indications:** Parkinson's disease
- **Side Effects:** Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions
- **Contraindications:** Hypertension, hallucinations, dyskinesias in last 14 d, history of melanoma or undiagnosed skin lesions

### Migraine
- **Mechanism of Action/Class:** Triptan (selective 5-hydroxytryptamine receptor agonist)
- **Generic Name:** sumatriptan
- **Trade Name:** Imitrex®
- **Dosing:** 25-100 mg PO qm
  - Maximum 200 mg/d
- **Indications:** Migraine
- **Side Effects:** Vertigo, chest pain, flushing, sensation of heat, hypertension crisis, peripheral vascular disease, coronary artery vasospasm, aciael dist, nausea, vomiting.
- **Contraindications:** Active bleeding, gastrointestinal bleeding, e.g. itraconazole, ritonavir

### EPILEPSY
- **Mechanism of Action/Class:** Anticonvulsant
- **Generic Name:** valproic acid
- **Trade Name:** Depakene®
- **Dosing:** Start at 100-200 mg PO OD
  - Increase by 200 mg/d up to 800-1,200 mg/d
- **Indications:** Essential febrile convulsion, myoclonic seizures, absence seizures
- **Side Effects:** Drowsiness, H/A, unsteadiness, dizziness, N/V, skin rash, agranulocytosis/aplastic anemia (rare)

### Stroke Prevention in AF
- **Mechanism of Action/Class:** Anticoagulant (direct thrombin inhibitor)
- **Generic Name:** dabigatran
- **Trade Name:** Pradaxa®
- **Dosing:** 110 mg PO bid or 150 mg PO bid
  - Ccr <30 mL/min, significant hemostatic imporation or CNS lesions within 6 mo with high risk of bleeding
- **Side Effects:** Dyspnea, gastritis, bleeding

### Table 25: Common Medications – Major Issues

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action/Class</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Parkinson's Disease</td>
<td>Dopamine precursor</td>
<td>levodopa + carbidopa</td>
<td>Sinemet®</td>
<td></td>
<td>Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions</td>
<td>Hypertension, hallucinations, dyskinesias in last 14 d, history of melanoma or undiagnosed skin lesions</td>
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<tr>
<td>Migraine</td>
<td>Triptan (selective 5-hydroxytryptamine receptor agonist)</td>
<td>sumatriptan</td>
<td>Imitrex®</td>
<td>25-100 mg PO qm, maximum 200 mg/d</td>
<td>Hemiplegic/basilar migraine, ischemic heart disease, CVD, uncontrolled HTN, use of ergotamine/5-HT1 agonist in past 24 h, use of MAO inhibitor in last 14 d, severe hepatic disease</td>
<td>Vertigo, chest pain, flushing, sensation of heat, hypertension crisis, peripheral vascular disease, coronary artery vasospasm, diac dist, nausea, vomiting.</td>
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<td></td>
<td>Ergot (5-HT1D receptor agonist)</td>
<td>dihydroergotamine</td>
<td>Migranal®</td>
<td>Nasal spray 0.5 mg/spray, maximum 4 sprays/d</td>
<td>Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled HTN, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction, use of triptans in last 24 h, use of MAO inhibitors in last 14 d</td>
<td>Coronary artery vasospasm, transient myocartiial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation; may cause significant rebound H/A</td>
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<td></td>
<td>Anticonvulsant</td>
<td>topiramate</td>
<td>Topamax®</td>
<td>25 mg OD PO in evening; may increase weekly by 25 mg/d to a max 50 mg bid</td>
<td>Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma</td>
<td>Fatigue, cognitive dysfunction, disturbed sleep, rashes, dry eye, aterial thrombosis, peripheral vascular disease, coronary artery vasospasm, high risk of acute tachycardia and HTN if withdrawal</td>
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<td></td>
<td>β-blocker</td>
<td>propranolol</td>
<td>Inderal®</td>
<td>80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q6-8h</td>
<td>Hypersensitivity, pregnancy, breastfeeding; caution with P450 interactions</td>
<td>Hypertension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, H/A, blood dyscrasias, nystagmus, N/V, constipation, sedation, taratogenic</td>
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<td></td>
<td>Anticonvulsant for partial ± 2° generalization, generalized tonic-clonic</td>
<td>carbamazepine</td>
<td>Tegretol®</td>
<td>Start at 100-200 mg PO OD-tid, increase by 200 mg/d up to 800-1,200 mg/d</td>
<td>History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d</td>
<td>Drowsiness, H/A, unsteadiness, dizziness, N/V, skin rash, agranulocytosis/aplastic anemia (rare)</td>
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<td>Anticonvulsant for partial, tonic-clonic, status epilepticus</td>
<td>phenytoin</td>
<td>Dilantin®</td>
<td>100 mg PO tid, maintenance dose up to 200 mg PO tid</td>
<td>Hypersensitivity, pregnancy, breastfeeding; caution with P450 interactions</td>
<td>Hypertension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, H/A, blood dyscrasias, nystagmus, N/V, constipation, sedation, taratogenic</td>
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<tr>
<td></td>
<td>Anticonvulsant for partial or generalized, absence seizures</td>
<td>valproic acid</td>
<td>Depakene®</td>
<td>10-15 mg/kg/d PO in divided doses, increase incrementally until therapeutic dose to max of 60 mg/kg/d</td>
<td>Hypersensitivity, hepatic disease, urea cycle disorders</td>
<td>Hypertensive failure, H/A, somnolence, alopecia, N/V, diarrhea, tremor, diplopia, thrombocytopenia, hypothyroidism, pancreatitis, encephalopathy</td>
</tr>
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<tr>
<td></td>
<td>Anticonvulsant for absence seizures</td>
<td>ethosuximide</td>
<td>Zarontin®</td>
<td>500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses</td>
<td>Hypersensitivity (succinimides)</td>
<td>CNS depression, blood dyscrasias, SLE, SJS, GI symptoms</td>
</tr>
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<tr>
<td></td>
<td>Anticoagulant (direct thrombin inhibitor)</td>
<td>dabigatran</td>
<td>Pradaxa®</td>
<td>110 mg PO bid or 150 mg PO bid</td>
<td>CCl &lt;30 mL/min, significant hemostatic impairment or CNS lesions within 6 mo with high risk of bleeding</td>
<td>Dyspnea, gastritis, bleeding</td>
</tr>
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</tr>
<tr>
<td></td>
<td>Anticoagulant (Factor Xa inhibitor)</td>
<td>rivaroxaban</td>
<td>Xarelto®</td>
<td>15 mg PO daily or 20 mg PO daily</td>
<td>Concomitant anticoagulant, hepatic disease, pregnancy, strong CYP34A and P-gp inhibitors e.g. iraconazole, ritonavir</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticoagulant (Factor Xa inhibitor)</td>
<td>apixaban</td>
<td>Eliquis®</td>
<td>2.5 mg PO bid or 5 mg PO bid</td>
<td>Active bleeding, gastrointestinal bleeding, recent cerebral infarction, active peptic ulcer disease with recent bleeding, he atic disease (spontaneous, hematuria) with coagulopathy</td>
<td>Bleeding (conjunctional, gastrointestinal, gingival, contusion, hematoma, disease with recent bleeding, he atic disease (spontaneous, hematuria) with coagulopathy</td>
</tr>
</tbody>
</table>
Table 25. Common Medications – Major Issues (continued)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action/Class</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to Moderate AD or DLB</td>
<td>Cholinesterase Inhibitor</td>
<td>donepezil</td>
<td>Aricept®</td>
<td>5 mg PO OD, may increase to 10 mg PO OD after 4-6 wk</td>
<td>Hyposensitivity to donepezil or to piperidine derivatives</td>
<td>Diarrhea, N/V, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>MS Disease Modifying Therapy</td>
<td>interferon-β-1b, interferon-β-1a SC</td>
<td>Betaseron® Rebif® Avonex®</td>
<td>0.25 mg (8 MU SC) every other day, 44 μg SC 3 times/wk, 30 μg IM once weekly</td>
<td>Pregnancy, hyposensitivity to natural or recombinant interferon-β</td>
<td>Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time)</td>
</tr>
<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>glatiramer acetate</td>
<td>Copaxone®</td>
<td>20 mg SC OD</td>
<td>Hyposensitivity to glatiramer or mannitol</td>
<td>Injection site reactions, nausea, transient chest pain, vasodilation</td>
</tr>
<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>natalizumab</td>
<td>Tyzab®</td>
<td>300 mg IV given over 1 h, every 4 wk</td>
<td>Hyposensitivity to natalizumab, progressive multifocal leukoencephalopathy (PML)</td>
<td>Rash, nausea, arthralgia, H/A, infections, rare risk of NML and melanoma</td>
</tr>
<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>fingolimod</td>
<td>Gilenya®</td>
<td>0.5 mg PO OD</td>
<td>Not available</td>
<td>Diarrhea, transaminitis, H/A, bradyarrhythmia, lymphopenia</td>
</tr>
<tr>
<td>Spasticity (i.e. MS)</td>
<td>Muscle Relaxant – Antispastic</td>
<td>baclofen</td>
<td>Lioresal®</td>
<td>5 mg PO tid, increase by 15 mg/d to max dose 80 mg/d in three divided doses</td>
<td>Hyposensitivity to baclofen</td>
<td>Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea</td>
</tr>
</tbody>
</table>

Landmark Neurology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCET</td>
<td>NEJM 1991;7:445-53</td>
<td>Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy</td>
</tr>
<tr>
<td>Interferon-β Multiple Sclerosis Study Group Trial</td>
<td>Neurology 1993;43:655-61</td>
<td>Interferon-β-1b reduces relapse rate and severity of relapses in RRMS</td>
</tr>
<tr>
<td>NINDS rPA</td>
<td>NEJM 1995;33:1581-1</td>
<td>rPA reduces mortality and long-term disability when administered within 3 h of acute stroke</td>
</tr>
<tr>
<td>SPARCL</td>
<td>NEJM 2006;35:549-59</td>
<td>The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA</td>
</tr>
<tr>
<td>ECASS 3</td>
<td>NEJM 2008;359:1317-29</td>
<td>rPA improved clinical outcomes when administered within 3 to 4.5 h of acute ischemic stroke</td>
</tr>
<tr>
<td>PROFESS</td>
<td>NEJM 2008;359:1238-51</td>
<td>ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention</td>
</tr>
<tr>
<td>RELY</td>
<td>NEJM 2009;361:1139</td>
<td>Dabigatran superior to warfarin for stroke prevention in patients with atrial fibrillation</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>NEJM 2011;365:883-891</td>
<td>Rivaroxaban noninferior to warfarin stroke prevention in patients with atrial fibrillation</td>
</tr>
<tr>
<td>ERS</td>
<td>NEJM 2011;365:981-992</td>
<td>Apixaban superior to warfarin for stroke prevention in patients with atrial fibrillation</td>
</tr>
<tr>
<td>CREST</td>
<td>NEJM 2010;363:11-23</td>
<td>Carotid stenting and endarterectomy had similar benefits in reduction of stroke, MI, and death in carotid stenosis, but in the periprocedural period, stenting had a higher rate of stroke, while endarterectomy had a higher rate of MI</td>
</tr>
<tr>
<td>INTERACT2</td>
<td>NEJM 2013;368:2355-65</td>
<td>Intensive lowering of blood pressure (sBP&lt;140) in spontaneous intracerebral hemorrhage did not improve mortality or severe disability but improved functional outcomes (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; P=0.04)</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>NEJM 2015;372:11-20</td>
<td>Intra-arterial treatment (intra-arterial thrombolysis, mechanical treatment, or both) for emergency recanalization administered within 6 h after stroke onset was effic ient and safe for acute ischemic stroke caused by proximal intracranial occlusion of the anterior circulation</td>
</tr>
</tbody>
</table>

References

Conna

Common Presenting Complaints

Drug Information

Epilepsy

General
Acronyms ................................................. 2
Basic Anatomy Review ............................... 2
Differential Diagnoses of Common
Neurosurgical Presentations ..................... 4

INTRACRANIAL PATHOLOGY
Intracranial Pressure Dynamics .................. 4
ICP/Volume Relationship
Cerebral Blood Flow
ICP Measurement
Elevated ICP
Herniation Syndromes ............................ 7
Treatment of Elevated ICP
Idiopathic Intracranial Hypertension
(Pseudotumour Cerebri) ......................... 8
Hydrocephalus ......................................... 9
CNS Tumours ........................................... 11
Metastatic Tumours
Astrocytoma
Meningioma
Vestibular Schwannoma (Acoustic Neuroma)
Pituitary Adenoma
Cerebral Abscess ..................................... 15
Blood .................................................... 16
Extradural ("Epidural") Hematoma
Subdural Hematoma
Cerebrovascular Disease ......................... 18
Subarachnoid Hemorrhage
Intracranial Aneurysms
Intracerebral Hemorrhage
Vascular Malformations ......................... 23
Arteriovenous Malformations, Cavernous
Malformations, and Dural Fistulas
Cerebrospinal Fluid Fistulas ..................... 24

EXTRACRANIAL PATHOLOGY
Approach to Limb/Back Pain ...................... OR23
Extradural Lesions ................................. 24
Root Compression
Cervical Disc Syndrome
Cervical Spondylosis
Lumbar Disc Syndrome
Cauda Equina Syndrome
Lumbar Spinal Stenosis
Neurogenic Claudication

Intradural Intramedullary Lesions .......... 29
Syringomyelia (Syrinx)
Spinal Cord Syndromes ......................... 29
Peripheral Nerves .................................. 30

SPECIALTY TOPICS
Neurotrauma ........................................... 30
Trauma Assessment
Head Injury
Brain Injury
Late Complications of Head/Brain Injury
Spinal Cord Injury
Fractures of the Spine
Neurologically Determined Death
Coma
Persistent Vegeative State
Pediatric Neurosurgery ......................... 36
Spinal Dysraphism
Intraventricular Hemorrhage
Hydrocephalus in Pediatrics
Dandy-Walker Malformation
Chiari Malformations
Craniosynostosis
Pediatric Brain Tumours
Functional Neurosurgery ....................... 39
Movement Disorders
Neuropsychiatric Disorders
Chronic Pain
Surgical Management of Epilepsy .......... 41
Surgical Management for Trigeminal Neuralgia 41

References ............................................ 42
Acronyms

AVF  arteriovenous fistula  EEG  electroencephalography  LOC  loss of consciousness  SAH  subarachnoid hemorrhage
AVM  arteriovenous malformation  EMG  electromyography  LP  lumbar puncture  SDH  subdural hemorrhage
BBB  blood brain barrier  GCS  Glasgow coma scale  MAP  mean arterial pressure  SIADH  syndrome of inappropriate antidiuretic hormone
CSF  cerebrospinal fluid  GSF  globus pallidus pars interna  NC  neurogenic claudication  SPECT  single photon emission computed tomography
CPA  cerebellar pontine angle  H/A  headache  NPH  normal pressure hydrocephalus  SRS stereotactic radiosurgery
CPP  cerebral perfusion pressure  IC  internal capsule  OPL  ossification of posterior longitudinal ligament
CVR  cerebral vascular resistance  ICF  intracellular fluid  PAG  periaqueductal grey matter
DBS  deep brain stimulation  ICH  intracerebral hemorrhage  PET  positron emission tomography  STN  subthalamic nucleus
DI  diabetes insipidus  ICP  intracranial pressure  PLL  posterior longitudinal ligament  UMN  upper motor neuron
ECF  extracellular fluid  IVH  intraventricular hemorrhage  PNET  primitive neuroectodermal tumor  VPL  ventral posterolateral
ECT  electroconvulsive therapy  ICH  intracerebral hemorrhage  PVM  ventral posteromedial  WBRT  whole brain radiation therapy

Basic Anatomy Review

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Figure 1 Basic surface anatomy

Figure 2. Magnetic resonance imaging (MRI) neuroanatomy. Magnetic resonance imaging (MRI) neuroanatomy. The left panel is a T1-weighted image; the right panel is T2-weighted.
Figure 3  Relationship of nerve roots to vertebral level in the cervical and lumbar spine
Note: AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement

Artery legend:
1. Anterior cerebral
2. Anterior communicating
3. Internal carotid
4. Middle cerebral
5. Posterior communicating
6. Posterior cerebral
7. Superior cerebellar
8. Basilar
9. Pontine
10. Anterior inferior cerebellar
11. Vertebral
12. Posterior inferior cerebellar
13. Anterior spinal
14. Posterior spinal
15. Anterior choroidal
16. Medial lenticulostriate
17. Lateral lenticulostriate
18. Penetrating branches of posterior spinal artery (P1 segment)

Figure 4. Vascular supply of the brain
Please see legend for artery names. 4A. Circle of Willis, most common variant. 4B. Vascular territories of the brain and brainstem, sagittal view, seen laterally. 4C. Vascular territories of the brain and brainstem, sagittal view, seen medially.
Differential Diagnoses of Common Neurosurgical Presentations

<table>
<thead>
<tr>
<th>Intracranial Mass Lesions</th>
<th>Disorders of the Spine</th>
<th>Peripheral Nerve Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorders of the Spine</strong></td>
<td><strong>Extradural</strong></td>
<td><strong>Neuropathies</strong></td>
</tr>
<tr>
<td>Peripheral Nerve Lesions</td>
<td>Degenerative: disc herniation, canal stenosis, spondylothesis/spondylosis</td>
<td>Traumatic</td>
</tr>
<tr>
<td><strong>Tumour</strong></td>
<td>Infection/inflammation: osteomyelitis, discitis</td>
<td>Entrapments</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Ligamentous: ossification of posterior longitudinal ligament (OPLL)</td>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Trauma: mechanical compression/instability, hematoma</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma</td>
<td></td>
</tr>
<tr>
<td>Vestibular schwannoma (acoustic neuroma)</td>
<td></td>
<td>Tumours (5% of all spinal tumours): astrocytomas, ependymomas, hemangioblastomas and dermoids</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>Syringomyelia: trauma, congenital, idiopathic</td>
<td>Infectious/inflammatory: TB, sarcoid, transverse myelitis</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Infectious/inflammatory: Traumatic, Encephalitis (see Infectious Diseases, ID19)</td>
<td></td>
</tr>
</tbody>
</table>

**Post/Inflammation**
- Cerebral abscess
- extradural abscess
- subdural empyema
- Encephalitis (see Infectious Diseases, ID19)
- Tumefactive MS

**Blood**
- Extradural (epidural) hematoma
- Subdural hematoma
- Ischemic stroke
- Hemorrhage: SAH, ICH, IVH

**Cyst**
- Arachnoid cyst
- Dermoid cyst
- Epidermoid cyst
- Cyst (3rd ventricle)

**INTRACRANIAL PATHOLOGY**

**Intracranial Pressure Dynamics**

**Table 1. Approach to Intracranial Pathology**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Time Frame</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Sudden</td>
<td>No H/A = occlusive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H/A = hemorrhagic</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hours to days</td>
<td>Affects entire CNS</td>
</tr>
<tr>
<td>Infectious</td>
<td>Days to weeks</td>
<td>Often a source of infection or immunodeficiency on history</td>
</tr>
<tr>
<td>Tumour</td>
<td>Months</td>
<td>Increased ICP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initially → H/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Progressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Worse in morning and/or wakes from sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As ICP increases:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blurry vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>projectile vomiting (may initially present without nausea)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cushing’s reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Respiratory irregularity</td>
</tr>
</tbody>
</table>
Table 2. Consequences of Common Brain Lesions

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Lobe</td>
<td>Abulia, disinhibition, apathy, executive dysfunction, deficits in orientation and judgment, ± primitive reflex re-emergence, ± contralateral upper motor neuron signs (upgoing Babinski reflex and pronator drift)</td>
</tr>
<tr>
<td>Fronto Eye Fields</td>
<td>Gaze deviation toward side of a destructive lesion</td>
</tr>
<tr>
<td></td>
<td>Gaze deviation away from irritative lesion (i.e. seizure)</td>
</tr>
<tr>
<td>Broca’s Area</td>
<td>Non-fluent, dysarthric, aphasia</td>
</tr>
<tr>
<td>Posterior inferior frontal gyrus of dominant hemisphere</td>
<td>Repetition impaired</td>
</tr>
<tr>
<td></td>
<td>Comprehension spared</td>
</tr>
<tr>
<td>Occipital Lobe</td>
<td>Contralateral homonymous hemianopsia</td>
</tr>
<tr>
<td>Parietal Lobe</td>
<td>Dressing apraxia, cortical sensory loss, lower homonymous quadrantopia.</td>
</tr>
<tr>
<td>Either side</td>
<td>Inattention or extinction of non-dominant side</td>
</tr>
<tr>
<td>Dominant side (Left)</td>
<td>Aphasia, Gerstmann’s syndrome</td>
</tr>
<tr>
<td>Non-dominant side (Right)</td>
<td>Hemispatial neglect, apraxias, agnosias (if temporal involvement)</td>
</tr>
<tr>
<td>Temporal Lobe</td>
<td>Hippocampus: anterograde amnesia</td>
</tr>
<tr>
<td></td>
<td>Upper homonymous hemianopsia</td>
</tr>
<tr>
<td></td>
<td>Wernicke’s aphasia (if left/dominant side)</td>
</tr>
<tr>
<td>Wernicke’s Area</td>
<td>Fluent aphasia</td>
</tr>
<tr>
<td>Posterior superior temporal gyrus of dominant hemisphere</td>
<td>Repetition impaired</td>
</tr>
<tr>
<td></td>
<td>Comprehension impaired</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>Resting tremor</td>
</tr>
<tr>
<td></td>
<td>Chorea</td>
</tr>
<tr>
<td></td>
<td>Athetosis</td>
</tr>
<tr>
<td></td>
<td>Hemiplegia if internal capsule involved</td>
</tr>
<tr>
<td>Subthalamic Nucleus</td>
<td>Contralateral hemiballismus</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Absent brainstem reflexes: oculocephalic, oculocephalotesticular, corneal, gag, and cough</td>
</tr>
<tr>
<td>Dorsal midbrain/Pineal Gland: Parinaud’s syndrome (supranuclear upward gaze palsy)</td>
<td></td>
</tr>
<tr>
<td>Pons: locked-in syndrome</td>
<td></td>
</tr>
<tr>
<td>Below red nucleus: decerebrate posture</td>
<td></td>
</tr>
<tr>
<td>Above red nucleus: decorticate posture</td>
<td></td>
</tr>
<tr>
<td>Reticular activating system (midbrain): reduced level of arousal</td>
<td></td>
</tr>
<tr>
<td>Cerebellar pontine angle: disequilibrium, ataxia and other CN V,VII,VIII deficits</td>
<td></td>
</tr>
<tr>
<td>Cerebellar Hemisphere</td>
<td>Intention tremor</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral limb ataxia</td>
</tr>
<tr>
<td></td>
<td>Fall towards side of lesion</td>
</tr>
<tr>
<td>Cerebellar Vermis</td>
<td>Truncal ataxia</td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
</tr>
</tbody>
</table>

ICP/Volume Relationship

- Monro-Kellie Doctrine: the brain is encased in a rigid skull with constant intracranial volume consisting of CSF, blood and brain.
- the increase in one constituent will: 1) necessitate the redistribution of CSF, blood and/or brain and 2) increase ICP.
- compensatory mechanisms initially maintain a normal ICP.
- Compensatory reserve (spatial compensation): 60-80mL in young people, 100-140mL in elderly (largely due to cerebral atrophy)
  - immediate: egress of CSF through foramen magnum to spinal canal, displacement of venous blood from sinuses into jugular veins
- once compensation is exhausted, ICP rises exponentially:
  - late: displacement of arterial blood (decreased CPP) eventually leading to ischemia, increasing brain edema or expanding mass displaces parenchyma into compartments under less pressure and expanding mass (Table 3)
  - end: cessation of cerebral perfusion when ICP>MAP, cerebral herniation down into foramen magnum

Figure 5. ICP volume curve
Cerebral Blood Flow

- brain receives about 15% of cardiac output (~750 mL/min)
- CBF is the vital parameter for brain function and depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR)
- CPP is dependent on the difference between mean arterial pressure (MAP) and Intracranial Pressure (ICP) (Normal CPP >50 mmHg)
- cerebral autoregulation: mechanism that maintains constant CBF despite changes in CPP, unless:
  - high ICP such that CPP <40 mmHg
  - MAP >150 mmHg or MAP <50 mmHg
  - increased CO₂ = increased CBF via vasodilation
  - O₂ <50 mmHg = increased CBF via vasodilation
  - brain injury: e.g. SAH, severe trauma

ICP Measurement

- normal ICP 10-15 mmHg for adult, 3-7 mmHg for child, 1-5 mmHg for infant; varies with patient position
  - moderate elevation >20 mmHg
  - severe elevation >40 mmHg

Acute Monitoring

- indications include: severe TBI (GCS <8) + abnormal CT; normal CT under some conditions
  - methods: “gold standard” is intraventricular catheter, (external ventricular drain (EVD)), is the most accurate method and allows therapeutic drainage of CSF. Non-invasive methods (including transcranial Doppler, CT/MRI, fundoscopy etc) fail to measure ICP accurately enough to be used as routine measurement techniques

Chronic Monitoring

- fibreoptic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

Elevated ICP

Etiology

- increased intracranial pressure
  - intracranial mass (tumour, cyst)
  - cerebral edema
    - vasogenic: BBB compromised (meningitis, hypertensive encephalopathy, tumour, late ischemia)
    - cytotoxic: BBB intact (cell death in: early ischemia, brain injury, encephalitis, status epilepticus)
    - interstitial: transudation of CSF into peri-ventricular white matter in hydrocephalus
    - osmotic: osmotic gradient increases intracellular free H₂O (acute hyponatremia, hepatic encephalopathy)
  - other space occupying lesions: depressed skull fracture, foreign body, pus/empyema

- increased intracranial blood volume
  - space occupying blood: epidural and subdural hematomas, intraparenchymal and subarachnoid hemorrhages
  - venous obstruction (venous sinus thrombosis, superior vena cava syndrome, cor pulmonale, venous sinus compression)
  - impaired autoregulation (hypotension, HTN, brain injury, status epilepticus)
  - vasodilatation (increased pCO₂/decreased pO₂/decreased extracellular pH)
  - increased intracranial CSF volume
  - increased production (rare): choroid plexus papilloma
  - hydrocephalus: obstructive vs. non-obstructive (see Table 6)
  - idiopathic intracranial HTN (pseudotumour cerebri) – see Idiopathic Intracranial Hypertension, NS8

ICP Measurement

- normal ICP 10-15 mmHg for adult, 3-7 mmHg for child, 1-5 mmHg for infant; varies with patient position
  - moderate elevation >20 mmHg
  - severe elevation >40 mmHg

Acute Monitoring

- indications include: severe TBI (GCS <8) + abnormal CT; normal CT under some conditions
  - methods: "gold standard" is intraventricular catheter, (external ventricular drain (EVD)), is the most accurate method and allows therapeutic drainage of CSF. Non-invasive methods (including transcranial Doppler, CT/MRI, fundoscopy etc) fail to measure ICP accurately enough to be used as routine measurement techniques

Chronic Monitoring

- fibreoptic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

Elevated ICP

Etiology

- increased intracranial pressure
  - intracranial mass (tumour, cyst)
  - cerebral edema
    - vasogenic: BBB compromised (meningitis, hypertensive encephalopathy, tumour, late ischemia)
    - cytotoxic: BBB intact (cell death in: early ischemia, brain injury, encephalitis, status epilepticus)
    - interstitial: transudation of CSF into peri-ventricular white matter in hydrocephalus
    - osmotic: osmotic gradient increases intracellular free H₂O (acute hyponatremia, hepatic encephalopathy)
  - other space occupying lesions: depressed skull fracture, foreign body, pus/empyema

- increased intracranial blood volume
  - space occupying blood: epidural and subdural hematomas, intraparenchymal and subarachnoid hemorrhages
  - venous obstruction (venous sinus thrombosis, superior vena cava syndrome, cor pulmonale, venous sinus compression)
  - impaired autoregulation (hypotension, HTN, brain injury, status epilepticus)
  - vasodilatation (increased pCO₂/decreased pO₂/decreased extracellular pH)
  - increased intracranial CSF volume
  - increased production (rare): choroid plexus papilloma
  - hydrocephalus: obstructive vs. non-obstructive (see Table 6)
  - idiopathic intracranial HTN (pseudotumour cerebri) – see Idiopathic Intracranial Hypertension, NS8

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  - hydrocephalus: obstructive vs. non-obstructive (see Table 6)
  - idiopathic intracranial HTN (pseudotumour cerebri) – see Idiopathic Intracranial Hypertension, NS8
Clinical Features

Table 3. Clinical Features of Elevated ICP

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Acutely Elevated ICP</th>
<th>Chronic Progressive ICP Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Both aggravated by stooping, coughing, straining. Morning headaches: vasodilatation due to increased CO2 with recumbency</td>
<td></td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Present in both, though greater predilection in acutely elevated ICP</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Lethargy if ICP = dBP or midbrain compression</td>
<td>Irritability, inattentiveness. Normal or modestly reduced LOC, confusion</td>
</tr>
<tr>
<td>GCS</td>
<td>Significant decline in GCS</td>
<td>Can be unchanged or modestly decreased</td>
</tr>
<tr>
<td>Optic Disc Changes</td>
<td>Subtle changes suggesting papilledema (subtle elevations in disc margin, mild disc hyperemia ± retinal hemorrhages (may take 24-48 h to develop)</td>
<td>Obvious papilledema</td>
</tr>
<tr>
<td>Visual Changes</td>
<td>Less common. Often not affected initially, however visual obscurations, flickering or blurring can occur</td>
<td>Optic atrophy/blindness due to chronic papilledema Enlarged blind spot, if advanced → episodic constrictions of visual fields (“grey-outs” lasting ~20 min) Differentiate from papillitis (usually unilateral with decreased visual acuity)</td>
</tr>
<tr>
<td>Extra-Ocular Movements</td>
<td>Less common. CN VI palsy: due to long intracranial course, more sensitive to ICP changes and thus earlier sign of acutely increased ICP Often falsely localizing (causative lesion remote to nerve) Upward gaze palsy and sunset eyes (especially in children with obstructive hydrocephalus)</td>
<td>Often full EDM</td>
</tr>
<tr>
<td>Herniation Syndromes</td>
<td>Often occur (see Table 4)</td>
<td>Present if acute on chronic presentation</td>
</tr>
<tr>
<td>Neurologic Deficits</td>
<td>Focal deficits present</td>
<td>Focal deficits can be present</td>
</tr>
</tbody>
</table>

Investigations
- patients with suspected elevated ICP require an urgent CT/MRI to identify etiology, assess for midline shift/herniation
- ICP monitoring where appropriate

Table 4. Herniation Syndromes

<table>
<thead>
<tr>
<th>Herniation Syndrome</th>
<th>Definition</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subfalcine</td>
<td>Cingulate gyrus herniates under falx</td>
<td>Lateral supratentorial lesion</td>
<td>Usually asymptomatic Warnings of impending transtentorial herniation Risk of ACA compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Central Tentorial (Axial)</td>
<td>Displacement of diencephalon through tentorial notch</td>
<td>Supratentorial midline lesion Diffuse cerebral swelling Late uncatal herniation</td>
<td>Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephal, medulla Decreased LOC (midbrain compression), EOM/upward gaze impairment (“sunset eyes”): compression of pretectum and superior colliculi (Patinaud’s syndrome) Risk of PCA compression Branstern (Duret) hemorrhage: secondary to shearing of basilar artery perforating vessels Diabetes insipidus (infection on pituatory stalk and hypothalamus), end-stage sign</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Lateral Tentorial (Uncal)</td>
<td>Uncus of temporal lobe herniates through tentorial notch</td>
<td>Lateral supratentorial lesion (often rapidly expanding traumatic hematoma)</td>
<td>Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) + ipsilateral EON paralysis, ptoxis (CN III compression) Decreased LOC (midbrain compression) Risk of PCA compression Contralateral hemiplegia ± extensor (upgoing) plantar response = ipsilateral hemiplegia (“Kernohan’s notch” – a false localizing sign resulting from pressure from the edge of the tent rium on the contralateral cerebral peduncle)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>4. Upward</td>
<td>Cerebellar vermis herniates through tentorial incisura</td>
<td>Posterior fossa mass, brainstem or cerebellar infarction, exacerbated by ventriculostomy or VP shunt</td>
<td>Cerebellar infa ct (superior cerebellar artery [SCA] compression) Hydrocephalus (cerebral/sylvian aqueduct compression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Tonsillar</td>
<td>Cerebellar tonsils herniates through foramen magnum</td>
<td>Infratentorial lesion Following central tentorial herniation Following LP in presence of intracranial mass lesion</td>
<td>Neck stiffness and head tilt (tonsillar impaction) Decreased LOC (midbrain compression) Flaccid paralysis Respiratory irregularities, respiratory arrest (compression of medulary respiratory centres) Blood pressure instability (compression of medulary cardiovascular centres)</td>
</tr>
</tbody>
</table>

Figure 7. Herniation types

Blood Brain Barrier
- Glucose and amino acids cross slowly Non-polar/lipids cross fast
- Infection/neopasm → destroy tight junctions → vasogenic edema

Cushing’s Triad of Acute Raised ICP
- Hypertension
- Bradycardia (late finding)
- Irregular respiratory pattern

Papilledema
- Optic disc swelling with blurred margins (most commonly bilateral)
- Larger blind spot
Treatment of Elevated ICP

- treatment principle: treat primary etiology (i.e. remove mass lesions, ensure adequate ventilation for example in ARDS)
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
targets: ICP <20 mmHg, CPP >65 mmHg, MAP >90 mmHg

Table 5. Management of Elevated ICP

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Intervention</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td>Elevate head of bed at 30° Maintain neck in neutral position</td>
<td>Increases 1. jugular venous patency 2. intracranial venous outflow with minimal effect on MAP</td>
</tr>
<tr>
<td>Fever Management</td>
<td>Acetaminophen or mechanical cooling</td>
<td>Decrease metabolic demands to decrease CBF and minimize brain injury</td>
</tr>
<tr>
<td>Prevent Hypotension</td>
<td>PRN: fluid, vasopressors, dopamine, norepinephrine</td>
<td>Maintains CBF</td>
</tr>
<tr>
<td>Normocarbia</td>
<td>Ventilate to pCO₂ 35-40 mmHg</td>
<td>Prevents vasodilatation</td>
</tr>
<tr>
<td>Adequate O₂</td>
<td>Target pO₂ &gt;60 mmHg</td>
<td>Prevents hypoxic brain injury</td>
</tr>
<tr>
<td>Osmolar Diuresis</td>
<td>Mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolarity of 315-320. Acts in 15-30 min, maintain sBP &gt;90 mmHg</td>
<td>Increase serum tonicity → osmotically drives fluid out of brain</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone</td>
<td>Decrease vasogenic edema over subsequent days around brain tumour, abscess, blood No proven value in head injury or stroke</td>
</tr>
<tr>
<td><strong>Aggressive Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>Usually Propofol</td>
<td>Reduces sympathetic tone</td>
</tr>
<tr>
<td></td>
<td>Others: barbiturates/codeine, or fentanyl/MgSO₄</td>
<td>Reduces HTN induced by muscle contraction</td>
</tr>
<tr>
<td></td>
<td>Light = barbituates/codeine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heavy = fentanyl/MgSO₄</td>
<td></td>
</tr>
<tr>
<td>Paralysis</td>
<td>Vecuronium</td>
<td>Reduces sympathetic tone</td>
</tr>
<tr>
<td>Barbiturate induced Coma (refractory ICP)</td>
<td>Phentobarbital 10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion</td>
<td>Reduce CBF and metabolism Decreases mortality, but no affect on neurologic outcome No role for the use of hypothermia in head injury</td>
</tr>
<tr>
<td>Hyperventilate</td>
<td>Target pCO₂ 30-35 mmHg</td>
<td>Decreases CBF and thus ICP but use for brief periods only</td>
</tr>
<tr>
<td>Drain CSF</td>
<td>Insert EVD (if acute) or shunt Drain 3-5 mL CSF</td>
<td>Reduces intracranial volume</td>
</tr>
<tr>
<td>Decompression</td>
<td>Decompressive craniectomy</td>
<td>Allows brain to swell while reducing risk of herniation</td>
</tr>
</tbody>
</table>

Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)

**Definition**
- raised ICP with papilledema, but without: mass, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)

**Etiology**
- unknown (majority), but associated with:
  - dural sinus thrombosis
  - habitus/diet: obesity, hypervitaminosis A
  - endocrine: reproductive age, menstrual irregularities, Addison’s/Cushing’s disease
  - hematologic: iron deficiency anemia, polycythemia vera
  - drugs: steroid withdrawal, tetracycline, amiodarone, lithium, nalidixic acid, oral contraceptive
  - risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones ("fat, female, fertile, forties")

**Epidemiology**
- incidence: general population ~1-2/100,000 per year; obese women of childbearing age 19-21/100,000

**Clinical Features**
- symptoms: H/A in >90%, nausea, impaired vision, pulsatile intracranial noise, diplopia can occur with CN VI palsy
- signs: CN VI palsy can occur (otherwise no neurologic deficits), visual acuity and field deficits, papilledema, optic atrophy
Hydrocephalus

- for hydrocephalus in children, see Pediatric Neurosurgery, NS36

Definition
- accumulation of excess CSF in the brain, functionally divided into obstructive and communicating
  - flow of CSF: produced by choroid plexus, lateral ventricles → foramen of Monroe → 3rd ventricle → cerebral/sylvian aqueduct → 4th ventricle → foramina of Luschka (lateral) and Magendie (medial) → subarachnoid space where CSF is re-absorbed by arachnoid villi/granulations into dural venous sinuses

Classification

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition</th>
<th>Etiology</th>
<th>Findings on CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive (Non-Communicating) Hydrocephalus</td>
<td>CSF Circulation blocked within ventricular system proximal to the arachnoid granulations</td>
<td>Acquired Aqueductal Stenosis: adhesions after infection, hemorrhage; gliosis, tumor (e.g. medulloblastoma)</td>
<td>Ventricular enlargement proximal to block (enlarged temporal horns, ballooning frontal and/or occipital horns, enlarged 3rd → 4th ventricles)</td>
</tr>
<tr>
<td>Non-Obstructive (Communicating) Hydrocephalus</td>
<td>Most commonly CSF absorption blocked at extraventricular site = arachnoid granulations, rarely CSF absorption is overwhelmed by increased production</td>
<td>Intraventricular lesions: tumours, e.g. 3rd ventricle colloid cyst, hematoma Mass causing tentorial herniation causing aqueduct/4th ventricle compression Others: neurosarcoidosis, abscess/ granulomas, arachnoid cysts</td>
<td>Ventricular enlargement → normal pressure hydrocephalus</td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus (NPH)</td>
<td>Persistent ventricular dilatation in the context of normal CSF pressure</td>
<td>Idiopathic (50%) Others: subarachnoid hemorrhage, meningitis, trauma, radiation-induced</td>
<td>Enlarged ventricles without increased prominence of cerebral sulci</td>
</tr>
<tr>
<td>Hydrocephalus Ex Vacuo</td>
<td>Ventricular enlargement resulting from atrophy of surrounding brain tissue</td>
<td>Normal aging Degenerative dementias see Neurology, N23 (Alzheimer’s, Frontal Temporal, Creutzfeldt-Jacob Disease)</td>
<td>Enlarged ventricles and sulci Cerebral atrophy</td>
</tr>
</tbody>
</table>

Etiology
- impaired CSF dynamics
  - obstruction of CSF flow
  - decreased CSF absorption
  - increased CSF production (rarely in choroid plexus papilloma – 0.4-1% of intracranial tumours)
- congenital and acquired causes

Investigations
- MRI-brain (with and without contrast): slit like ventricles and distended perioptic subarachnoid space, but otherwise normal
- rule out: venous sinus thrombosis, mass, infection, hydrocephalus
- LP findings: opening pressure >20 mm H2O
- normal CSF analysis
- ophthalmologic: fields, acuity, papilledema

Treatment
- lifestyle change: encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic, or furosemide; discontinue offending medications
- surgery: if above fail → serial LPs, shunts, optic nerve sheath decompression (if progressive impairment of visual acuity)
- long term: 2 yr follow-up, repeat imaging to rule out occult tumour, ophthalmology follow-up
Epidemiology

- Estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1,000 live births

Clinical Features

- Acute hydrocephalus: signs and symptoms of acutely elevated ICP (see Table 3)
- Chronic/gradual onset hydrocephalus: (weeks to months) (i.e. NPH) presents with a classic triad (Hakim’s Triad)
  - Ataxia (magnetic gait) + apraxia (pressure of ventricle on lower extremity motor fibres → gait disturbance)
  - Incontinence (pressure on cortical bowel/bladder centre)
  - Dementia (pressure on frontal lobes)

Investigations

- Imaging
  - CT/MRI findings (see Table 6)
  - Ultrasound (through anterior fontanelle in infants): ventriculomegaly, size and location of lesions (e.g. IVH)
  - Mantle radiosonde cisternography can test CSF flow and absorption rate (unreliable)
- ICP monitoring (e.g. LP, EVD) may be used to investigate NPH and test response to shunting (lumbar tap test)

Treatment

- External ventricular drain (EVD)
- Intermittent LPs for transient communicating hydrocephalus (SAH, IVH in premature infants)
- Surgical: surgical removal of obstruction (if possible) or excision of choroid plexus papilloma
- Eliminating obstruction (i.e. excision of mass, posterior fossa decompression for Chiari Malformation)
- Endoscopic
  - Endoscopic third ventriculostomy (ETV) ± choroid plexus cauterization (for obstructive hydrocephalus)
  - Endoscopic placement of aqueductal stent
- Shunt
  - Ventriculoperitoneal (VP): most common shunt
  - Ventriculopleural (VPl)
  - Ventriculoatrial (VA)
  - Lumboperitoneal: for communicating hydrocephalus and pseudotumour cerebri

Shunt Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction</td>
<td>Obstruction by choroid plexus Buildup of proteinaceous accretions, blood, cells (inflammatory or tumour) Infection Disconnection or damage</td>
<td>Acute hydrocephalus signs and symptoms of Increased ICP “Shunt series” (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration) CT Radionuclide “shuntogram”</td>
<td></td>
</tr>
<tr>
<td>Infection (3-6%)</td>
<td>S. epidermidis S. aureus P. acnes Gram-negative bacilli</td>
<td>Fever, N/V, anorexia, irritability Meningitis Pneumonitis Signs and symptoms of shunt obstruction Shunt nephritis (VA shunt)</td>
<td>CBC Blood culture Tap shunt for C&amp;P (LP usually NOT recommended)</td>
</tr>
<tr>
<td>Overshunting</td>
<td>Silt ventricle syndrome, collapse of ventricles leading to occlusion of shunt ports by ependymal lining Chronic or recurring headaches often relieved when lying down CT/MRI Silt-like ventricles on imaging Subdural hematoma Collapsing brain tears bridging veins (especially common in NPH patients) Secondary craniosynostosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus</td>
<td>Asymptomatic Headaches, vomiting, somnolence</td>
<td>CT</td>
</tr>
<tr>
<td>Seizures</td>
<td>Ventricular shunts only</td>
<td></td>
<td>EEG</td>
</tr>
<tr>
<td>Inguinal Hernia</td>
<td>Increased intraperitoneal pressure/fluid results in hernia becoming apparent</td>
<td>Inguinal swelling, discomfort</td>
<td>U/S</td>
</tr>
</tbody>
</table>
CNS Tumours

Classification
- primary vs. metastatic (e.g. primary in breast, lung), intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, but can be devastating due to mass effect in fixed volume of skull (e.g. most meningiomas, WHO Grade I)
- malignant: implies rapid growth, invasiveness, possibly drop-metastases to spinal cord from a primary CNS tumour (rare)
- classification of nervous system tumours (* = most common) 
  - neuroepithelial
    - astrocytic tumours
      - oligoastrocytic tumours: oligoastrocytoma
      - neuronal and mixed neuronal glial tumours: ganglion cell tumours, cerebral neurocytomas
      - embryonal tumours: medulloblastoma, primitive neuroectodermal tumours (PNET)
      - other: pineal, ependymal, and choroid plexus tumours
  - meningeal: meningiomas*, mesenchymal, hemangioblastomas
  - cranial and paraspinal nerves: schwannoma, neurofibroma
  - lymphomas and hematopoietic: primary CNS lymphoma, plasmacytoma
  - germ cell: germinomas, teratomas, choriocarcinomas
  - sellar region: craniopharyngiomas, spindle cell oncocytoma, pituitary adenomas*
  - cysts: epidermoid/dermoid cysts, colloid cysts
  - local extension: chordomas, glomus jugulare tumours
  - metastatic tumours: lung*, breast*

Familial Syndromes Associated with CNS Tumours
- see Medical Genetics, MG7

Investigations
- CT, MRI, stereotactic biopsy (tissue diagnosis and molecular markers for prognosis), metastatic workup, tumour markers (i.e. germ cell tumours)

Treatment
- conservative: serial Hx, Px, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce ICP, cytotoxic cerebral edema, pharmacologic (i.e. pituitary adenoma)
- surgical: total or partial excision (decompressive, palliative), shunt if hydrocephalus
- radiotherapy: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (e.g. Gamma Knife*)
- chemotherapy: e.g. alkylating agents (i.e. temozolomide (GBM)*, vincristine, cyclophosphamide, etc.)
Table 8. Tumour Location: Etiology and Clinical Presentation

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>Supratentorial</th>
<th>Infratentorial (Posterior Fossa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;15 yr Incidence: 2.5/100,000/yr 60% infratentorial</td>
<td>Astrocytoma (all grades) (50%) Craniopharyngioma (2-5%) Others: pineal region tumours, choroid plexus tumours, ganglioglioma, DNET</td>
<td>Medulloblastoma (15-20%) Cerebellar astrocytoma (15%) Ependymoma (9%) Brainstem astrocytoma</td>
</tr>
<tr>
<td>Age &gt;15 yr 80% supratentorial</td>
<td>High grade astrocytoma (12-15%, e.g. GBM) Metastasis (15-30%, includes infratentorial) Meningioma (15 20%) Low grade astrocytoma (8%) Pituitary adenoma (5-8%) Oligodendroglioma (5%) Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts</td>
<td>Metastasis Acoustic neuroma (schwannoma) (5-10%) Hemangioblastoma (2%) Meningioma</td>
</tr>
</tbody>
</table>

Clinical Presentation

**Shared Features** (from elevated ICP)
- Headache: usually worse in AM and made worse with straining, coughing
- Nausea/Vomiting
- Papilledema
- Diplopia: CN VI palsy

**Distinguishing Features**
- Seizure: commonly the first symptom
- Progressive neurological deficits (70%)
- Frontal lobe: hemiparesis, dysphasia, personality changes, cognitive changes
- Temporal lobe: auditory/olfactory hallucinations, memory deficits, contralateral superior quadrantanopsia
- Mental Status Change: depression, apathy, confusion, lethargy
- “Tumour TIA” - stroke like symptoms caused by a) occlusion of vessel by tumour cells b) hemorrhage c) 2nd to "steal phenomenon" - blood is shunted from ischemic regions to non-ischemic regions
- Endocrine disturbance - with pituitary tumours (see Endocrinology, E19)
- Brainstem involvement: cranial nerve deficits and long tract signs
- Nausea/Vomiting: compression on vagal nucleus/area postrema
- Diplopia: direct compression CN VI
- Vertigo
- Nystagmus
- Truncal Ataxia + Titubation: cerebellar vermis lesions
- Limb Ataxia, dysmetria, intention tremor: cerebellar hemisphere lesions
- Obstructive hydrocephalus more common than supratentorial lesions

Metastatic Tumours

**Brain Metastasis**
- most common intra-cranial tumour in adults (~50% of all brain tumours)
- afflict ~25% of patients with any cancer
- hematogenous spread most common
- 80% are hemispheric, often at grey-white matter junction or temporal-parietal-occipital lobe junction
- likely emboli spreading to terminal MCA branches

**Investigations**
- identify primary tumour
  - full metastatic workup (CXR, CT chest/abdo, abdominal U/S nuclear medicine scan/PET, mammogram)
  - CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
  - MRI more sensitive, especially for posterior fossa
  - consider biopsy in unusual cases or if no primary tumour identified

**Treatment**
- medical
  - phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  - dexamethasone to reduce edema given with ranitidine
  - chemotherapy (e.g. small cell lung cancer), but difficult delivery across BBB
- radiation
  - stereactic radiosurgery (highly focused fraction of radiation targeted to tumour): for discrete, deep-seated/inoperable tumours
  - multiple lesions: use WBRT; consider stereactic radiosurgery if <3 lesions
  - post-operative adjuvant RT consideration
- surgical
  - single/solitary lesions: use surgery and radiation

**Prognosis**
- median survival without treatment once symptomatic is ~1 mo, with optimal treatment 6-9 mo. The disease-specific Graded Prognostic Assessment (Ds-GPA) is a useful prognostic index. Prognosis varies depending on primary tumour type and extent of systemic tumour burden
Astrocytoma

- most common primary intra-axial brain tumour, common in 4th-6th decades

Table 9. World Health Organization Astrocytoma Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Typical CT/MRI Findings</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – Pilocytic astrocytoma</td>
<td>± mass effect, ± enhancement</td>
<td>&gt;10 yr, cure if gross total resection</td>
</tr>
<tr>
<td>II – Low grade/diffuse*</td>
<td>Mass effect, no enhancement</td>
<td>5 yr</td>
</tr>
<tr>
<td>III – Anaplastic*</td>
<td>Complex enhancement</td>
<td>1.5-2 yr</td>
</tr>
<tr>
<td>IV – Glioblastoma multiforme (GBM)</td>
<td>Necrosis (ring enhancement)</td>
<td>12 mo, 10% at 2 yr</td>
</tr>
</tbody>
</table>

*IDH mutant WHO Gr II/III tumours have a better overall prognosis than IDH wild-type; following IDH stratification, the chromosomal 1p/19q codeletion has prognostic value in IDH mutated grade II-III gliomas after adjustment for tumour proliferation, age, and adjuvant treatment

Clinical Features

- sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
- symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

Investigations

- CT/MRI with contrast: variable appearance depending on grade
  - hypodense on CT, hypointense on T1 MRI, hyperintense on T2 MRI
  - low grade: most do not enhance and have calcification on CT
  - high grade: most enhance with CT contrast dye/gadolinium, possibly with central necrosis (especially if IDH wildtype)

Treatment

- low grade diffuse astrocytoma
  - close follow-up, radiation, chemotherapy, and surgery all valid options
  - de-differentiation to more malignant grade; typically occurs faster when diagnosed after age 45
  - surgery: not curative, trend towards better outcomes
  - radiotherapy alone or post-operative prolongs survival (retrospective evidence)
  - chemotherapy: usually reserved for tumour progression

- high grade astrocytomas (anaplastic astrocytoma and GBM)
  - goal is to prolong "quality" survival
  - surgery
    - gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant temozolomide
    - except: near end-of-life; or extensive brainstem, bilateral, or dominant lobe GBM involvement
    - awake craniotomy for tumours in 'eloquent' regions (e.g. speech and language regions or near motor strip)
  - stereotactic biopsy if resection not possible, followed by fractionated radiation with 2 cm margin
  - expectant (based on functional impairment – Karnofsky score <70; patient's/family's wishes)
  - chemotherapy: ~20% response rate, temozolomide (agent of choice); better response to temozolomide predicted by MGMT gene hypermethylation
  - multiple gliomas: WBRT ± chemotherapy

Meningioma

- most common primary intracranial tumour, arising from arachnoid membrane
- often calcified, may cause hyperostosis of adjacent bone (detectable on imaging)
- classically see Psammoma bodies ("meningocytic whorls") on histology
- location: 70% occur along the parasagittal convexity, falx cerebri, and sphenoid bone; other locations: tuberculum sellae, foramen magnum, olfactory groove, and CP angle

Clinical Features

- middle aged, slight female predominance (M:F = 1:1.8), high progesterone receptors (increase in size with pregnancy)
- many are asymptomatic and can be an incidental finding; when symptoms occur focal neurologic deficits specific to location, ± seizures, symptoms of increased ICP
- molecular changes: between 40-80% of meningiomas contain mutations in chromosome 22 (involved in suppressing tumour growth); some have extra copies of PDGFR and EGFR; some are associated with NF2, if presence of neurofibromatosis type 2
Investigations
- **CT with contrast**: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed, usually solitary (10% multiple, likely with loss of NF2 gene/22q12 deletion)
- **MRI with contrast**: characterization of mass and provides a better assessment of the patency of dural venous sinuses
- **angiography**
  - most are supplied by external carotid feeders (meningeal vessels)
  - can assess venous sinus involvement, "tumour blush" commonly seen (prolonged contrast image)

Treatment
- **conservative management**: asymptomatic and/or non-progressive on CT/MRI – serial monitoring for interval growth changes
- **surgery**: curative if complete resection and indicated when symptomatic and/or documented growth on serial CT/MRI
- **endovascular**: embolization for highly vascularized, likely bloody, tumours to facilitate surgery
- **radiation**: SRS may be an option for lesions <3 cm partially occluding the superior sagittal sinus; SRS or XRT for non-resectable, recurrent atypical/malignant meningiomas

Prognosis
- >90% 5 yr survival, recurrence rate variable (often ~10–20%)
- depends on extent of resection
- Simpson’s classification: degree of surgical resection completeness with symptomatic recurrence

Vestibular Schwannoma (Acoustic Neuroma)
- slow-growing (average of 1-10 mm/yr), benign posterior fossa tumour (8-10% of tumours)
- arises from vestibular nerve of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of neurofibromatosis type II
- epidemiology: 1.5/100,000; all age groups affected, peaks at 4th-6th decades

Clinical Features
- **early clinical trial**: (tumour <2 cm) unilateral progressive hearing loss 98%, tinnitus, and disequilibrium (compression of CN VIII)
- **later clinical features**
  - tumour usually >2 cm: ootalgia, facial numbness + weakness, changes to taste (due to CN V and VII compression, respectively)
  - tumour usually >4 cm: ataxia, H/A, N/V, diplopia, cerebellar signs (due to brainstem compression; obstructive hydrocephalus)

Investigations
- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/species); CT with contrast 2nd choice
- audiogram, brainstem evoked potentials, calorics tests

Treatment
- expectant: serial imaging (CT/MRI q6mo) and audiometry if tumour is small, hearing is still preserved, high perioperative risk, or elderly patient
- radiation: stereotactic radiosurgery or fractionated radiotherapy
- surgery: if lesion >3 cm, brainstem compression, edema, hydrocephalus
- curable if complete resection (almost always possible)
- operative complications: CSF leak, meningitis, required shunt; CN V, VII, VIII dysfunction (proportional to tumour size; only significant CNVIII disability if bilateral)
- implica ion for testing of family members of NF2 mutation carrier

**Pituitary Adenoma**
- primarily from anterior pituitary, 3rd-4th decades, M=F; associated with MEN-1 syndrome
- incidence in autopsy studies approximately 20%
- classification
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
  - most common functional: prolactinomas, adrenocorticotropic, growth-hormone producing
  - differential diagnosis: parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid aneurysm

Clinical Features
- mass effects
  - H/A
  - bitemporal hemianopia (compression of optic chiasm) hydrocephalus (3rd ventricle compression)
  - invasive adenomas: CN III, IV, V1, V2, VI palsy (cavernous sinus compression); proptosis and chemosis (cavernous sinus occlusion)
Cerebral Abscess

Definition
• pus in brain substance, surrounded by tissue reaction (capsule formation)

Etiology
• modes of spread: 10-60% of patients have no cause identified
• pathogens
  - Streptococcus (most common), often anaerobic or microaerophilic
  - Staphylococcus (penetrating injury)
  - Gram-negatives, anaerobes (Bacteroides, Fusobacterium)
  - in neonates: Proteus and Citrobacter (exclusively)
  - immunocompromised: fungi and protozoa (Toxoplasma, Nocardia, Candida albicans, Listeria monocytogenes, Mycobacterium, and Aspergillus)

Sources of Pus/Infection
• four routes of microbial access to CNS
  1. hematogenous spread: arterial and retrograde venous
    - adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
    - children: congenital cyanotic heart disease with R to L shunt
    - immunosuppression (AIDS – toxoplasmosis)
  2. direct implantation (dural disruption)
    - trauma
    - iatrogenic (e.g. following LP, post-operative)
    - congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site (e.g. otitis media, mastoiditis, sinusitis osteomyelitis, dental abscess)
  4. spread from PNS (e.g. viruses: rabies, herpes zoster)
• common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
    - treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
    - treatment: surgical drainage and antibiotics, 20% mortality
  - meningitis, encephalitis (see Infectious Diseases, ID18)
  - cerebral abscess

endocrine effects (see Endocrinology, E15)
• hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
• ACTH production: Cushing’s disease, hyperpigmentation
• GH production: acromegaly/gigantism
• panhypopituitarism: due to compression of pituitary (hypothyroidism, hypoadrenalism, hypogonadism)
• diabetes insipidus (DI) – rare, except in apoplexy

pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
• abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, panhypopituitarism
  and DI
• CSF rhinorrhea and seizures (rare)
• signs and symptoms of subarachnoid hemorrhage (rare)

Investigations
• formal visual fields, CN testing
• endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose FSH/LH, IGF-1), electrolytes, urine electrolytes, and osmolarity
• imaging (MRI with and without contrast)

Treatment
• medical
  - for apoplexy: rapid corticosteroid administration ± surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing’s: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
  - endocrine replacement therapy
• surgical
  - endoscopic trans-sphenoidal, trans-ethmoidal, and less commonly trans-cranial approaches (i.e. for significant suprasellar extension)
• post-operative concerns: DI, adrenal insufficiency (AI), CSF leak
  - DI and AI: AM cortisol serum sodium and osmolality, urine output and specific gravity (treatment AI: glucocorticoids; DI: desmopressin/DDAVP)
  - CSF rhinorrhea: test for β transferrin

Figure 14. Cavernous Sinus
Risk Factors
- lung abnormalities (infection, AV fistulas; especially Osler-Weber-Rendu syndrome [i.e. hereditary hemorrhagic telangiectasia])
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess, poor dentition

Clinical Features
- focal neurological signs and symptoms
  - H/A, decreased LOC; hemiparesis and seizures in 50%
  - mass effect, increased ICP and sequelae (cranial enlargement in children)
  - hemiparesis and seizures in 50%
  - ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

Complications
- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

Investigations
- CT scan often first test in emergency department
- MRI
  - imaging of choice
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)
  - WBC/ESR, may be normal, blood cultures rarely helpful and LP contraindicated if large mass
  - CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

Treatment
- aspiration ± excision and send for Gram stain, acid fast bacillus (AFB), CandS, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin (6-8 wk therapy)
  - revise antibiotics when C&S known
  - anti-convulsants (1-2 yr)
- follow-up CT is critical (do weekly initially, more frequent if condition deteriorates)

Prognosis
- mortality with appropriate therapy ~10%, permanent deficits in ~50%

### Table 10. Comparison of Epidemiology and Etiology of Intracranial Bleeds

<table>
<thead>
<tr>
<th>Types of Hematoma/Hemorrhage</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>CT Features</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epideral Hematoma</td>
<td>Skull fracture causing middle meningeal bleed</td>
<td>M:F&gt;4:1, associated with trauma</td>
<td>Hyperdense lenticular mass with sharp margins, usually limited by suture lines</td>
<td>Craniotomy</td>
<td>Good with prompt management (Note: respiratory arrest can occur from uncal herniation)</td>
</tr>
<tr>
<td>Acute SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, associated with trauma</td>
<td>No lucid interval, hemiparesis, papillary changes</td>
<td>Hyperdense crescentic mass, crossing suture lines</td>
<td>Craniotomy if bleed &gt;1 cm thick</td>
</tr>
<tr>
<td>Chronic SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, EOH abscesses, anticoagulated</td>
<td>Often asymptomatic, minor H/A, confusion, signs of increased ICP</td>
<td>Hyperdense crescentic mass, crossing suture lines</td>
<td>Burr hole to drain; craniotomy if recurs</td>
</tr>
<tr>
<td>SAH</td>
<td>Trauma, spontaneous (aneurysma, idiopathic, AVM)</td>
<td>Age 55-60, 20% cases under age 45</td>
<td>Sudden onset thunderclap H/A, signs of increased ICP</td>
<td>Hyperdense blood in cisterns/ fissures (sensitivity decreases over time)</td>
<td>Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if need be</td>
</tr>
<tr>
<td>ICH</td>
<td>HTN, vascular abnormality, tumours, infections, coagulopathy</td>
<td>Age &gt;55, male, drug use (cocaine, EOH, amphetamine)</td>
<td>TIA-like symptoms, signs of increased ICP</td>
<td>Hyperdense parenchymal collection</td>
<td>Medical: decrease BP, control ICP; Surgical craniotomy</td>
</tr>
</tbody>
</table>

### Figure 15. Cerebral abscess on CT

**Figure 15:** Cerebral abscess on CT

- **1. Surrounding edema**
- **2. Central low density (pus)**
- **3. Ring enhancement**

### Recommendations for Duration of Antibiotic Therapy for Brain Abscesses


**Summary:**
1. Prudent period of 4-6 weeks of antibiotic therapy for surgically treated abscesses.
2. 6-8 weeks of IV treatment for abscesses treated medically only.
3. 6-8 weeks of IV treatment for multiple abscesses when larger ones are treated surgically.

**Methods:** Systematic literature search using MEDLINE database or studies during 1988-2008 to methodologically evaluate all studies pertaining to brain abscesses.

**Results:** Several recommendations were made by extracting evidence; for duration of antibiotic therapy, it was noted that IV antibiotic therapies were usually >4 weeks. No studies have evaluated the duration of antibiotic therapy on outcome.

Without evidence to safely evaluate endovenous therapy time, authors agreed with British Society for Antimicrobial Chemotherapy recommendations (see summary).
**Extradural (“Epidural”) Hematoma**

**Etiology**
- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

**Epidemiology**
- young adult, M:F = 4:1; rare before age 2 or after age 60
- 1-4% of traumatic head injuries

**Clinical Features**
- classic sequence (seen in <30%); post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilatation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, aphasia, seizures, HTN, and respiratory distress
- deterioration can take hours to days

**Investigations**
- CT without contrast: “lenticular-shaped” usually limited by suture lines but not limited by dural attachments

**Treatment**
- admission, close neurological observation with serial CT indicated if all of the following are present
  - small volume clot, minimal midline shift (MLS <5 mm), GCS >8, no focal deficit
  - otherwise, craniotomy to evacuate clot, follow-up CT
- patients with initial EDH >10mL on CT within 2 hours or EDH in temporoparietal region are more likely to develop epidural hematoma enlargement and require close CT follow-up at 5-6 hr post impact
- mannitol pre-operative if elevated ICP or signs of brain herniation

**Prognosis**
- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-operative
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)

**Subdural Hematoma**

**Table 11 Comparison of Epidemiology and Etiology of Acute and Chronic SDH**

<table>
<thead>
<tr>
<th></th>
<th>Acute SDH</th>
<th>Chronic SDH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Course</strong></td>
<td>1-2 d after bleeding onset</td>
<td>≥15 d after bleeding onset</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration</td>
<td>Blood within the subdural space evokes an inflammatory response: Fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot (forming a hygroma) Course is determined by the balance of rebleeding from neomembranes and resorption of fluid</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Trauma, acceleration-deceleration injury, anticoagulants, alcohol, cerebral atrophy, infant head trauma</td>
<td>Older, alcoholics, patients with CSF shunts, anticoagulants, coagulopathies</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>No lucid period, signs and symptoms can include: altered LOC, pupillary irregularity, hemiparesis</td>
<td>Often due to minor injuries or no history of injury May present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ≤ seizures, progressive dementia, gait problem Obtundation disproportionate to focal deficit; “the great imitator” of dementia, tumours</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>CT: Hyperdense concave “crescentic” mass, crossing suture lines</td>
<td>CT: hypodense (liquefied clot), crescentic mass</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Craniotomy if clinically symptomatic, if hematoma &gt; 1 cm thick or if MLS &gt; 5 mm (optimal if surgery &lt; 4 h from onset Otherwise observe with serial imaging</td>
<td>Seizure prophylaxis only if post-traumatic seizure Reverse coagulopathies Burr hole drainage of liquefied clot indicated if symptomatic or thickness &gt; 1 cm; craniotomy if recurs more than twice</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Poor overall since the brain parenchyma is often injured (mortality range is 50-90%, due largely to underlying brain injury) Prognostic factors: initial GCS and neurologica status, post-operative ICP</td>
<td>Good overall as brain usually undamaged, but may require repeat drainage</td>
</tr>
</tbody>
</table>

*Use Of Drains Vs. No Drains After Burr-Hole Evacuation For Treatment Of Chronic Subdural Hematoma*  
*Cochrane Database Syst Rev. 2016 Aug 31;(8):CD011402*  
**Summary**
- some evidence that post-operative drainage is effective in reducing the symptomatic recurrence of chronic subdural hematomas  
- The effect of drainage on the occurrence of surgical complications, mortality, and poor functional outcomes is uncertain due to low-quality evidence  
- No strong evidence of increase in complications when drains are used  
**Methods** comprehensive search strategy databases extracting 9 RCTs (n=989) comparing external subdural drains with no drains after burr-hole evacuation for treatment of chronic subdural hematomas  
**Results** significant reduction in the risk of recurrence with sub-dural drains (RR 0.45, 95% CI 0.32-0.61), no strong evidence of increase in complications (RR 0.70, 95% CI 0.71-1.32), mortality (RR 0.70, 95% CI 0.45-1.33), poor functional outcome (RR 0.68, 95% CI 0.44-1.05).
Cerebrovascular Disease

Ischemic Cerebral Infarction (80%)
- embolic, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc. (see Neurology, N50)

Intracranial Hemorrhage (20%)
- SAH, spontaneous ICH, IVH

Subarachnoid Hemorrhage

Definition
- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

Etiology
- trauma (most common)
- spontaneous
  - ruptured aneurysms (75-80%)
  - idiopathic (14-22%)
  - AVMs (4-5%)
- coagulopathies (iatrogenic or primary), vasculitides, tumours, cerebral artery dissections (<5%)

Epidemiology
- ~10 28/100,000 population/yr
- peak age 55-60, 20% of cases occur under age 45

Risk Factors
- HTN
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance abuse (cigarette smoking, cocaine, alcohol)
- conditions associated with high incidence of aneurysms (see Intracranial Aneurysms, NS20)

Clinical Features of Spontaneous SAH
- sudden onset (seconds) of severe “thunderclap” H/A usually following exertion and described as the “worst headache of my life” (up to 97% sensitive, 12-25% specific)
- N/V, photophobia
- meningismus (neck pain/stiffness, positive Kernig's and Brudzinski's sign)
- decreased LOC (due to either raised ICP, ischemia, seizure)
- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20–40% (due to sudden raised ICP compressing central retinal vein)
- reactive HTN

Hunt and Hess Grade
(clinical grading scale for SAH)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Sx or mild H/A and/or mild meningeal irritation</td>
</tr>
<tr>
<td>2</td>
<td>Grade 1 + CN palsy</td>
</tr>
<tr>
<td>3</td>
<td>Confusion/lethargy, mild hemiparesis, or aphasia</td>
</tr>
<tr>
<td>4</td>
<td>GCS &lt;15 but &gt;8, moderate-severe hemiparesis, mild rigidity</td>
</tr>
<tr>
<td>5</td>
<td>Coma (GCS &lt;9), decerebrate, moribund appearance</td>
</tr>
</tbody>
</table>

Mortality of Grade 1-2, 20%, increased with grade

Hemorrhage in Older Patients with Extensive Middle-Cerebral-Artery Stroke
NEJM 2014;370:1091-1100

Purpose: To determine if early decompressive hemicraniectomy reduces mortality among patients >60 yr.

Study: 112 patients >60 yr (median age 70 yr) with malignant MCA infarction randomly assigned to conservative ICU treatment versus hemicraniectomy. Endpoint was survival without severe disability (modified Rankin scale score 0-4).

Results: The proportion of patients who survived without severe disability was 38% in the hemicraniectomy group and 18% in the control group (OR 2.91, 95% CI 1.06-7.49). Modified Rankin scale scores in hemicraniectomy versus control group in terms of percentages of patients: 0-2, 0%, 0% 3 or moderate disability (7%, 3%), 4 or moderate severe disability (32%, 15%), 5 or severe disability (28%, 13%) and 6 or death (33%, 7%). Infections were more frequent in the hemicraniectomy group and hemiation more frequent in the control group.

Conclusions: Hemicraniectomy increased survival without severe disability among patients >60 yr with a malignant MCA infarction.
sentinel bleeds
• represents undiagnosed SAH
• SAH-like symptoms lasting <1 d ("thunderclap H/A")
• may have blood on CT or LP
• ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
• differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

Investigations
• non-contrast CT – for diagnosis of SAH
  • 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  • may be negative if small bleed or presentation delayed several days
  • acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
• lumbar puncture (highly sensitive) – for diagnosis of SAH if CT negative but high suspicion:
  • elevated opening pressure (>18 cm H2O)
  • bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12 h, lasts 2 wk
  • RBC count usually >100,000/mm³ without significant drop from first to last tube (in contrast to traumatic tap)
  • elevated protein due to blood breakdown products
• four vessel cerebral angiography ("gold standard" for aneurysms)
  • demonstrates source of SAH in 80-85% of cases
  • angiogram negative SAH: repeat angiogram in 7–14 d, if negative → "perimesencephalic SAH"
• MRA and CTA: sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

Non traumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule

Background: Two rules for SAH diagnosis exist. A clinical prediction rule states that patients with acute severe H/A but without the clinical variables age >40 yr, neck pain, loss of consciousness, or onset of H/A with exertion are at low risk for SAH. An imaging prediction rule bases diagnosis on non-contrast cranial CT for patients within 6 h of H/A onset.

Methods: Matched case-control study of 55 patients at 21 emergency departments between 2000 and 2011, and diagnoses were verified by lumbar puncture.

Results: The clinical prediction rule for diagnosis of SAH was 97% sensitive, 22.7% specific, and had a negative likelihood ratio of 0.13. Using the imaging prediction rule resulted in a false negative rate of 21%.

Conclusions: Performing the clinical and imaging rules together has the potential for maximizing sensitivity of prediction and reducing rates of lumbar puncture, but using imaging alone can result in missed cases.

The Vasograde: A Simple Grading Scale For Prediction Of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage
Stroke. 2015;46(7):1826-31

Background: Patients are classically at risk of delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage. We validated a grading scale—the VASOGRADE for prediction of DCI.

Method: We used data of 3 phase II randomized clinical trials and a single hospital series to assess the relationship between the VASOGRADE and DCI.

Results: In a cohort of 746 patients, the VASOGRADE significantly predicted DCI (P<0.001). The VASOGRADE-Yellow had a tendency for increased risk for DCI (odds ratio [OR], 3.1; 95% CI, 0.7–12.2) when compared with VASOGRADE-Green; those with VASOGRADE-Red had a high risk of DCI (OR, 3.1; 95% CI, 0.7–16.2).

Conclusions: The VASOGRADE results validated previously published risk charts in a large and diverse sample of subarachnoid hemorrhage patients, which a low DCI risk stratification on presentation after subarachnoid hemorrhage. It could help to select patients at high risk of DCI, as well as standardize treatment protocols and research studies.
Intracranial Aneurysms

**Prognosis**
- 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
- 30% of survivors have moderate to severe disability
- a major cause of mortality is rebleeding, for untreated aneurysms:
  - risk of rebleed: 4% on first day, 15-20% within 2 wk, 50% by 6 mo
  - if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  - only prevention is early clipping or coiling of “cold” aneurysm
  - rebleed risk for “perimesencephalic SAH” is approximately same as for general population

**Epidemiology**
- prevalence 1-4% (20% have multiple)
- F>M; age 35-65 yr

**Types**
- saccular (berry)
  - most common type
  - located at branch points of major cerebral arteries (Circle of Willis)
  - 85-95% in carotid (anterior) system, 5-15% in vertebrobasilar (posterior) circulation
- fusiform
  - atherosclerotic
  - more common in vertebrobasilar system, rarely rupture
- infectious
  - secondary to any infection of vessel wall, 20% multiple
  - 60% *Streptococcus* and *Staphylococcus*
  - 3-15% of patients with bacterial endocarditis

**Complications**
- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood – can lead to delayed cerebral ischemia and death
- onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
- clinical features (new onset ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor e.g. pronator drift)
- risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
- “symptomatic” vasospasm in 20-30% of SAH patients
- “radiographic” vasospasm in 30-70% of arteriograms performed 7 d following SAH
- diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
- risk of cerebral infarct and death
- treatment
  - hyperdynamic (“triple H”) therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
  - direct vasodilatation via angioplasty or intra-arterial verapamil for refractory cases
- delayed cerebral ischemia: neurological deterioration persisting more than 1 hour in the absence of any obvious contributing physiological, radiological or laboratory abnormalities
  - peaks 4-10 days post ictus
  - can progress to cerebral infarction and is associated with significant morbidity and mortality
  - mechanism behind DCI is unclear but includes vasospasm, vascular dysautoregulation, neurotoxic effects from the blood, inflammation, micro-thrombi and cortical spreading depolarizations
  - it is an essential target for SAH management
- hydrocephalus (15-20%): due to blood obstructing arachnoid granules
  - can be acute or chronic, requires extraventricular drain (EVD) or shunt, respectively
- neurogenic pulmonary edema
- hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECFV loss), not SIADH
- diabetes insipidus
cardiac: arrhythmia (>50% have ECG changes), MI, CHF

**Intracranial Aneurysms**
Risk Factors
• autosomal dominant polycystic kidney disease (15%)
• fibromuscular dysplasia (7-21%)
• AVMs
• connective tissue diseases (Ehlers-Danlos, Marfan)
• family history
• bacterial endocarditis
• Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
• atherosclerosis and HTN

Trauma

Clinical Presentation
• rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
• sentinel hemorrhage (“thunderclap H/A”) → requires urgent clipping/coiling to prevent catastrophic bleed
• mass effect (giant aneurysms)
  • internal carotid or anterior communicating aneurysm may compress:
    • the pituitary stalk or hypothalamic causing hypopituitarism
    • the optic nerve or chiasm producing a visual field defect
  • basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
  • posterior communicating artery aneurysm may produce CN III palsy
  • intracavernous aneurysms (CN III, IV, V1, V2, VI)
• distal embolization (e.g. amaurosis fugax)
• seizures
• H/A (without hemorrhage)
• incidental CT or angiography finding (asymptomatic)

Investigations
CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

Treatment
• ruptured aneurysms
  • overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
  • treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling) or flow diversion stents, wrapping (last resort)
  • choice of surgery vs. coiling not yet well defined: consider location, size, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition; in general:
    • clipping: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    • coiling: superficial > deep, broad aneurysmal base branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
• unruptured aneurysms
  • average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  • no clear evidence on when to operate: need to weigh life expectancy
  • risk of morbidity/mortality of SAH (20% 50%) vs. surgical risk (2%-5%)
  • generally treat unruptured aneurysms >10 mm
  • consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
  • follow smaller aneurysms with serial angiography

Table 12. Five Year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Cavernous Carotid</th>
<th>AC/MC/IC</th>
<th>Vertebrobasilar/PC/PComm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>0%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>7-12</td>
<td>0%</td>
<td>2.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>13-24</td>
<td>3%</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
<tr>
<td>≥24</td>
<td>6.4%</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>

AC = anterior cerebral/anterior communicating artery; IC = internal carotid artery; MC = middle cerebral artery; PC = posterior cerebral artery; PComm = posterior communicating artery.

Long-Term, Serial Screening for Intracranial Aneurysms in Individuals with a Family History of Aneurysmal Subarachnoid Hemorrhage: A Cohort Study
Lancet Neurol 2014; 13:385-392
Purpose: To examine the yield of long-term serial screening for intracranial aneurysms for individuals with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) (two or more first degree relatives who have had aSAH or unruptured intracranial aneurysms).

Study: Screening results from April 1 1993 to April 1 2013 were reviewed in a cohort study. MRA or CTA was done from age 16-18 to 65-70 yr. After a negative screen, individuals were advised to contact the clinic in 5 yr for follow-up.

Results: Aneurysms were identified in 11% of individuals at first screening (n=459), 8% at second screening (n=261), 5% at third screening (n=128), and 5% at fourth screening (n=84). Smoking (OR 2.7, 95% CI 1.2-5.9), history of previous aneurysms (3.9, 1.2-12.3), and familial history of aneurysms (3.5, 1.6-8.1) were significant risk factors for aneurysm at first screening. History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening (HR 4.5, 95% CI 1.1-18.7).

Conclusions: The benefit of long-term screening in individuals with a family history of aSAH is substantial up to and after 10 yr of follow-up and two initial negative screens.

The Unruptured Intracranial Aneurysm Treatment Score
Neurology 2015;85(10):881-9
Objective: to develop an unruptured intracranial aneurysm (UIA) treatment score (UIATS) model that includes and quantifies key factors involved in clinical decision making in the management of UIAs and to assess agreement for this model among specialists in UIA management and research.

Methods: An international multidisciplinary (neurosurgery, neuroradiology, neurology, clinical epidemiology) group of 69 specialists was convened to develop and validate the UIATS model using a Delphi consensus method.

Results: The UIATS accounts for 29 key factors in UIA management.

Conclusions: This novel UIA decision guidance study captures an excellent consensus among highly informed individuals on UIA management, irrespective of their underlying specialty.
Intracerebral Hemorrhage

Definition
- hemorrhage within brain parenchyma, accounts for ~10% of strokes
- can dissect into ventricular system (IVH) or through cortical surface (SAH)

Etiology
- HTN (usually causes bleeds at putamen, thalamus, pons, and cerebellum)
- hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
- vascular anomalies
  - aneurysm, AVMs, and other vascular malformations (see Vascular Malformations, NS23)
  - venous sinus thrombosis
  - arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
- tumors (1%): often malignant (e.g. GBM, lymphoma, metastases)
- drugs (amphetamine, cocaine, alcohol, anticoagulants, etc.)
- coagulopathy (iatrogenic, leukemia, TTP, aplastic anemia)
- CNS infections (fungal, granulomas, herpes simplex encephalitis)
- post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
- eclampsia
- post operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
- idiopathic

Epidemiology
- 12-15 cases/100,000 population/yr

Risk Factors
- increasing age (mainly >55 yr)
- male gender
- HTN
- Black/Asian > Caucasian
- previous CVA of any type (23x risk)
- both acute and chronic heavy alcohol use; cocaine, amphetamines
- liver disease
- anticoagulants

Clinical Features
- TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
- gradual onset of symptoms over minutes-hours, usually during activity
- H/A, N/V, and decreased LOC are common
- specific symptoms/deficits depend on location of ICH

Investigations
- baseline severity score such as the ICH Score should be performed as part of the initial workup
- hyperdense blood on non-contrast CT
- CTA routine, if spot sign (contrast in the hematoma) demonstrated there is high likelihood of clot growth

Treatment
- medical
  - decrease MAP to pre-morbid level or by ~20% (target BP 140/90) in ED
  - check PT/INR, and correct coagulopathy
  - control raised ICP (see Intracranial Pressure Dynamics, NS4)
  - corticosteroids should NOT be used for elevated ICP in ICH
  - levetiracetam/phenytoin for seizure prophylaxis
  - follow electrolytes (SIADH common)
  - angiogram to rule out vascular lesion unless >45 yr, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~0%)
- surgical
  - craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
  - indications
    - symptoms of raised ICP or mass effect
    - rapid deterioration (especially if signs of brainstem compression)
    - favourable location (e.g. cerebellar, non-dominant hemisphere)
    - young patient (<50 yr)
    - if tumour, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)
  - contraindications
    - small bleed: minimal symptoms, GCS >10
    - poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
    - medical reasons (e.g. very elderly, severe coagulopathy, difficult location [e.g. basal ganglia, thalamus])

ICH Score Components
- GCS score
- ICH volume
- Presence of intraventricular hemorrhage
- Infrafrontal origin
- Age

Early Surgery Versus Initial Conservative Treatment in Patients With Spontaneous Supratentorial Lobar Intracerebral Hematomas (STICH-II): A Randomized Trial
Lancet. 2013 Aug 3; 382(9890): 397-408
Summary: The STICH II (international, parallel-group trial comparing early surgical hematoma evacuation within 12 hour of randomization + medical treatment vs initial medical treatment alone) results confirm that early surgery does not increase the rate of death or disability at 6 months and might have a small but clinically relevant survival advantage for patients with spontaneous superficial intracerebral hemorrhage without intraventricular hemorrhage.

Location of ICH
- Basal Ganglia/Internal Capsule (50%)
- Thalamus (15%)
- Cerebral White Matter (15%)
- Cerebellum/Brainstem – usually pons (15%)
- Other (5%)

Spetzler-Martin AVM Grading Scale

<table>
<thead>
<tr>
<th>Item Score</th>
<th>Spetzler-Martin AVM Grading Scale</th>
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<tbody>
<tr>
<td>Size</td>
<td>Item Score</td>
</tr>
<tr>
<td>0-3 cm</td>
<td>1</td>
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<tr>
<td>3.1-6.0 cm</td>
<td>2</td>
</tr>
<tr>
<td>&gt;6 cm</td>
<td>3</td>
</tr>
<tr>
<td>Location</td>
<td>Item Score</td>
</tr>
<tr>
<td>None eloquent</td>
<td>0</td>
</tr>
<tr>
<td>Eloquent</td>
<td>1</td>
</tr>
<tr>
<td>Deep Venous Drainage</td>
<td>Item Score</td>
</tr>
<tr>
<td>Not present</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
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</table>

AVM grades calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table. e.g. a 2 cm tumour in none eloquent location without deep venous drainage = Grade I
Vascular Malformations

Types
- arteriovenous malformations (AVMs)
- cavernous malformations (= cavernomas, cavernous hemangiomas/angiomas)
- venous angioma
- capillary telangiectasias
- arteriovenous fistula (AVF) (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- “angiographically occult vascular malformations” (any type, 10% of malformations)

Arteriovenous Malformations, Cavernous Malformations, and Dural Fistulas

<table>
<thead>
<tr>
<th>Table 13 Comparison of Pathoetiology, Clinical Presentation, and Treatment of Arteriovenous Malformations, Cavernous Malformations, and Dural Fistula’s</th>
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<tbody>
<tr>
<td><strong>Arteriovenous Malformation</strong></td>
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<td><strong>Definition</strong></td>
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<td><strong>Epidemiology</strong></td>
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<td><strong>Clinical Features</strong></td>
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<tr>
<td><strong>Investigations</strong></td>
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<td><strong>Treatment</strong></td>
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<tr>
<td><strong>Prognosis</strong></td>
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Cerebrospinal Fluid Fistulas

**Etiology**
- cranial or spinal
- traumatic: after head trauma, iatrogenic (post-transsphenoidal surgery, post skull base surgery)
- nontraumatic: high pressure (hydrocephalus, tumour), normal pressure (bone erosion secondary to infection, congenital defect)

**Clinical Features**
- otorrhea or rhinorrhea (clear fluid)
- low pressure headaches (worse when sitting up)
- confirmatory testing for CSF: β transferrin test, quantitative glucose analysis of fluid, “ring sign”, “reservoir sign”

**Investigations**
- CT (detect pneumocephalus, fractures, skull base defects), water contrast CT cisternography

**Treatment**
- lower ICP (avoid straining, acetazolamide to reduce CSF production, modest fluid restriction)
- persistent leak: may require continuous lumbar drainage via percutaneous catheter
- surgical indications: traumatic leak lasting >2 wk, spontaneous leaks, delayed onset of leak after trauma or surgery, leaks complicated by meningitis

EXTRACRANIAL PATHOLOGY

Approach to Limb/Back Pain

- see Orthopedics, OR23

Extradural Lesions

![Vascular supply of spinal cord](image)

**Posterior spinal aa.**
- Post spinal (sensory)
- Ventral horn (motor)
- Dorsal horn (sensory)
- Lateral horn (autonomic)
- Fasciculus gracilis
- Fasciculus cuneatus
- Dorsal funiculus
- Ventral funiculus
- Anterior spinal cord
- Spinothalamic tract (afferent)
- Anterior corticospinal tract (efferent)
- Ventral horn
- Posterior spinal artery
- Thoracic aorta
- Intercostal a.
- Branch to vertebral body & dura mater
- Dorsal branch of intercostal a.
- Spinal a.
- Arachnoid mater
- Dura mater
- Anterior spinal a.
- Branch to vertebral body & dura mater
- Posterior spinal a.
- Post. & ant. reticular aa.
- Anterior segmental medullary a.

**Stereotactic Radiosurgery For Cavernous Malformations (CM)**

**Summary**
- Stereotactic radiosurgery is a safe intervention for CMs, with advantages of reducing rebleed risk in patients with repeated pretreatment hemorrhage. Treating 50% with single bleed in less than 2 months. However, the morbidity of repeated hemorrhage outweighs any radiosurgery-related morbidity and early active management of deep-seated CMs should be considered.

**Methods**
- Retrospective analysis of 113 patients with 79 brainstem and 39 thalamic/basal ganglia CMs treated with gamma knife surgery.

**Results**
1. Patients with multiple symptomatic hemorrhages before radiosurgery (n=41): rebleed rate decreased from 30.5% per lesion to 15% for the first 2 years after radiosurgery and 0% for the subsequent years. Pretreatment multiple bleeds led to permanent deficits in 72% of these patients.
2. Patients with ≤1 symptomatic bleed before radiosurgery (n=77): natural history is uncertain due to short period between presenting bleed and treatment (median 1 year). Rate of hemorrhage was 3.5% for the first 2 years and 1.2% subsequently. Pretreatment hemorrhages led to permanent deficits in 43% of these patients (significantly lower than multiple-bleeds group, p<0.001).
3. Permanent adverse radionecrosis effects were rare (0.7%) and minor in both groups.
4. Posttreatment hemorrhages led to persistent deficits in 7.3% of patients.

**RED FLAGS for Back Pain**

**Back Pain**

- **Bowel/Badder (retention or incontinence)**
- **Anesthesia (saddle)**
- **Fatigue**
- **Cauda Equina**

- **Urinary retention or incontinence, fecal incontinence or loss of anal sphincter tone, saddle anesthesia, uni/bi lateral, leg weakness/pain**
- **Malignancy**

- **Age ≥50 yr, previous Hx of cancer, pain unreleaved by bed rest, constitutional symptoms**
- **Infection**
  - Increased ESR, IV drug use, immunosuppressed, fever
- **Compression Fracture**
  - **Age >50 yr, trauma, prolonged steroid use**
**Root Compression**

- radiculopathy is a pain and/or sensorimotor deficit syndrome that involves compression of a nerve root. Nerve compression generally occurs as a result of disc herniation, degenerative disc diseases (spondylosis), instability and rarely, masses
- patients generally present with referred pain, sensory changes (numbness and/or tingling) or weakness. Whereas patients might sometime describe sensory changes in a dermatomal distribution, the referred pain will not be in a dermatomal distribution. The areas of pain and altered sensorium may be incongruent
- muscle innervation has less overlap than sensory innervation and hence is a better predictor of level of pathology

**Differential Diagnosis**
- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

**Cervical Disc Syndrome**

**Etiology**
- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C6-C7 (C7 root)

**Clinical Features**
- pain in arm follows nerve root distribution, worse with neck extension, ipsilateral rotation, and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

**Investigations**
- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- only consider EMG, nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue

**Treatment**
- **conservative**
  - no bedrest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics, NSAIDs are more efficacious
  - avoid cervical manipulation, like traction
- **surgical indications**
  - anterior cervical discectomy is usual approach
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurological deficit

**Prognosis**
- 95% improve spontaneously in 4-8 wk

**Table 14. Lateral Cervical Disc Syndromes**

<table>
<thead>
<tr>
<th></th>
<th>C4-5</th>
<th>C5-6</th>
<th>C6-7</th>
<th>C7-T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root Involved</td>
<td>C5</td>
<td>C6</td>
<td>C7</td>
<td>C8</td>
</tr>
<tr>
<td>Incidence</td>
<td>2%</td>
<td>19%</td>
<td>69%</td>
<td>10%</td>
</tr>
<tr>
<td>Sensory</td>
<td>Shoulder</td>
<td>Thumb</td>
<td>Middle finger</td>
<td>Ring finger, 5th finger</td>
</tr>
<tr>
<td>Motor</td>
<td>Deltoid, biceps, supraspinatus</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Digital flexors, intrinsic</td>
</tr>
<tr>
<td>Reflex</td>
<td>No change</td>
<td>Biceps, brachioradialis</td>
<td>Triceps</td>
<td>Finger jerk (Hoffmann’s sign)</td>
</tr>
</tbody>
</table>
Cervical Spondylosis

Definition
- progressive degenerative process of cervical spine leading to canal stenosis – congenital spinal stenosis, degeneration of intervertebral discs, hypertrophy of lamina, dura, or ligaments, subluxation, altered mobility, telescoping of the spine due to loss of height of vertebral bodies, alteration of normal lordotic curvature
- resultant syndromes: mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression)

Epidemiology
- typically begins at age 40-50, M>F, most commonly at the C5-C6 > C6-C7 levels

Pathogenesis
- any of: disc degeneration/herniation, osteophyte formation, ossification, and hypertrophy of ligaments
- pathophysiology includes static compression, dynamic compression and vascular compromise

Clinical Features
- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling’s test)
- the earliest symptoms are gait disturbance and lower extremity weakness or stiffness
- occipital H/A is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder and arm pain, paresthesias and numbness
- cervical spondylotic myelopathy (CSM) may present with
  - weakness (upper > lower extremity), lower extremity weakness (corticospinal tracts) is most worrisome complaint
  - decreased dexterity, loss of fine motor control
  - sensory changes
  - UMN findings such as hyperreflexia, clonus, and Babinski reflex
  - funicular pain, characterized by burning and stinging ± Lhermitte’s sign (lightning-like sensation down the back with neck flexion)

Investigations
- x-ray of cervical spine ± flexion/extension (alignment, fractures)
- MRI most useful for determination of compression of the neural element
- CT is only used for better determination of bony anatomy (i.e. OPLL)
- EMG/nerve conduction studies reserved for peripheral nerve investigation

Treatment
- nonsurgical: prolonged immobilization with cervical bracing (limit movement to minimize cumulative trauma to spinal cord), bed rest, anti-inflammatory medications
- surgical: anterior approach (anterior cervical disectomy or corpectomy), posterior approach (decompressive cervical laminectomy)
- In multilevel CSM, an anterior approach is associated with better postoperative neural function but has a higher complication and reoperation rate than the posterior group
- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain
- complete remission almost never occurs. Surgical decompression may stop progression of disease

Lumbar Disc Syndrome

Etiology
- postero-laterally herniated disc compressed nerve root exiting BELOW the level of the disc or the traversing nerve root
- far lateral disc herniation compressed nerve root AT the level of the disc or the exiting nerve root
- central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

Clinical Features
- initial back pain, then leg pain > back pain
- limited back movement (especially forward flexion) due to pain
- motor weakness, dermatomal sensory changes, decreased reflexes
- exacerbation with valsalva; relief with flexing the knee or thigh
- nerve root tension signs
  - straight leg raise (SLR, Laségue’s test) or crossed SLR (pain should occur at less than 60º) suggests L5, S1 root involvement
  - femoral stretch test suggests L2, L3, or L4 root involvement

Efficacy and Safety of Surgical Decompression in Patients with Cervical Spondylotic Myelopathy: Results of the AOSpine North America Prospective Multi-centre Study

Purpose: Evaluate impact of surgical decompression on functional, CQL, and disability outcomes 1 yr post-surgery in patients with cervical spondylotic myelopathy.

Methods: 278 patients with mild to severe symptomatic cervical spondylotic myelopathy and MRI evidence of spinal cord compression were followed for 1 yr following surgical decompression. Outcomes (mJOA score, Nurick grade, Neck Disability Index, Short Form-36v2) were compared to preoperative values. Treatment-related complication data was collected.

Results: There was significant improvement (P<0.05) from baseline in mJOA score, Nurick grade, NDI score, and all SF-36v2 health dimensions other than general health. 18.7% of patients experienced complications with no significant differences among the severity groups.

Conclusion: Surgical decompression of cervical spondylotic myelopathy is associated with improved function, disability, and QOL outcomes at 1 yr.
Investigations
- MRI is modality of choice
- x-ray spine (only to rule out other lesions), CT (bony anatomy)
- myelogram and post-myelogram CT (only if MRI is contraindicated)

Treatment
- conservative (same as cervical disc disease)
- surgical indications: same as cervical disc + cauda equina syndrome

Prognosis
- 95% improve spontaneously within 4-8 wk
- those who do not improve with conservative treatment achieve symptom relief quicker with surgery than continuation of conservative management; however, the long-term outcome after surgery is comparable to conservative therapy
- do not follow patients with serial MRIs; clinical status is more important at guiding management

Table 15. Lateral Lumbar Disc Syndromes

<table>
<thead>
<tr>
<th>Root Involved</th>
<th>Incidence</th>
<th>Pain</th>
<th>Sensory</th>
<th>Lateral leg</th>
<th>Motor</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3-4</td>
<td>&lt;10%</td>
<td>Femoral pattern</td>
<td>Medial leg</td>
<td>Lateral foot</td>
<td>Tibialis anterior (dorsiflexion)</td>
<td>Patellar</td>
</tr>
<tr>
<td>L4-5</td>
<td>45%</td>
<td>Sciatic pattern</td>
<td>Dorsal foot to hallucis</td>
<td></td>
<td>Extensor hallucis longus (hallux extension)</td>
<td>Medial hamstrings</td>
</tr>
<tr>
<td>L5-S1</td>
<td>45%</td>
<td>Sciatic pattern</td>
<td></td>
<td></td>
<td>Gastrocnemius, soleus (plantar flexion)</td>
<td>Achilles</td>
</tr>
</tbody>
</table>

Table 16. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome

<table>
<thead>
<tr>
<th>Conus Medullaris Syndrome</th>
<th>Cauda Equina Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual, unilateral</td>
</tr>
<tr>
<td>Spontaneous Pain</td>
<td>Rare, if present usually bilateral, symmetric in perineum or thighs</td>
</tr>
<tr>
<td>Sensory Deficit</td>
<td>Saddle; bilateral and symmetric; sensory dissociation</td>
</tr>
<tr>
<td>Motor Deficit</td>
<td>Symmetric; paresis less marked; fasciculations may be present</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Only ankle jerk absent (preserved knee jerk)</td>
</tr>
<tr>
<td>Autonomic Symptoms (bladder dysfunction, impotence, etc.)</td>
<td>Urinary retention and atonic anal sphincter prominent early; impotence frequent</td>
</tr>
<tr>
<td></td>
<td>Sphincter dysfunction presents late; impotence less frequent</td>
</tr>
</tbody>
</table>

Cauda Equina Syndrome

Etiology
- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumour

Clinical Features
- usually acute (develops in less than 24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness/paraparesis in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
  - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
  - bilateral sensory loss or pain: depends on the level affected
  - saddle area (S2-S5) anesthesia
  - sexual dysfunction (late finding)

Investigations
- urgent MRI to confirm compression of S2-S3-S4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present; volumes controversial but anything over 250 cc in a healthy individual is cause for concerns
Treatment
- surgical decompression (<48 h) to preserve bowel, bladder, and sexual function, and/or to prevent progression to paraplegia
- Consult radiation oncology for urgent symptomatic management if palliative oncology patient

Prognosis
- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

Lumbar Spinal Stenosis

Etiology
- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

Clinical Features
- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

Investigations
- MRI is the optimal investigation to confirm and localize the level of stenosis (unlike nerve root compression which can be localized with clinical exam)

Treatment
- conservative: NSAIDs, analgesia
- surgical: laminectomy with root decompression (the role of fusion may need to be considered if the amount of bone removed with the laminectomy results in destabilization)

Neurogenic Claudication

Etiology
- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

Clinical Features
- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

Investigations
- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

Treatment
- same as for lumbar spinal stenosis

Surgical vs. Non-Operative Treatment for Lumbar Spinal Stenosis Four-Year Results of the Spine Outcomes Research Trial (SPORT)

Spine 2010. 35(14): 1329-1338

Objective: To compare 4 year outcomes of surgery to non-operative care for spinal stenosis.
Methods: Surgical candidates from 13 centers in 11 U.S. states with at least 12 weeks of symptoms and confirmatory imaging were enrolled in a randomized cohort (RC) or observational cohort (OC). Treatment was standard decompressive laminectomy or standard non-operative care. Primary outcomes were SF-36 bodily pain (BP) and physical function (PF) scales and the modified Oswestry Disability index (ODI) assessed at 6 weeks, 3 months, 6 months and yearly up to 4 years.
Conclusions: Patients with symptomatic spinal stenosis treated surgically compared to those treated non-operatively maintain substantially greater improvement in pain and function through four years.

Key Features of Neurogenic vs. Vascular Claudication

Neurogenic Claudication: dermatomal distribution with positional relief occurring over minutes
Vascular Claudication: sclerotomal distribution with relief occurring with rest over seconds
Intradural Intramedullary Lesions

Syringomyelia (Syrinx)

Definition
- Cystic cavitation of the spinal cord
- Presentation is highly variable, usually progresses over months to years
- Initially pain, weakness; later atrophy and loss of pain and temperature sensation

Etiology
- 70% are associated with Chiari I malformation, 10% with basilar invagination
- Post-traumatic
- Tumour
- Tethered cord

Clinical Features
- Nonspecific features for any intramedullary spinal cord pathology
  - Initially pain, weakness, atrophy, then loss of pain and temperature (spinothalamic tract) in upper extremities (central syrinx) with progressive myelopathy over years
  - Sensory loss with preserved touch and proprioception (DCML) in a band-like distribution at the level of cervical syrinx
  - Dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - Painless neuropathic arthropathies (Charcot’s joints), especially in the shoulder and neck due to loss of pain and temperature sensation

Investigations
- MRI is best method, myelogram with delayed CT

Treatment
- Treat underlying cause (e.g., posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)
- Rarely does the syrinx need to be shunted, only when progressive and size allows for insertion of tube

Spinal Cord Syndromes

Complete Spinal Cord Lesion
- Bilateral loss of motor/sensory and autonomic function at ≥4 segments below lesion/injury, with UMN signs
- About 3% of patients with complete injuries will develop some recovery within 24 h, beyond 24 h, no distal function will recover

Incomplete Spinal Cord Lesion
- Any residual function at ≥4 segments below lesion
- Signs include sensory/motor function in lower limbs and “sacral sparing” (perianal sensation, voluntary rectal sphincter contraction)

Table 17. Comparison Between Incomplete Spinal Cord Lesion Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Etiology</th>
<th>Motor</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown-Séquard</td>
<td>Hemisection of cord</td>
<td>Ipsilateral LMN weakness at the lesion</td>
<td>Ipsilateral loss of vibration and proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral UMN weakness below the lesion</td>
<td>Contralateral loss of pain and temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preserved light touch</td>
</tr>
<tr>
<td>Anterior Cord</td>
<td>Anterior spinal artery compression or occlusion</td>
<td>Bilateral LMN weakness at the lesion</td>
<td>Preserved vibration and proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bilateral UMN weakness below the lesion</td>
<td>Bilateral loss of pain and temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preserved light touch</td>
</tr>
<tr>
<td>Central Cord</td>
<td>Syringomyelia tumours, spinal hyperextension injury</td>
<td>Bilateral motor weakness: Upper limb weakness (LMN lesion) &gt; Lower limb weakness (UMN lesion)</td>
<td>Variable bilateral suspended sensory loss</td>
</tr>
<tr>
<td>(most common)</td>
<td></td>
<td></td>
<td>Loss of pain and temperature &gt; loss of vibration and proprioception</td>
</tr>
<tr>
<td>Posterior Cord</td>
<td>Posterior spinal artery infarction, trauma</td>
<td>Preserved</td>
<td>Bilateral loss of vibration, proprioception, light touch at and below the lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preserved pain and temperature</td>
</tr>
</tbody>
</table>

American Spinal Injury Association Impairment Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Complete, no motor/sensory below neurological level including S4/5</td>
</tr>
<tr>
<td>B</td>
<td>Incomplete, sensory but not motor function preserved below neurological level including S4/5</td>
</tr>
<tr>
<td>C</td>
<td>Incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade &lt;3</td>
</tr>
<tr>
<td>D</td>
<td>Incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade ≥3</td>
</tr>
<tr>
<td>E</td>
<td>Normal motor and sensory function</td>
</tr>
</tbody>
</table>

Figure 24. T1 weighted MRI of syringomyelia

Figure 25. Spinal cord lesion syndromes
Peripheral Nerves

• see Neurology, N36

Classification

Table 18. Seddon's Classification of Peripheral Nerve Injury

<table>
<thead>
<tr>
<th>Nerve Injury</th>
<th>Description</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurapraxia (class I)</td>
<td>Axon structurally intact but fails to function</td>
<td>Within hours to months (average 6-8 wk)</td>
</tr>
<tr>
<td>Axonotmesis (class II)</td>
<td>Axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury</td>
<td>Spontaneous axonal recovery at 1 mm/d, max at 1-2 yr</td>
</tr>
<tr>
<td>Neurotmesis (class III)</td>
<td>Nerve completely transected</td>
<td>Need surgical repair for possibility of recovery</td>
</tr>
</tbody>
</table>

Etiology

• ischemia
• nerve entrapment – nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve

Investigations

• clinical exam: power, sensation, reflexes, localization via Tinel's sign (paresthesias elicited by tapping along the course of a nerve)
• electrophysiological studies: EMG, nerve conduction study (assess nerve integrity and monitoring recovery after 2-3 wk post-injury)
• labs: blood work (e.g. CBC, TSH, Vitamin B12), CSF
• imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography, angiogram if vascular damage is suspected

Treatment

• early neurosurgical consultation if injury is suspected

Table 19. Treatment by Injury Type

<table>
<thead>
<tr>
<th>Injury</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrapment</td>
<td>Conservative: prevent repeated stress/injury, physiotherapy, NSAIDs, local anesthesia/steroid injection</td>
</tr>
<tr>
<td></td>
<td>Surgical: nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy failure of medical management</td>
</tr>
<tr>
<td>Stretch/contusion</td>
<td>Follow-up clinically for recovery; exploration if no recovery in 3 mo</td>
</tr>
<tr>
<td>Axonotmesis</td>
<td>If no evidence of recovery, resect damaged segment</td>
</tr>
<tr>
<td></td>
<td>Prompt physical therapy and rehabilitation to increase muscle function, maintain joint ROM, maximize return of useful function</td>
</tr>
<tr>
<td></td>
<td>Recovery usually incomplete</td>
</tr>
<tr>
<td>Neurotmesis</td>
<td>Surgical repair of nerve sheath unless known to be intact (suture nerve sheaths directly if ends approximate or nerve graft (usually sural nerve))</td>
</tr>
<tr>
<td></td>
<td>Clean laceration: early exploration and repair</td>
</tr>
<tr>
<td></td>
<td>Contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 d</td>
</tr>
</tbody>
</table>

Complications

• neuropathic pain: with neuroma formation
• complex regional pain syndrome: with sympathetic nervous system involvement

SPECIALTY TOPICS

Neurotrauma

Trauma Management (see Emergency Medicine, ER7)

Indications for Intubation in Trauma

1. depressed LOC (patient cannot protect airway); usually GCS ≤8
2. need for hyperventilation
3. severe maxillofacial trauma: patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management

• if basal skull fracture suspected, avoid nasotracheal intubation as may inadvertently enter brain
• note: intubation prevents patient’s ability to verbalize for determining GCS

Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye Response</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 spontaneous</td>
<td>5 oriented</td>
<td>6 obeys commands</td>
</tr>
<tr>
<td>3 opens eyes to voice</td>
<td>4 confused</td>
<td>5 localizes to pain</td>
</tr>
<tr>
<td>2 opens eyes to pain</td>
<td>3 inappropriate words</td>
<td>4 withdraws from pain</td>
</tr>
<tr>
<td>1 no eye opening</td>
<td>2 incomprehensible sounds</td>
<td>3 flexion to pain (decorticate posture)</td>
</tr>
<tr>
<td>1 no response</td>
<td>2 extension to pain (decrebrate posture)</td>
<td></td>
</tr>
<tr>
<td>T intubated</td>
<td>1 no response</td>
<td></td>
</tr>
</tbody>
</table>

Best response for each component recorded individually: (e.g. E4V3M2) w/13 is mild injury; 9-12 is moderate injury; ≤8 is severe injury
Trauma Assessment

Initial Management

ABCs of Trauma Management
- see Emergency Medicine, ER2

NEUROLOGICAL ASSESSMENT

Mini-History
- period of LOC, post-traumatic amnesia, loss of bowel/bladder control, loss of sensation, weakness, type of injury/accident

Neurological Exam
- GCS
- head and neck (lacerations, bruises, basal skull fracture signs, facial fractures, foreign bodies)
- spine (palpable deformity, midline pain/tenderness)
- eyes (pupillary size and reactivity)
- brainstem (breathing pattern, CN palsies)
- cranial nerve exam
- motor exam, sensory exam (only if GCS is 15), reflexes
- sphincter tone, saddle sensation
- record and repeat neurological exam at regular intervals

Investigations
- spinal injury precautions (cervical collar) are continued until C-spine is cleared
- C,T,L-spine x-rays
  - AP, lateral, odontoid views for C-spine (must see from C1 to T1; swimmer's view if necessary) or CT
  - rarely done: oblique views looking for pars interarticularis fracture (“Scottie dog” sign)
- CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
- cross and type, ABG, CBC, drug screen (especially alcohol)
- chest and pelvic x-ray as indicated

TREATMENT

Treatment for Minor Head Injury (GCS 13-15)
- observation over 24-48 h
- wake every hour
- judicious use of sedatives or pain killers during monitoring period
- outpatient: advise patients to undergo stepwise approach to return to play and return to school (include references for these new recommendations)

Treatment for Severe Head Injury (GCS ≤8)
- clear airway and ensure breathing (if GCS ≤8, intubate)
- secure C-spine
- maintain adequate BP
- monitor for clinical deterioration
- monitor and manage increased ICP if present (see Herniation Syndromes, NS7)

Admission required if:
- skull fracture (indirect signs of basal skull fracture, see Head Injury, NS32)
- confusion, impaired consciousness, concussion with >5 min amnesia
- focal neurological signs, extreme H/A, vomiting, seizures
- unstable spine
- use of alcohol
- poor social support
Head Injury

Epidemiology
- M:F = 2-3:1

Pathogenesis
- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

Scalp Injury
- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

Skull Fractures
- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
  - internal fractures into sinus may lead to meningitis, pneumocephalus
  - risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray, rely on clinical signs
  - retroauricular ecchymoses (Battle’s sign)
  - periorbital ecchymoses (raccoon eyes)
  - hemotympanum
  - CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

Cranial Nerve Injury
- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VIII: repair of ossicles
- CN injuries that improve
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
  - CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

Arterial Injury
- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

Intracranial Bleeding
- see Blood, NS16 and Cerebrovascular Disease, NS18

Brain Injury

Primary Impact Injury
- mechanism of injury determines pathology: penetrating injuries, direct impact
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- concussion: a trauma-induced alteration in mental status
  - American Academy of Neurology (AAN) Classification
  - no parenchymal abnormalities on CT
- coup (damage at site of blow) and contrecoup (damage at opposite site of blow) (Figure 27)
  - acute decompression causes cavitation followed by a wave of acute compression
- contusion (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space-occupying lesion on CT

The Canadian CT Head Rule for Patients with Minor Head Injury
Lancet 2001;357:1391-1396
CT Head is only required for patients with minor head injuries with any one of the following
High Risk (for neurological intervention)
- GCS score <15 at 2 h after injury.
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture (hemotympanum, “raccoon” eyes, cerebrospinal fluid otorrhea/ rhinorrhea, Battle’s sign)
- Vomiting ≥2 episodes
- Age ≥65 yr.

Medium Risk (for brain injury on CT)
- Amnesia after impact >30 min.
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs).

Minor Head Injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

Figure 27. CT showing coup-contrecoup injury

AAN Classification
Grade 1: altered mental status <15 min
Grade 2: altered mental status >15 min
Grade 3: any loss of consciousness

SIADH → hyponatremia
DI → hypernatremia
Secondary Pathologic Processes
• same subsequent biochemical pathways for each traumatic etiology
• delayed and progressive injury to the brain due to
  • high glutamate release → NMDA receptor activation → cytotoxic cascade
  • cerebral edema
  • intracranial hemorrhages
  • ischemia/infarction
  • raised ICP, intracranial HTN
  • hydrocephalus

Extracranial Conditions
• hypoxemia
  • due to trauma to the chest, upper airway, brainstem
  • extremely damaging to vulnerable brain cells
  • leads to ischemia, raised ICP
• hypovolemia
  • leads to raised ICP (secondary to vasodilation)
  • systemic hypotension
  • caused by blood loss (e.g. ruptured spleen)
  • loss of cerebral autoregulation leads to decreased CPP ischemia
• hypothermia
  • leads to increased brain metabolic demands → ischemia
  • fluid and electrolyte imbalance
  • iatrogenic (most common)
  • SIADH caused by head injury
  • diabetes insipidus (DI)
  • may lead to cerebral edema and raised ICP
  • coagulopathy

Intracranial Conditions
• raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

Brain Injury Outcomes
• mildly traumatic (GCS 13-15): post-concussive symptoms: H/A, fatigue, dizziness
• nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
• moderately traumatic (GCS 9-12): proportional to age (>40) and CT findings; 60% good recovery 26% moderately disabled, 7% severely disabled 7% vegetative/dead
• severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

Late Complications of Head/Brain Injury
• seizures: 5% of head injury patients develop seizures
  • incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
  • post-traumatic seizure may be immediate, early, or late
  • presence of early (within first wk) post-traumatic seizure raises incidence of late seizures
• meningitis: associated with CSF leak from nose or ear
• hydrocephalus: acute hydrocephalus or delayed normal pressure hydrocephalus (NPH)
• Post-Concussion Syndrome (PCS)/neuro-psychiatric effects

Spinal Cord Injury
• see Orthopedics, OR22 and Emergency Medicine, ER9

NEUROGENIC AND SPINAL SHOCK
1. neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by
  • interruption of sympathetics (unopposed parasympathetics) below the level of injury
  • loss of muscle tone due to skeletal muscle paralyis below level of injury → venous pooling (relative hypovolemia)
  • blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the spinal cord injury, causing flacid paralysis and areflexia for variable periods

Whiplash-Associated Disorders
• definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck
Initial Management of SCI
- major causes of death in SCI are aspiration and shock
- the following patients should be treated as having a SCI until proven otherwise:
  - all victims of significant trauma
  - minor trauma patients with decreased LOC or compla nts of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

Stabilization and Initial Evaluation in the Hospital
1. ABCs, immobilization (backboard/head strap), oxygenation, Foley catheter to urometer, temperature regulation
2. hypotension: maintain SBP >90 mmHg with pressors (dopamine), hydration, and atropine
   ■ DVT prophylaxis
3. monitor CBC/electrolytes
4. focused history (see Trauma Assessment, NS29)
5. spine palpation: point tenderness or deformity
6. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
7. sensory level assessment: pinprick, light touch, and proprioception
8. evaluation of reflexes
9. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
10. radiographic evaluation
    ■ 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction
    ■ flexion-extension views to disclose occult instability
    ■ CT scan (bony injuries) typically most trauma centres use CT as the modality of choice for looking at fractures, very sensitive with the high resolution scanners
    ■ MRI mandatory if neurological deficits (soft tissue injuries)

Medical Management Specific to SCI
- option: methylprednisolone (given within 8 h of injury) this is controversial and you need to confer with Neurosurgery service
- ± decompression in acute non penetrating SCI

Fractures of the Spine

FRACTURES AND FRACTURE-DISLOCATIONS OF THE THORACIC AND LUMBAR SPINE
- assess ligamentous instability using flexion/extension x-ray views of ± MRI
- thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
  ■ anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
  ■ middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
  ■ posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspous, and ligamentum ligaments

Types of Injury

Table 20. Denis Classification of Spinal Trauma

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression Fracture (58%)</td>
<td>Produced by flexion Posterior ligamentum complex (supraspinous and interspinous ligaments, ligamentum flavum, and intervertebral joint capsules) remain intact Fractures are stable but lead to kyphotic deformity</td>
</tr>
<tr>
<td>Burst Fracture (17%)</td>
<td>Stable: anterior and middle columns parted with bone retropulsed nearby Hallmark is pedicle widening on AP x-ray Spinal cord (seen on x-ray and CT) posterior column is uninjured Unstable: same as the stable but with posterior column disruption (usually ligamentous)</td>
</tr>
<tr>
<td>Flexion Distraction Injury (6%)</td>
<td>Hyperflexion and distraction of posterior elements Middle and posterior columns fail in distraction Classic: Chance = horizontal fracture through posterior arch, pedicles, posterior vertebral body Can be purely ligamentous, i.e. through PLL and disc</td>
</tr>
<tr>
<td>Fracture-Dislocation (6%)</td>
<td>Anterior and cranial dislocation of superior vertebral body → 3 column failure Three types: (1) flexion-rotation, (2) flexion-distraction, (3) shear/hyperextension (rare)</td>
</tr>
</tbody>
</table>

Management of Thoracolumbar Injury
- severity and management based on TLICS classification
FRACTURES OF THE CERVICAL SPINE

Types of Injury

Table 21. Fracture Patterns of the Cervical Spine

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 Vertebral Fracture (Jefferson fracture)</td>
<td>Vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas) pushing the lateral masses of the atlas outward and disrupting the ring of the atlas Also can cause an occipital condylar fracture</td>
</tr>
<tr>
<td>Odontoid Fracture</td>
<td>Causes C1 and odontoid of C2 to move independently of C2 body This occurs because Normally C1 vertebra and odontoid of C2 are a single functional unit Alar and transverse ligaments on posterior aspect of odontoid usually remain intact after injury Patients often report a feeling of instability and present holding their head with their hands Type II fracture the most common</td>
</tr>
<tr>
<td>C2 Vertebral Fracture (hangman fracture)</td>
<td>Bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3 (spondylolisthesis of axis) Usually neurologically intact</td>
</tr>
<tr>
<td>Clay-Shoveler Fracture</td>
<td>Avulsion of spinous process, usually C6 or C7</td>
</tr>
</tbody>
</table>

Imaging

- AP spine x-ray (open-mouth and lateral view), CT

Treatment

- immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
- Type II and III odontoid fractures
- consider surgical fixation for comminution, displacement, or inability to maintain alignment with external immobilization
- confirm stability after recovery with flexion-extension x-rays

Neurologically Determined Death

Definition

- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascula activity may persist for up to 2 wk

Criteria of Diagnosis

- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/ poisoning, temperature >32ºC, no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes: pupillary light reflex, corneal reflexes, oculocephalic response, caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides), pharyngeal and tracheal reflexes, cough with tracheal suctioning, absent respiratory drive at PaCO2 >60 mmHg or >20 mmHg above baseline (apnea test)
- 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
- confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

Coma

Definition

- an unrousable state in which patients show no meaningful response to environmental stimuli

Pathophysiology

- lesions affecting the cerebral cortex bilaterally, the reticular activating system (RAS) or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

Classification

- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B12)
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
- infections (meningitis, encephalitis)
- trauma (concussion, diffuse axonal damage)
Investigations and Management
- **ABCs**
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP, EEG

**Persistent Vegetative State**

**Definition**
- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- "awake but not aware"
- follows comatose state

**Etiology/Prognosis**
- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

---

**Pediatric Neurosurgery**

**Spinal Dysraphism**

- spinal dysraphism refers to a spectrum of congenital anomalies resulting in a defective neural arch through which CNS elements are herniated
- the spectrum is divided largely into aperta (visible lesion; no skin covering) and occulta (no visible lesion; skin covering)

**Table 22. Summary of Spinal Dysraphic Anomalies**

<table>
<thead>
<tr>
<th>SPINA BIFIDA OCCULTA</th>
<th>MENINGOCELE (SPINA BIFIDA APERTA)</th>
<th>MYELOMENINGOCELE (SPINA BIFIDA APERTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Congenital absence of a spinous process and a variable amount of lamina No visible exposure of meninges or neural tissue</td>
<td>Herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>15-20% of the general population; most common at L5 or S1</td>
<td>0.1-0.2% of live births</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Failure of fusion of posterior neural arch</td>
<td>Primary failure of neural tube closure</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>No obvious clinical signs Presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia)</td>
<td>Most common in lumbosacral area Usually no disability, low incidence of associated anomalies, and hydrocephalus Sensory and motor changes distal to anatomic level producing varying degrees of weakness Urinary and fecal incontinence Hydrocephalus (65-85% of patients) Most have Type II Chiari malformation (see Chiari Malformations, NS38)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Plain film: absence of the spinous process and minor amounts of the neural arch U/S, MRI to exclude spinal anomalies</td>
<td>Plain films, CT, MRI, U/S, echo, GU investigations</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Requires no treatment</td>
<td>Surgical excision and tissue repair</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Generally good prognosis</td>
<td>Good prognosis with surgical treatment</td>
</tr>
</tbody>
</table>

---

Figure 29. Spina bifida Occulta, Meningocele, Myelomeningocele
Intraventricular Hemorrhage

- see Pediatrics, P63

Hydrocephalus in Pediatrics

Etiology
- congenital
  - aqueductal anomalies, primary aqueductal stenosis in infancy
  - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  - Dandy-Walker malformation (2-4%)
  - Chiari malformation, especially Type II
  - myelomeningocele
- acquired
  - post meningitis
  - post hemorrhage (SAH, IVH)
  - masses (vascular malformation, neoplastic)

Clinical Features
- symptoms and signs of hydrocephalus are age related in pediatrics
- increased head circumference (HC), bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding, and vomiting
- "cracked pot" sound on cranial percussion
- scalp vein dilation (increased collateral venous drainage)
- sunset sign – forced downward deviation of eyes
- episodic bradycardia and apnea

Investigations
- skull x-ray, U/S, CT, MRI, ICP monitoring

Treatment
- similar to adults (see Hydrocephalus Treatment, NS9)

Dandy-Walker Malformation

Definition
- atresia of foramina of Magendie and Luschka, resulting in:
  - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic cerebellar hemispheres
  - can be detected in utero
  - posterior fossa cyst, enlarged posterior fossa
  - dilatation of 4th ventricle (also 3rd and lateral ventricles)
- associated anomalies
  - hydrocephalus (90%)
  - agenesis of corpus callosum (17%)
  - occipital encephalocele (7%)

Epidemiology
- 2-4% of pediatric hydrocephalus

Clinical Features
- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

Investigations
- ultrasound, CT, MRI

Treatment
- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
  - e.g. ventriculoperitoneal (VP) shunt, cystoperitoneal (CP) shunt, lumboperitoneal (LP) shunt,
    ventriculoatrial (VA) shunt, lumbar drain

Prognosis
- 75-100% survival, 50% have normal IQ
Chiari Malformations

Definition
• malformations at the medullary-spinal junction

Etiology
• unclear, likely maldevelopment/dysgenesis during fetal life

Categories

Table 23. Categories of Chiari Malformations

<table>
<thead>
<tr>
<th>Category</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Cerebellar tonsils lie below the level of the foramen magnum</td>
<td>Part of cerebellar vermis, medulla, and 4th ventricle extend through the foramen magnum often to midcervical region</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Average age at presentation 15 yr</td>
<td>Present in infancy</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Many are asymptomatic</td>
<td>Find ngs due to brainstem and lower cranial nerve dysfunction</td>
</tr>
<tr>
<td></td>
<td>Pain (69%), weakness (56%), numbness (52%), loss of tempera-ture sensation (40%)</td>
<td>Neurogenic dysphagia (69%), apnea (58%), stridor (56%), aspiration (40%), arm weakness (27%), downbeat nystagmus</td>
</tr>
<tr>
<td></td>
<td>Central cord syndrome (65%)</td>
<td>Respiratory arrest is the most common cause of mortality</td>
</tr>
<tr>
<td></td>
<td>Foramen magnum compression syndrome (22%), Cerebellar syndrome (11%),</td>
<td>Usually associated with myelomingocele and hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Syringomyelia (60%), Hydrocephalus (10%)</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>MRI</td>
<td>MRI</td>
</tr>
<tr>
<td>Treatment</td>
<td>Symptomatic patients (early surgery recommended; &lt;2 yr post symptom onset) → suboccipital craniectomy, duraplasty</td>
<td>Preserved When symptomatic, check the shunt first. Then consider surgical decompression (which does not reverse intrinsic brainstem abnormalities) → cervical laminectomy, duraplasty</td>
</tr>
</tbody>
</table>

Craniosynostosis

Definition
• premature closure of the cranial suture(s)

Classification
• sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
• coronal: expansion in superior and lateral direction (brachiocephaly)
• metopic (trigonocephaly)
• lambdoid: least common

Epidemiology
• 0.6/1,000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

Clinical Features
• skull deformity raised ICP ± hydrocephalus
• ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
• must differentiate between positional plagiocephaly (secondary to back sleeping)

Investigations
• plain radiographs, CT scan

Treatment
• parental counselling about nature of deformity, associated neurological symptoms
• surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)
Pediatric Brain Tumours

- see Tumours, NS11

Epidemiology
- 20% of all pediatric cancers (second only to leukemia)
- 60% of pediatric brain tumours are infratentorial
- pediatric brain tumours arise from various cellular lineages
  - glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see Astrocytoma, NS12)
  - primitive nerve cells: supratentorial PNET
  - 90% of neonatal brain tumours, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
  - neuronal cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma (schwanoma), pituitary adenoma, others

Clinical Features
- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escapes diagnosis due to expansile cranium and neural plasticity in children

Table 24. Overview of Childhood Primary Brain Tumours*

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Clinical Features</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic (low grade) Astrocytoma</td>
<td>Usually in posterior fossa</td>
<td>Well circumscribed</td>
</tr>
<tr>
<td></td>
<td>Benign, good prognosis</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>A primitive neuroectodermal tumour (PNET)</td>
<td>In cerebellum → compresses 4th ventricle → hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Highly malignant</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>In 4th ventricle → hydrocephalus</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>Often cerebellar</td>
<td>Associated with von Hippel-Lindau syndrome with retinal angiomas</td>
</tr>
<tr>
<td></td>
<td>Can produce EPO → secondary polycythemia</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Causes bitemporal hemianopsia (thus often confused with pituitary adenoma)</td>
<td>Most common supratentorial childhood tumour</td>
</tr>
<tr>
<td></td>
<td>Most common supratentorial childhood tumour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

* See also, Familial Cancer Syndromes, Medical Genetics chapter page (TBD)

Functional Neurosurgery

Movement Disorders

- see Neurology, Tremor, N31, Parkinson’s Disease, N32, Dystonia, N33, and Multiple Sclerosis, N52

Table 25. Surgical Targets for Movement Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td>Intractable contralateral bradykinesia/tremor</td>
<td>Simultaneous, bilateral surgery/stimulation is most common</td>
<td>39-48% improvement in Unified Parkinson Disease Rating Scale (UPDRS) scores</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%)</td>
</tr>
<tr>
<td></td>
<td>Failure of medical management (advanced disease)</td>
<td>Preferred target: anterodorsal subthalamic nucleus (STN)</td>
<td>More effective than medical management in advanced PD</td>
<td>Paresthesia</td>
</tr>
<tr>
<td></td>
<td>Drug-induced dyskinesias (see dystonia, below)</td>
<td>Other targets: stereotactic ablation (gallium) stimulation of posteroventral globus pallidus pars interna (GPi)</td>
<td>Early intervention may reduce severity, course, and progression of disease</td>
<td>Involuntary movements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudal zona incerta</td>
<td>Of little benefit for patients with atypical presentations</td>
<td>Cognitive functioning: decreased lexical fluency, impaired executive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus</td>
<td></td>
<td>(STN &gt; GPi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Psychiatric: depression, mania, anxiety, apathy (STN &gt; GPi)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Contralateral primary (generalized) dystonia: cervical and tardive dystonias (GPi)</td>
<td>Preferred target (primary dystonia): stereotactic ablation (gallium) stimulation of posteroventral GPi</td>
<td>Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDRS) score</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%)</td>
</tr>
<tr>
<td></td>
<td>Contralateral secondary dystonias (i.e. drug-induced: L-dopa, neuropetics; STN)</td>
<td>Secondary dystonia: stimulation of anterdorsal STN</td>
<td>Secondary dystonia: 62-89% improvement in dystonias</td>
<td>Minor effects on cognitive functioning (especially decreased lexical fluency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulation of ventral posterior lateral (VPL) thalamic nucleus</td>
<td>Delayed effects: weeks to months</td>
<td>(STN &gt; GPi)</td>
</tr>
<tr>
<td>Tremor</td>
<td>Contralateral appendicular ET (first disorder to be treated by DBS; DBS is viable alternative to Rx)</td>
<td>Preferred target: stereotactic ablation (thalamotomy)/stimulation of Vim nucleus of thalamus</td>
<td>Durable reductions in essentail tremor rating scale (ERTS) scores</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%)</td>
</tr>
<tr>
<td></td>
<td>Intention tremor (IT) resulting from demyelination of cerebellar outflow tracts (e.g. in multiple sclerosis)</td>
<td>Other targets: stimulation of caudal zona incerta</td>
<td>Reduced dosage of medications</td>
<td>Paresthesia/pain</td>
</tr>
<tr>
<td></td>
<td>Brachial tremor (Holmes tremor)</td>
<td>Parkinsonian tremor: stimulation of anterdorsal STN</td>
<td>Conflicting data on vocal/facial tremor</td>
<td>Dysarthria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minor effects on cognitive functioning (especially decreased lexical fluency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tolerance may develop over time</td>
</tr>
</tbody>
</table>
Neuropsychiatric Disorders

- see Neurology N20 and Psychiatry for Tourette’s Syndrome, Obsessive Compulsive Disorder and Depression

Table 26. Surgical Targets for Neuropsychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive Compulsive Disorder (OCD)</td>
<td>Severe symptoms refractory to medical management</td>
<td>Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC)</td>
<td>Currently under investigation</td>
<td>Reportedly 25-75% response rate</td>
</tr>
<tr>
<td>Tourette’s Syndrome</td>
<td>Severe symptoms refractory to medical management</td>
<td>Stimulation of midline intralaminar nuclei of the thalamus Stimulation of motor and limbic portions of GPi Stimulation of the anterior limb of the IC</td>
<td>Currently under investigation</td>
<td>Reportedly &gt;70% reduction in vocal or motor tics + urge</td>
</tr>
<tr>
<td>Major Depressive Disorder (MDD)</td>
<td>Severe depression refractory to medical management and ECT</td>
<td>Stimulation of the subgenual cingulate cortex</td>
<td>Currently under investigation</td>
<td>Reportedly 60% response rate; 35% remission rate</td>
</tr>
</tbody>
</table>

Chronic Pain

Table 27. Surgical Targets for Chronic Pain

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain</td>
<td>Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, post-operative neuropathic pain) complex regional pain syndrome</td>
<td>Preferred target: stimulation of the contralateral VPL VPM thalamic nuclei ± periventricular/periaqueductal grey matter (PVG/PAG) Other targets: stimulation of the contralateral IC Stimulation of the contralateral motor cortex For post-operative neuropathic pain, surgical procedure may be aimed at correcting any identifiable residual deformity from prior spine surgery. Surgery is not primary modality if no structurally correctable radiologic findings</td>
<td>47% improvement in perception of pain intensity Less favourable results in central pain syndromes and poorly localized pain</td>
<td>Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder</td>
</tr>
<tr>
<td>Nociceptive Pain</td>
<td>Severe, intractable, organic nociceptive pain</td>
<td>Bilateral (most common) stimulation of the PVG/PAG</td>
<td>Reportedly 63% improvement in perception of pain intensity</td>
<td>Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder</td>
</tr>
</tbody>
</table>
Surgical Management of Epilepsy

- see Neurology, N19 for the medical treatment of epilepsy

Indications
- medically refractory seizures, usually defined as seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing; other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

Procedure
- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common

Outcomes
- 41-79% of adult patients are seizure free for 5 yr after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

Morbidity
- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anteromedial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 yr

Predictors
- positive predictive factors for seizure freedom following anteromedial temporal lobectomy
  - hippocampal sclerosis (unilateral)
  - focal localization of interictal epileptiform discharges
  - absence of pre-operative generalized seizures
  - tumoural cause
  - complete resection of the lesion

Surgical Management for Trigeminal Neuralgia

- reserved for cases refractory to medical management; see Neurology, N42 for medical management

Surgical Options
- trigeminal nerve branch procedures
  - local blocks (phenol, alcohol)
  - neurectomy of the trigeminal branch
  - nerve branches
  - V1 block at the supraorbital, supratrochlear nerves
  - V2 block at the foramen rotundum or infraorbital nerves
  - V3 block at the foramen ovale
- percutaneous trigeminal rhizotomy
  - glycerol injection
  - mechanotrauma via catheter balloon
  - radiofrequency thermocoagulation
  - Gamma Knife® radiosurgery
  - microvascular decompression
  - posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable Teflon® felt
Obstetrics

Emily Bartsch, Stephanie Searle, and Curtis Sobchak, chapter editors
Sangwoo Leem and Mark Shafarenko, associate editors
Jin Kyu Kim and Shubham Shan, EBM editors
Dr. Richard Pittini and Dr. Amanda Selk, staff editors

Acronyms ............................................. 2
Basic Anatomy Review ............................... 2
Pregnancy .............................................. 2
Diagnosis of Pregnancy

Maternal Physiologic Adaptations to Pregnancy . 3

Antepartum Care ......................................... 4
Preconception Counselling
Initial Prenatal Visit
Nausea and Vomiting
Hyperemesis Gravidarum
Subsequent Prenatal Visits
Prenatal Screening and Diagnostic Tests

Counselling of the Pregnant Woman ................. 9
Nutrition
Lifestyle
Medications
Immunizations
Radiation

Antenatal Fetal Surveillance ......................... 12
Fetal Movements

Obstetrical Hemorrhage .............................. 13
Placenta Previa
Abruptio Placentae
Vasa Previa

Obstetrical Complications ............................ 15
Preterm Labour
Premature Rupture of Membranes
Postterm Pregnancy
Intrauterine Fetal Death (Demise)
Intrauterine Growth Restriction
Macrosomia
Polyhydramnios/Oligohydramnios

Multi-Fetal Gestation and Malpresentation . . . 21
Twin-Twin Transfusion Syndrome
Breech Presentation

Hypertensive Disorders of Pregnancy .............. 23
Hypertension in Pregnancy

Medical Complications of Pregnancy ............... 25
Iron and Folate Deficiency Anemia
Diabetes Mellitus
Group B Streptococcus
Urinary Tract Infection
Infections During Pregnancy
Venous Thromboembolism

Normal Labour and Delivery ........................ 30
Definition of Labour
The Cervix
The Fetus
Four Stages of Labour

The Cardinal Movements of the Fetus During Delivery
Analgesic and Anesthetic Techniques in Labour and Birth
Fetal Monitoring in Labour

Induction of Labour ................................... 36
Induction Methods
Augmentation of Labour

Abnormalities and Complications of Labour and Delivery ......................... 37
Abnormal Progression of Labour (Dystocia)
Shoulder Dystocia
Umbilical Cord Prolapse
Uterine Rupture
Amniotic Fluid Embolus
Chorioamnionitis
Meconium

Operative Obstetrics ................................. 41
Operative Vaginal Delivery
Forceps
Vacuum Extraction
Lacerations
Episiotomy
Cesarean Delivery
Trial of Labour after Cesarean Section (TOLAC)

Puerperal Complications ............................. 43
Postpartum Hemorrhage
Retained Placenta
Uterine Inversion
Postpartum Pyrexia
Mastitis
Postpartum Mood Alterations

Postpartum Care ........................................ 46
Breastfeeding and Drugs

Common Medications ................................. 47

References .............................................. 48
Basic Anatomy Review

Placenta
- site of fetal nutritive, respiratory, and excretory function
- discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- produces hormones such as progesterone, placental lactogen, estrogen, relaxin, β-hCG, and IGFs
- poor implantation can lead to spontaneous abortion
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see Obstetrical Hemorrhage, OB13)

Pregnancy

Diagnosis of Pregnancy

History
- symptoms: amenorrhea, nausea and/or vomiting, breast tenderness, urinary frequency, and fatigue
- obstetrical and gynecological history
- obtain the year, location, mode of delivery, duration of labour, sex, gestational age, birth weight, and complications of every pregnancy; organize into GTPAL format
  - Gravidity (G)
    - G: total number of pregnancies of any gestation (multiple gestation=one pregnancy)
    - includes current pregnancy, abortions, ectopic pregnancies, and hydatidiform moles
Maternal Physiologic Adaptations to Pregnancy

Table 1. Physiologic Changes During Pregnancy

| Skin | Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation), spider angiomas, palmar erythema due to increased estrogen, striae gravidarum due to connective tissue changes |
| Cardiovascular | Hyper-dynamic circulation  
| | Increased CO, H, and blood volume  
| | Decreased blood pressure: decreased PVR and decreased venous return from enlarging uterus compressing IVC and pelvic veins  
| | Increased venous pressure leads to risk of varicose veins, hemorrhoids, leg edema |
| Hematologic | Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit  
| | β-hCG: peptide hormone composed of α and β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy  
| | • positive in serum 9 d post-conception, positive in urine 28 d after first day of LMP  
| | • plasma levels usually double every 1.4-2.0 d, peak at 8-10 wk, then fall to a plateau until delivery levels less than expected suggest: ectopic pregnancy, abortion, inaccurate dates, and some normal pregnancies  
| | • levels greater than expected suggest: multiple gestation, molar pregnancy, Trisomy 21, or inaccurate dates |
| Respiratory | Increased incidence of nasal congestion  
| | Hyperdynamic circulation  
| | Increased D: consumption to meet increased metabolic requirements  
| | Elevated diaphragm (i.e. patient appears more "barrel-chested")  
| | Increased minute ventilation leads to decreased CO2 resulting in mild respiratory alkalosis that helps CO2 diffuse across the placenta from fetal to maternal circulation  
| | Decreased TLC, FRC, and RV  
| | No change in VC and FEV: |
| Gastrointestinal | GERD due to increased intra-abdominal pressure and progesterone (causing decreased sphincter tone and delayed gastric emptying)  
| | Increased gallstones due to progesterone causing increased gallbladder stasis  
| | Constipation due to progesterone causing decreased GI motility and hemorrhoids as a result of constipation and increased intra-abdominal pressure |
| Genitourinary | Increased urinary frequency due to increased total urinary output  
| | Increased incidence of UTI and pyelonephritis due to urinary stasis (see Urinary Tract Infection, OB28)  
| | Glycosuria that can be physiologic especially in the 3rd trimester, consider testing for GDM if noted in first 2 trimesters  
| | Ureters and renal pelvis dilation (P>L): due to progesterone-induced smooth muscle relaxation and uterine enlargement  
| | Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 35-44 mmol/L), uric acid, and BUN |
| Neurologic | Increased incidence of carpal tunnel syndrome and Bell’s palsy |
| Endocrine | Thyroid: moderate enlargement (not clinically detectable) and increased basal metabolic rate  
| | Increased total thyroxine and thyroxine binding globulin (TBG)  
| | Free thyroxine index and TSH levels are normal  
| | Adrenal: maternal cortisol rises throughout pregnancy (total and free)  
| | Calcium: decreased total maternal Ca2+ due to decreased albumin  
| | Free ionized Ca2+ (i.e. active) proportion remains the same due to parathyroid hormone (PTH), results in increased bone resorption and gut absorption, increased bone turnover (but no loss of bone density due to estrogen inhibition) |

Parity (TPAL)  
- T: number of term infants delivered (>37 wk)  
- P: number of premature infants delivered (20-36+6 wk)  
- A: number of abortions (loss of intrauterine pregnancy prior to viability of fetus <20 wk and/or <500 g fetal weight)  
  - induced (therapeutic) and spontaneous (miscarriage)  
- L: number of living children

Physical Signs  
- Goodell's sign: softening of the cervix (4-6 wk)  
- Chadwick's sign: bluish discoloration of the cervix and vagina due to pelvic vasculature engorgement (6 wk)  
- Hegar's sign: softening of the cervical isthmus (6-8 wk)  
- uterine enlargement  
- breast engorgement, areola darkening, and prominent vascular patterns

Investigations  
- β-hCG: peptide hormone composed of α and β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy  
  - positive in serum 9 d post-conception, positive in urine 28 d after first day of LMP  
  - plasma levels usually double every 1.4-2.0 d, peak at 8-10 wk, then fall to a plateau until delivery  
  - levels less than expected suggest: ectopic pregnancy, abortion, inaccurate dates, and some normal pregnancies  
  - levels greater than expected suggest: multiple gestation, molar pregnancy, Trisomy 21, or inaccurate dates  
- U/S:  
  - transabdominal  
  - 5 wk amenorrhea: gestational sac visible  
  - 6 wk: fetal pole visible  
  - 7-8 wk: fetal heart activity visible  
  - transvaginal  
  - 6-8 wk: intrauterine pregnancy visible
Antepartum Care

• can be provided by obstetrician, family physician, midwife, or multidisciplinary team (based on patient preference and risk factors)

Preconception Counselling

• 3-8 wk GA is a critical period of organogenesis, so early preparation is vital
• past medical history: optimize illnesses and medications prior to pregnancy (see Medical Complications of Pregnancy, OB25, and Medications, OB10)
• supplementation
  • folic acid: encourage diet rich in folic acid and supplementation 8-12 wks pre-conception until end of T1 to prevent NTDs
    • 0.4-1 mg daily in all women; 5 mg if previous NTD, antiepileptic medications, DM, or BMI >35 kg/m²
  • iron supplementation, prenatal vitamins
• risk modification
  • lifestyle: balanced nutrition and physical fitness
  • medications: discuss teratogenicity of medications so they may be adjusted or stopped if necessary
  • infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV, TB testing based on travel and health care worker, history of varicella or vaccination, parvovirus immunity if exposed to small children, cytomegalovirus immunity if health care worker, toxoplasmosis serology if cats or gardening, last pertussis vaccine
  • genetic testing as appropriate for high risk groups (see Prenatal Screening, Table 2); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay, birth anomalies, genetic diseases, consanguinity
  • social: smoking, alcohol, drug use, domestic violence (see Family Medicine, FM11, FM12, FM26)

Initial Prenatal Visit

• usually within 8-12 wk of the first day of LMP or earlier if <20 or >35 yr old, bleeding, very nauseous, or other risk factors present

History

• gestational age by dates from the first day of the LMP
  • Naegle’s rule: 1st day of LMP + 1 y + 7 days – 3 months
  • e.g. LMP = 1 Apr 2014, EDC = 8 Jan 2015 (modify if cycle >28 d by adding number of d >28)
  • if LMP unreliable, get a dating ultrasound which could coincide with nuchal translucency at ~12 wk
  • dates should change if T1 U/S is greater than 5 days in difference from LMP due date
  • history of present pregnancy (e.g. bleeding, N/V) and all previous pregnancies
  • past medical, surgical, and gynecological history
  • prescription and non-prescription medications
  • family history: genetic diseases, birth defects, multiple gestation, consanguinity
  • social history: smoking, alcohol, drug use, domestic violence (see Family Medicine, FM11, FM12, FM26)

Physical Exam

• complete physical exam to obtain baseline patient information  BP and weight important for interpreting subsequent changes

Investigations

• blood work
  • CBC, blood group and Rh status, antibody screen, infection screening as per preconception counselling
  • urine R&B, midstream urine C&S
  • screen for bacteriuria and proteinuria
• pelvic exam
  • Pap smear (only if required according to patient history and provincial screening guidelines), cervical or urine PCR for N gonorrhoeae (GC) and C. trachomatis

Nausea and Vomiting

Epidemiology

• affects 50-90% of pregnant women
• often limited to T1 but may persist beyond this
Management
- rule out other causes of N/V
- weigh frequently, assess level of hydration, test urine for ketones
- non-pharmacological
  - avoid mixing fluids and solids, frequent small meals (bland, dry, salty are better tolerated)
  - electrolyte oral solutions (Pedialyte®, Gatorade®)
  - stop prenatal vitamins
  - increase sleep/rest
  - ginger (maximum 1,000 mg/d)
  - acupuncture, acupressure
- pharmacological
  - first line: Diclectin® (10 mg doxylamine succinate with vitamin B6) 4 tablets PO daily (1 q am, 1 q lunch and 2 qhs) up to maximum of 8 tablets/day
  - if no improvement, try dimenhydrinate (50-100 mg q4-6h PO), followed by hydroxyzine, pyridoxine, phenothiazine, or metoclopramide
  - vitamin B6 lollipops
  - if patient dehydrated, assess fluid replacement needs and resuscitate accordingly
- severe/refractory
  - consider homecare with IV fluids and parenteral anti-emetics, hospitalization

Hyperemesis Gravidarum

Definition
- intractable N/V, usually presents in T1 then diminishes; occasionally persists throughout pregnancy
- affects ~1% of pregnancies

Etiology
- multifactorial with hormonal, immunologic, and psychological components
- rapidly rising β-hCG ± estrogen levels may be implicated

Investigations
- rule out systemic causes: GI inflammation, pyelonephritis, thyrotoxicosis
- rule out other obstetrical causes: multiple gestation, GTN, HELLP syndrome
- CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
- ultrasound

Management
- thiamine supplementation may be indicated
- non-pharmacological (see Nausea and Vomiting)
- pharmacological options
  - Diclectin® (for dosage, see Nausea and Vomiting)
  - Dimenhydrinate can be safely used as an adjunct to Diclectin® (1 suppository bid or 25 mg PO qid)
  - other adjuncts: hydroxyzine, pyridoxine, phenothiazine, metoclopramide
  - also consider: ondansetron or methylprednisolone
  - if severe: admit to hospital, NPO initially then small frequent meals; correct hypovolemia, electrolyte disturbance, and ketosis; TPN (if very severe) to reverse catabolic state

Complications
- maternal
  - dehydration, electrolyte and acid-base disturbances
  - Mallory-Weiss tear
  - Wernicke’s encephalopathy, if protracted course
  - death
- fetal: usually none, IUGR is 15x more common in women losing >5% of pre-pregnancy weight

Subsequent Prenatal Visits

Timing
- for uncomplicated pregnancies, SOGC recommends q4-6 wk until 30 wk, q2-3 wk from 30 wk, and q1-2 wk from 36 wk until delivery

Assess at Every Visit
- estimated GA
- history: fetal movements, uterine bleeding, leaking, cramping, questions, concerns
- physical exam: BP, weight gain, SFH, Leopold’s maneuvers (T3) for lie, position, and presentation of fetus
- investigations: urinalysis for glucosuria and proteinuria in high risk women; fetal heart rate starting at 10-12 wk using Doppler U/S
**Leopold’s Maneuvers**
- performed after 30-32 wk gestation
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver: to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

Figure 2. Leopold’s maneuvers (T3)
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**Prenatal Screening and Diagnostic Tests**

**Screening Tests**
- testing should only occur following counselling and with informed consent from the patient

**Table 2. High-Risk Population Screening Tests**

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Population(s) at Risk</th>
<th>Screening Test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia (AR)</td>
<td>Mediterranean, South East Asian, Western Pacific, African, Middle Eastern, Caribbean, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis, or HPLC</td>
</tr>
<tr>
<td>Sickle Cell (AR)</td>
<td>African, Caribbean, Mediterranean Middle Eastern, Indian, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis, or HPLC</td>
</tr>
<tr>
<td>Cystic Fibrosis (CF)  (AR)</td>
<td>Family history of CF in patient or partner or medical condition linked to CF like male infertility</td>
<td>CFTR gene DNA analysis</td>
</tr>
<tr>
<td>Tay Sachs Disease (AR)</td>
<td>Ashkenazi Jewish*, French Canadians, Cajun</td>
<td>Enzyme assay HEXA, or DNA analysis HEXA gene</td>
</tr>
<tr>
<td>Fragile X Syndrome (X-linked)</td>
<td>Family history – confirmed or suspected</td>
<td>DNA analysis: FMR-1 gene</td>
</tr>
</tbody>
</table>

AR = autosomal recessive; HEXA = hexosaminidase A; HPLC = high performance liquid chromatography
*If both partners are Ashkenazi Jewish, test for Canavan disease and Familial Dysautonomia (FD); if family history of a specific condition, look for carrier status: e.g. Gaucher, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners are positive, refer for genetic counseling.

**Table 3. Gestation-Dependent Screening Investigations**

<table>
<thead>
<tr>
<th>Gestational Age (wk)</th>
<th>Investigations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-12</td>
<td>Dating U/S, possible Pap smear, chlamydia/gonorrhoea testing, urine C&amp;S, HIV, VDRL, HepBSAg, Rbella IgG, Parovirus IgM or IgG if high risk (small child at home or daycare worker/primary teacher), Varicella IgG if no history of disease/immunization, CBC, blood group and screen, urine cultures to detect asymptomatic bacteriuria</td>
<td>Measures cell free fetal DNA in maternal circulation</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>NIPT</td>
<td>Measures cell free fetal DNA in maternal circulation</td>
</tr>
<tr>
<td>10-12</td>
<td>CVS</td>
<td>Measures cell free fetal DNA in maternal circulation</td>
</tr>
<tr>
<td>11-14</td>
<td>Enhanced FTS IPS Part 1</td>
<td>Measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Nuchal translucency on U/S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. p-HCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. PAPP-A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. PlGF (enhanced FTS only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. AFP (enhanced FTS only)</td>
</tr>
<tr>
<td>11-14</td>
<td>Nuchal translucency U/S</td>
<td>Measures</td>
</tr>
<tr>
<td>15-16 to term</td>
<td>Amniocentesis</td>
<td>Measures</td>
</tr>
<tr>
<td>15-20</td>
<td>IPS Part 2</td>
<td>Measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. MSAAF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. p-HCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Unconjugated estrogen (estradiol or µE3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Inhibin A</td>
</tr>
</tbody>
</table>
Table 3. Gestation-Dependent Screening Investigations (continued)

<table>
<thead>
<tr>
<th>Gestational Age (wk)</th>
<th>Investigations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-20</td>
<td>MSS</td>
<td>Measures 1. MSAFP&lt;br&gt;2. β-hCG&lt;br&gt;3. Unconjugated estrogen (estriol or μE3)&lt;br&gt;4. Inhibin A</td>
</tr>
<tr>
<td>18-20 to term</td>
<td>Fetal movements (quickening)</td>
<td></td>
</tr>
<tr>
<td>18-20</td>
<td>U/S for dates, fetal growth, and anatomy assessment</td>
<td></td>
</tr>
<tr>
<td>24-28</td>
<td>Gestational Diabetes Screen 50 g OGCT</td>
<td>See Diabetes Mellitus, OB26</td>
</tr>
<tr>
<td>28</td>
<td>Repeat CBC, RhIG for all Rh negative women</td>
<td></td>
</tr>
<tr>
<td>35-37</td>
<td>GBS screen</td>
<td>See Group B Streptococcus, OB27</td>
</tr>
<tr>
<td>6 wk postpartum</td>
<td>Discuss contraception, menses, breastfeeding, depression, mental health, support Physical exam: breast exam, pelvic exam including Pap smear (only if due as per provincial screening)</td>
<td></td>
</tr>
</tbody>
</table>

Maternal serum screen is also referred to as Triple Screen; if Inhibin A is also tested, it is referred to as Quadruple Screen

ULTRASOUND SCREENING
8-12 wk GA: dating ultrasound (most accurate form of pregnancy dating)
- measurement of crown-rump length (margin of error: ± 5 d)
- change EDC to U/S date if >5 d discrepancy from EDC based on LMP
11-14 wk GA: NTUS
- measures the amount of fluid behind the neck of the fetus
- early screen for Trisomy 21 (may also detect cardiac and other aneuploidies like Turner’s syndrome)
- NT measurement is necessary for the FTS and IPS Part 1
18-20 wk GA: growth and anatomy U/S (margin of error: ± 10 d)
- earlier or subsequent ultrasounds performed when medically indicated

NON-INVASIVE PRENATAL TESTING (NIPT)
- analyses maternal blood for circulating cell free fetal DNA (ccffDNA) at 10 wk GA onwards. Requires dating ultrasound for accuracy

Advantage
- in high risk women (>age 35) highly sensitive for Trisomy 21 (>99.5%), specificity (>99.8%) - can also look for trisomy 18, 13 and some X and Y disorders as well as common microdeletions
- not harmful to the pregnancy, results available in 7-10 day

Disadvantages
- does not screen for ONTD
- high cost to patient (only covered in some provinces in certain cases)
- unclear how accurate yet in low risk women (<35)
- need to confirm with invasive testing
- does not test for all aneuploidy

Table 4. Comparison of FTS, MSS, and IPS

<table>
<thead>
<tr>
<th>FTS</th>
<th>MSS</th>
<th>IPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-14 wk</td>
<td>15-20 wk</td>
<td>11-13 wk U/S-Nuchal Translucency&lt;br&gt;11-14 wk: FTS blood&lt;br&gt;15-20 wk: MSS blood including inhibin</td>
</tr>
<tr>
<td>Risk estimate for 1. Down syndrome (Trisomy 21): increased NT, increased β-hCG, decreased PAPP-A&lt;br&gt;2. Trisomy 18: increased NT, decreased PAPP-A, decreased β-hCG</td>
<td>Risk estimate for 1. ONTD: increased MSAFP (sensitivity 80-90%)&lt;br&gt;2. Trisomy 21: decreased MSAFP, increased β-hCG, decreased μE3 (sensitivity 65%)&lt;br&gt;3. Trisomy 18: decreased MSAFP, decreased β-hCG, decreased μE3, decreased inhibin (sensitivity 80%)&lt;br&gt;Only offered alone if patient missed the time window for FTS or FTS&lt;br&gt;8% baseline false positive rate for Trisomy 21, lower for NTD and Trisomy 18&lt;br&gt;Patients with positive screen should be offered U/S, amniocentesis, or NIPT (covered in some provinces, self-pay in others)</td>
<td>Risk estimate for ONTD, Trisomy 21, Trisomy 18&lt;br&gt;Sensitivity ~85-90%&lt;br&gt;2% false positive rate&lt;br&gt;Patients with positive screen should be offered U/S and/or amniocentesis or NIPT (covered in some provinces, self-pay in others)</td>
</tr>
</tbody>
</table>

Note: In twins, FTS, MSS, and IPS are not applicable; screen with NT, NIPT for chromosomal abnormalities and MSAFP for ONTDs
Diagnostic Tests

Indications
- age >35 yr (increased risk of chromosomal anomalies)
- risk factors in current pregnancy
- abnormal U/S
- abnormal prenatal screen (IPS, FTS, or MSS)
- past history/family history of
  - chromosomal anomaly or genetic disease
  - either parent a known carrier of a genetic disorder or balanced translocation
  - consanguinity
  - >3 spontaneous abortions

AMNIOCENTESIS
- U/S-guided transabdominal extraction of amniotic fluid

Indications
- identification of genetic anomalies (15-16 wk gestation) as per indications above
- confirmation of positive NIPT testing
- positive FTS/IPS
- assessment of fetal lung maturity (T3) via the L/S ratio (lecithin:sphingomyelin)
  - if >2:1, RDS is less likely to occur

Advantages
- also screens for ONTD (acetylcholinesterase and amniotic AFP) – 96% accurate
- in women >35 yr, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- more accurate genetic testing than CVS

Disadvantages
- 1/200 risk of procedure related pregnancy loss, 1/100 for multiple gestations
- results take 14-28 d; QF-PCR or FISH can be done on chromosomes X, Y, 21, 22, 13, 18 to give preliminary results in 48 h

CHORIONIC VILLUS SAMPLING
- biopsy of fetal-derived chorion using a transabdominal needle or transcervical catheter at 10-12 wk

Advantages
- enables pregnancy to be terminated earlier than with amniocentesis
- rapid karyotyping and biochemical assay within 48 h, including FISH analysis
- high sensitivity and specificity

Disadvantages
- 1-2% risk of procedure related pregnancy loss
- does not screen for ONTD
- 1-2% incidence of genetic mosaicism “false negative” results

ISOIMMUNIZATION SCREENING

Definition
- isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigenic stimulation with RBC of another individual

Etiology
- maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
- anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
- risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16%
- sensitization routes
- incompatible blood transfusions
- previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy, abortion)
- invasive procedures in pregnancy (e.g. prenatal diagnosis, cerclage, D&C)
- any type of abortion
- labour and delivery

Investigations
- screening with indirect Coombs test at first visit for blood group, Rh status, and antibodies
- Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage by estimating volume of fetal blood volume that entered maternal circulation
- detailed U/S for hydrops fetalis
• MCA dopplers are done to assess degree of fetal anemia; if not available, bilirubin is measured by serial amniocentesis to assess the severity of hemolysis
• cordocentesis for fetal Hb should be used cautiously (not first line)

**Prophylaxis**
- exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
- Rhogam® (300 µg) given to all Rh negative and antibody screen negative women in the following scenarios:
  - routinely at 28 wk GA (provides protection for ~12 wk)
  - within 72 h of the birth of an Rh positive fetus
  - with any invasive procedure in pregnancy (CVS, amniocentesis)
  - in ectopic pregnancy
  - with miscarriage or therapeutic abortion
  - with an antepartum hemorrhage
  - with trauma
- a Kleihauer-Betke test or Flow cytometry can be used to determine whether more than 300 µg of RhIg is required (>30 mL fetal blood)
- if Rh negative and Ab screen positive, follow mother with serial monthly Ab titres throughout pregnancy ± ultrasounds as needed (Rhogam® has no benefit)

**Treatment**
- falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
- intrauterine transfusion of O-negative pRBCs may be required for severely affected fetus or early delivery of the fetus for exchange transfusion

**Complications**
- anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, ascites
- severe cases can lead to fetal hydrops (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)

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**Counselling of the Pregnant Woman**

**Nutrition**
- Canada’s Food Guide to Healthy Eating suggests
  - 3-4 servings of milk products daily (greater if multiple gestation)
  - a daily caloric increase of ~100 cal/d in the 1st trimester, ~300 cal/d in the second and third trimesters and ~450 cal/d during lactation
  - daily multivitamin should be continued in the 2nd trimester for women who do not consume an adequate diet; otherwise, routine vitamin supplementation is not necessary (avoid excess vitamin A)
- nutrients important during pregnancy
  - folate: 0.4 mg/d for first 12 wk (5 mg/d if high risk)
  - foods rich in folic acid include: spinach, lentils, chick peas, asparagus, broccoli, peas, brussels sprouts, corn, and oranges
  - calcium: 1200-1500 mg/d
  - maintains integrity of maternal bones, skeletal development of fetus, breast milk production
  - vitamin D: 1,000 IU
  - promotes calcium absorption
  - iron: 0.8 mg/d in T1, 4.5 mg/d in T2, and >6 mg/d in T3
  - supports maternal increase in blood cell mass, supports fetal and placental tissue
  - required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
  - iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see Iron Deficiency Anemia, OB25)
- essential fatty acids – supports fetal neural and visual development
- contained in vegetable oils, margarines, peanuts, fatty fish

**Caffeine**
- diuretic and stimulant that readily crosses placenta
- less than 300 mg/d is not thought to contribute to miscarriage or preterm birth (ACOG)
- relationship between caffeine and IUGR is unknown (ACOG)
- SOGC states 1-2 cups/d are safe during pregnancy

**Herbal Teas and Preparations**
- not enough scientific information about safety of various herbs and herbal products to recommend their use during pregnancy
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- chamomile has been reported to exhibit adverse effects on the uterus
- raspberry leaf tea often used at term to promote labour
Foodborne Illnesses

- Microbiological contamination of food may occur through cross-contamination and/or improper food handling
  - Listeriosis (Listeria monocytogenes) and toxoplasmosis (Toxoplasma gondii) are of concern during pregnancy
  - Avoid consumption of raw meats, fish, shellfish, poultry, hotdogs, raw eggs, and unpasteurized dairy products
  - Avoid unpasteurized soft cheeses, deli meats, smoked salmon, and pates as they may be sources of Listeria

- Chemical contamination of food
  - Current guideline for mercury of 0.5 ppm in fish is not considered harmful for the general population, including pregnant women
  - Health Canada advises pregnant women to limit consumption of top predator fish such as shark, swordfish, king mackerel, tilefish

Lifestyle

- Exercise under physician guidance; “talk test” = should be able to speak while exercising; avoid supine position after 20 weeks GA
  - Absolute contraindications
    - Ruptured membranes, preterm labour, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestations (>3), placenta previa after 28th wk, persistent 2nd or 3rd trimester bleeding, uncontrolled type 1 DM, uncontrolled thyroid disease, or other serious cardiovascular, respiratory, or systemic disorder
  - Relative contraindications
    - Previous preterm birth, mild/moderate cardiovascular or respiratory disorder, anemia (Hb ≤100 g/L), malnutrition or eating disorder, twin pregnancy after 28th wk, other significant medical conditions

- Weight gain: optimal gain depends on pre-pregnancy BMI (varies from 6.8-18.2 kg)
  - General rule: 1-3.5 kg/wk during T1, then 0.45 kg/wk until delivery

- Work: strenuous work, extended hours and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
  - Air travel is acceptable in second trimester; airline cut off for travel is 36-38 wk gestation depending on the airline, to avoid giving birth on the plane

- Sexual intercourse: may continue, except in patients at risk for: abortion, preterm labour, or placenta previa; breast stimulation may induce uterine activity and is discouraged in high-risk patients near term

- Smoking: assist/encourage to reduce or quit smoking
  - Increased risk of decreased birth weight, placenta previa/abruption, spontaneous abortion, preterm labour, stillbirth

- Alcohol: no amount of alcohol is safe in pregnancy; encourage abstinence from alcohol during pregnancy; alcohol increases incidence of abortion, stillbirth, and congenital anomalies
  - Fetal alcohol syndrome (see Pediatrics, P24)
  - Cocaine: microcephaly, growth retardation, prematurity, abruptio placentae

- Biopsychosocial considerations: discuss birth plan, offer community maternal resources

Medications

- Most drugs cross the placenta to some extent
- Very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
- Use any drug with caution and only if necessary
- Analgesics: acetaminophen preferable to ASA or ibuprofen

Table 5. Documented Adverse Effects, Contraindicated Medication

<table>
<thead>
<tr>
<th>Contraindicated Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Fetal renal defects, IUGR, oligohydramnios</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Stains infant’s teeth, may affect long bone development</td>
</tr>
<tr>
<td>Retinoids (e.g. Acutane&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>CNS, craniofacial, cardiac, and thymic anomalies</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Mobius syndrome (congenital facial paralysis with or without limb defects), spontaneous abortion, preterm labour</td>
</tr>
</tbody>
</table>
Table 6. Documented Adverse Effects, Weigh Benefits vs. Risks, and Consider Medication Change

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmorphogenesis, congenital anomalies)</td>
</tr>
<tr>
<td>Valproate</td>
<td>ONTD in 1%</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>ONTD in 1-2%</td>
</tr>
<tr>
<td>Lithium</td>
<td>Ebstein’s cardiac anomaly, goitre, hyponatremia</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR, fetal warfarin syndrome (nasal hypoplasia, epiphyseal stippling, optic atrophy, mental retardation, intracranial hemorrhage)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Maternal liver damage (acute fatty liver)</td>
</tr>
<tr>
<td>Sulpha drugs</td>
<td>Anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Grey baby syndrome (fetal circulatory collapse 2° to toxic accumulation)</td>
</tr>
</tbody>
</table>

Immunizations

Intrapartum
- administration is dependent on the risk of infection vs. risk of immunization complications
- safe: tetanus toxoid, diphtheria, influenza, hepatitis B, pertussis
- avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, varicella
- contraindicated: oral typhoid
- the Public Health Agency of Canada recommends:
  - all pregnant women receive the influenza vaccine
  - all pregnant women at 26 weeks of pregnancy or later, who have not received a dose of pertussis-containing vaccine in adulthood, should receive Tdap vaccination in pregnancy

Postpartum
- rubella vaccine for all non-immune mothers. If they’ve had an adult booster and remain non-immune, they should not be revaccinated
- hepatitis B vaccine should be given to infant within 12 h of birth if maternal status unknown or positive – follow-up doses at 1 and 6 mo
- any vaccine required/recommended is generally safe postpartum

Radiation

- ionizing radiation exposure is considered teratogenic at high doses
  - if indicated for maternal health, should be done
- imaging not involving direct abdominal/pelvic high dosage radiation is not associated with adverse effects
  - higher dosage to fetus: plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen, pelvis, lumbar spine
- most investigations involve minimal radiation exposure
- radioactive isotopes of iodine are contraindicated
- no known adverse effects from U/S or MRI (long-term effects of gadolinium unknown, avoid if possible)

Table 7. Approximate Fetal Doses from Common Diagnostic Procedures

<table>
<thead>
<tr>
<th>Examination</th>
<th>Estimated Fetal Dose (rad)</th>
<th>Number of Exams Safe in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain Film</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.14</td>
<td>35</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0.11</td>
<td>45</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.17</td>
<td>29</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>0.009</td>
<td>555</td>
</tr>
<tr>
<td>Chest (2 views)</td>
<td>&lt;0.001</td>
<td>5000</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.8</td>
<td>6</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0.24</td>
<td>2</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.006</td>
<td>833</td>
</tr>
<tr>
<td>Chest</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antenatal Fetal Surveillance

Fetal Movements

- Patients will generally first notice fetal movement ("quickening") at 18-20 wk in primigravidas; can occur 1-2 wk earlier in multigravidas; can occur 1-2 wk later if placenta is implanted on the anterior wall of uterus
- If the patient is concerned about decreased fetal movement, she is counselled to choose a time when the fetus is normally active to count movements (usually recommended after 26 wk)
- All high risk women should be told to do FM counts
  - If there is a subjective decrease in fetal movement, try drinking juice, eating, changing position, or moving to a quiet room and count for 2 h; ≥6 movements in 2 h expected
  - If there are <6 movement counts in 2 h, patient should present to labour and delivery triage

Non-Stress Test

Definition

- FHR tracing ≥20 min using an external Doppler to assess FHR and its relationship to fetal movement (see Fetal Monitoring in Labour, OB33)

Indication

- Any suggestion of uteroplacental insufficiency or suspected compromise in fetal well-being

Table 8. Classification of Antepartum Non-Stress Test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal NST (Previously &quot;Reactive&quot;)</th>
<th>Atypical NST (Previously &quot;Non-Reactive&quot;)</th>
<th>Abnormal NST (Previously &quot;Non-Reactive&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>110-160 bpm</td>
<td>100-110 bpm or &gt;160 bpm for &lt;30 min</td>
<td>Bradycardia &lt;100 bpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rising baseline</td>
<td>Tachycardia &gt;160 for &gt;30 min</td>
</tr>
<tr>
<td>Variability</td>
<td>6-25 bpm (moderate) or ≤5 (absent or minimal) for &lt;40 min</td>
<td>5 (absent or minimal) for 40-80 min</td>
<td>≤5 for 80 min Sinusoidal 25 bpm for &gt;10 min</td>
</tr>
<tr>
<td>Decelerations</td>
<td>None or occasional variable &lt;30 s</td>
<td>Variable decelerations 30-60 s duration</td>
<td>Variable decelerations &gt;60 s Late deceleration(s)</td>
</tr>
<tr>
<td>Accelerations in Term Fetus</td>
<td>2 accelerations with acme of ≥15 bpm, lasting ≥15 s in ≤40 min</td>
<td>2 accelerations with acme of ≥15 bpm, lasting 15 s ≥40-80 min</td>
<td>&lt;2 accelerations with acme of ≥15 bpm, lasting 15 s ≥80 min</td>
</tr>
<tr>
<td>Accelerations in Preterm Fetus (&lt;32 wk)</td>
<td>&gt;2 accelerations with acme of ≥10 bpm, lasting 10 s in &lt;40 min</td>
<td>&lt;2 accelerations with acme of ≥10 bpm, lasting 10 s in 40-80 min</td>
<td>&lt;2 accelerations with acme of ≥10 bpm, lasting 10 s in &gt;80 min</td>
</tr>
<tr>
<td>Action</td>
<td>FURTHER ASSESSMENT OPTIONAL, based on total clinical picture</td>
<td>FURTHER ASSESSMENT REQUIRED</td>
<td>URGENT ACTION REQUIRED</td>
</tr>
</tbody>
</table>

Adapted from: SOGC, Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline, September 2007

Operating Characteristics

- False positive rate depends on duration; false negative rate = 0.2-0.3%

Interpretation

- Normal: at least 2 accelerations of FHR >15 bpm from the baseline lasting >15 s in 20 min
- Abnormal: <2 accelerations of FHR in 40 min
- If no observed accelerations or fetal movement in the first 20 min, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 min

Biophysical Profile

Definition

- U/S assessment of the fetus ± NST

Indications

- Post-term pregnancy
- Decreased fetal movement
- IUGR
- Any other suggestion of fetal distress or uteroplacental insufficiency
Operating Characteristics
• false positive rate ≤30%, false negative rate = 0.1%

Table 9. Scoring of the BPP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reassuring (2 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tone (limb extension then flexion)</td>
<td></td>
</tr>
<tr>
<td>At least one episode of limb extension followed by flexion</td>
<td></td>
</tr>
<tr>
<td>Movement</td>
<td>Three discrete movements</td>
</tr>
<tr>
<td>Breathing</td>
<td>At least one episode of breathing lasting at least 30 s</td>
</tr>
<tr>
<td>AFV*</td>
<td>Fluid pocket of 2 cm in 2 axes</td>
</tr>
</tbody>
</table>

*AFV is a marker of chronic hypoxia, all other parameters indicate acute hypoxia

Interpretation
• 8: perinatal mortality rate 1:1,000; repeat BPP as clinically indicated
• 6: perinatal mortality 31:1,000; repeat BPP in 24 h
• 0-4: perinatal mortality rate 200:1,000; deliver fetus if benefits of delivery outweigh risks

Obstetrical Hemorrhage

Definition
vaginal bleeding from 20 wk to term

Differential Diagnosis
• bloody show (shedding of cervical mucous plug) – most common etiology in T3
• placenta previa
• abruptio placentae – most common pathological etiology in T3
• vasa previa
• cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
• uterine rupture
• other: bleeding from bowel or bladder, abnormal coagulation

Table 10. Comparison of Placenta Previa and Abruptio Placentae

<table>
<thead>
<tr>
<th></th>
<th>Placenta Previa</th>
<th>Abruptio Placentae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Abnormal location of the placenta near, partially or completely over the internal cervical os</td>
<td>Premature separation of a normally implanted placenta after 20 wk GA</td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>0.5-0.8% of all pregnancies</td>
<td>1-2% of all pregnancies</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>History of placenta previa (4-8% recurrence risk)</td>
<td>Previous abruption (recurrence rate 5-16%)</td>
</tr>
<tr>
<td></td>
<td>Multiparity</td>
<td>Maternal HTN (chronic or gestational HTN in 50% of abruptions) or vascular disease</td>
</tr>
<tr>
<td></td>
<td>Increased maternal age</td>
<td>Cigarette smoking (&gt;1 pack/d), excessive alcohol consumption, cocaine</td>
</tr>
<tr>
<td></td>
<td>Multiple gestation</td>
<td>Multiparity and/or maternal age &gt; 35 yr</td>
</tr>
<tr>
<td></td>
<td>Uterine tumour (e.g. fibroids) or other uterine anomalies</td>
<td>PPROM</td>
</tr>
<tr>
<td></td>
<td>Uterine scar due to previous abortion, C/S, D&amp;C, myxomatosis</td>
<td>Rapid decompression of a distended uterus (polyhydramnios, multiple gestation)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>PAINLESS</td>
<td>Usually PAINFUL</td>
</tr>
</tbody>
</table>

Placenta Previa

Definition
• placenta implanted in the lower segment of the uterus, presenting ahead of the leading pole of the fetus
• placental position is described in relation to the internal os as “mm away” or “mm of overlap”

Clinical Features
• PAINLESS bright red vaginal bleeding (recurrent), may be minimized and cease spontaneously but can become catastrophic
• mean onset of bleeding is 30 wk GA, but onset depends on degree of previa
• physical exam
  • do not perform pelvic exam until ruling out placenta previa
  • uterus soft and non-tender
  • presenting fetal part high or displaced
  • FHR usually normal
  • shock/anemia correspond to degree of apparent blood loss

Greater than 20 mm of overlap over the internal os in the third trimester of pregnancy is highly predictive of the need for a C/S. Any degree of overlap after 35 wk is an indication for a C/S.
• complications
  • fetal
    ◆ perinatal mortality low but still higher than with a normal pregnancy
    ◆ prematurity (bleeding often dictates early C/S)
    ◆ intrauterine hypoxia (acute or IUGR)
    ◆ fetal malpresentation
    ◆ PPROM
    ◆ risk of fetal blood loss from placenta especially if incised during C/S
  • maternal
    ◆ <1% maternal mortality
    ◆ hemorrhage and hypovolemic shock, anemia, acute renal failure, pituitary necrosis (Sheehan syndrome)
    ◆ placenta accreta – especially if previous uterine surgery, anterior placenta previa
    ◆ hysterectomy

Investigations
• transvaginal U/S is more accurate than transabdominal U/S at diagnosing placenta previa at any gestational age
• if the placenta lies between 20 mm of overlap and 20 mm away from the internal os after 20 wk, transvaginal ultrasounds should be repeated in the third trimester as continued change in the placental location is likely

Management
• goal: keep pregnancy intrauterine until the risk of delivery < risk of continuing pregnancy
• stabilize and monitor
  ◆ maternal stabilization: large bore IV with hydration, O₂ for hypotensive patients
  ◆ maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, INR/PTT, platelets, fibrinogen, FDP, type and cross match)
  ◆ electronic fetal monitoring
  ◆ U/S assessment: when fetal and maternal condition permit, determine fetal viability, gestational age, and placental status/position
• Rhogam® if mother is Rh negative
• determine extent of fetomaternal transfusion so that appropriate dose of Rhogam® can be given
• GA <37 wk and minimal bleeding: expectant management
  ◆ admit to hospital
  ◆ limited physical activity, no douches, enemas, or sexual intercourse
  ◆ consider corticosteroids for fetal lung maturity
  ◆ delivery when fetus is mature or hemorrhage dictates due to maternal or fetal compromise
• GA ≥37 wk, profuse bleeding, or L/S ratio is >2:1 – deliver by C/S

Abruptio Placentae

Definition
• premature partial or total placental detachment caused by bleeding at the decidual-placental interface
• occurring >20 wk gestation

Clinical Features
• classification
  ◆ total (fetal death inevitable) vs. partial
  ◆ external/revealed/apparent: blood dissects downward toward cervix
  ◆ internal/concealed/occult (20%): blood dissects upward toward fetus
  ◆ most are mixed
• presentation
  ◆ usually PAINFUL (80%) vaginal bleeding (bleeding not always present if abruption is concealed), uterine tenderness, uterine contractions/hypertonus
  ◆ pain: sudden onset, constant, localized to lower back and uterus
  ◆ shock/anemia out of proportion to apparent blood loss
  ◆ ± fetal distress, fetal demise (15% present with demise), bloody amniotic fluid (fetal presentation typically normal)
  ◆ ± coagulopathy

Complications
• fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
• maternal complications: <1% maternal mortality, DIC (in 20% of abruptions), acute renal failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), amniotic fluid embolus

Investigations
• clinical diagnosis, U/S not sensitive for diagnosing abruption (sensitivity = 15%)

Management
• maternal stabilization: large bore IV with hydration, O₂ for hypotensive patients
• maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, PTT/PT, platelets, fibrinogen, FDP, type and cross match)
• EFM
• blood products on hand (red cells, platelets, cryoprecipitate) because of DIC risk
• Rhogam® if Rh negative
  • Kleihauer-Betke test may confirm abruption
• mild abruption
  • GA <37 wk: use serial Hct to assess concealed bleeding, deliver when fetus is mature or when hemorrhage dictates
  • GA ≥37 wk: stabilize and deliver
• moderate to severe abruption
  • hydrate and restore blood loss and correct coagulation defect if present
  • vaginal delivery if no contraindication and no evidence of fetal or maternal distress or fetal demise
  • C/S if live fetus and fetal or maternal distress develops with fluid/blood replacement, labour fails to progress, or if vaginal delivery otherwise contraindicated

**Vasa Previa**

**Definition**
• unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord into membranes of placenta or succenturiate (accessory) lobe

**Epidemiology**
• 1 in 5 000 deliveries – higher in twin pregnancies

**Clinical Features**
• PAINLESS vaginal bleeding and fetal distress (tachy-to-bradyarrhythmia in a sinusoidal pattern)
• if undiagnosed, 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of exsanguination)
• if diagnosed antenatally on ultrasound without labour or symptoms, then 97% survival

**Investigations**
• Apt test (NaOH mixed with the blood) can be done immediately to determine if the source of bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
• Wright stain on blood smear and look for nucleated red blood cells (in cord, not maternal blood)

**Management**
• emergency C/S (since bleeding is from fetus, a small amount of blood loss can have catastrophic consequences)

**Obstetrical Complications**

**Preterm Labour**

**Definition**
• labour between 20 and 37 wk gestation

**Etiology**
• idiopathic (most common)
• maternal: infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), HTN, DM, chronic illness, mechanical factors; previous obstetric, gynecological, and abdominal surgeries; socio-environmental (poor nutrition, smoking, drugs, alcohol, stress)
• maternal fetal: PPROM (common), polyhydramnios, placenta previa, placental abruption, or placental insufficiency
• fetal: multiple gestation, congenital abnormalities of fetus, fetal hydrops, stress
• uterine: excessive enlargement (hydramnios, multiple gestation), malformations (intracavitary leiomyomas, septate uterus, mullerian duct abnormalities)

**Epidemiology**
• preterm labour complicates about 10% of pregnancies

**Risk Factors**
• prior history of spontaneous PTL is the most important risk factor
• prior history of large or multiple cervical excisions (cone biopsy) or mechanical dilatation (D&C)
• cervical length: measured by transvaginal U/S (cervical length >30 mm has high negative predictive value for PTL before 34 wk)
• identification of bacterial vaginosis and ureaplasma urealyticum infections; routine screening not supported by current data, but it is reasonable to screen high risk women
• family history of preterm birth
• smoking
• late maternal age
• multiple gestation
Predicting PTL
- fetal fibronectin: a glycoprotein in amniotic fluid and placental tissue
  - positive if >50 ng/mL; NPV > PPV
  - in symptomatic women (i.e. preterm contractions), fetal fibronectin is most effectively combined
    with U/S detecting cervical length
  - if cervical length is not short and fetal fibronectin is negative, preterm labour is highly unlikely

Clinical Features
- regular contractions (2 in 10 min, >6/h)
- cervix >1 cm dilated, >80% effaced, or length <2.5 cm

Management
A. Initial
- transfer to appropriate facility if stable
- hydration (NS at 150 mL/h)
- bed rest in LLDP
- sedation (morphine)
- avoid repeated pelvic exams (increased infection risk)
- U/S examination of fetus (GA, BP, position, placenta location, estimated fetal weight)
- prophylactic antibiotics; (for GBS) important to consider if PPROM (e.g. erythromycin controversial, but may help to delay delivery)

B. Suppression of Labour – Tocolysis
- does not inhibit preterm labour completely but may delay delivery (used for <48 h) to allow for
  - betamethasone valerate (Celestone®) and/or transfer to appropriate centre for care of the premature
  - requirements (all must be satisfied)
    - preterm labour
    - live, immature fetus, intact membranes, cervical dilatation of <4 cm
    - absence of maternal or fetal contraindications
  - contraindications
    - maternal: bleeding (placenta previa or abruption), maternal disease (HTN, DM, heart disease), preclampsia or eclampsia, chorioamnionitis
    - fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)
  - agents
    - calcium channel blockers: nifedipine
      - 20 mg PO loading dose followed by 20 mg PO 90 min later
      - 20 mg can be continued q3-8h for 72 h or to a max of 180 mg
      - 10 mg PO q20min x 4 doses
    - contraindications: nifedipine allergy, hypotension, heart dysfunction, concurrent beta-mimetics or MgSO₄ use, transdermal nitrates, or other antihypertensive medications
    - prostaglandin synthesis inhibitors: indomethacin
      - 1st line for early preterm labour (<30 wk GA) or polyhydramnios
      - 50-100 mg PR loading dose followed by 50 mg q6h x 8 doses for 48 hours
    - magnesium sulphate
      - was previously used for tocolysis; currently, only indicated for prevention of eclampsia or for neuroprotection if preterm delivery is inevitable between 24 and 34+6 wks GA for neuroprotection
      - 4 g IV loading dose followed by 1 g q1h maintenance until birth

C. Enhancement of Fetal Pulmonary Maturity
- betamethasone valerate (Celestone®) 12 mg IM q24h x 2 doses or dexamethasone 6 mg IM q12h x 4 doses
  - 28-36+6 wk GA: reduces incidence of RDS
  - 24-28 wk GA: reduces severity of RDS, overall mortality and rate of IVH
  - specific maternal contraindications: active TB

D. Cervical Cerclage
- definition: placement of cervical sutures at the level of the internal os, usually at the end of the first trimester or in the second trimester and removed in the third trimester
- indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
  - emerging evidence indicates that progesterone suppositories are superior to cerclage in preventing preterm labour of singletons not due to cervical incompetence
  - diagnosis of cervical incompetence
    - obstetrical Hx silent cervical dilation, 2nd trimester losses, procedures on cervix
    - ability of cervix to hold an inflated Foley catheter during a hysterosonogram
  - proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. osmization of the cervix, connective tissue disorder)

Positive fetal fibronectin in cervicovaginal fluid (>50 ng/mL) at 24 wk gestation predicted spontaneous PTL at <34 wk with sensitivity of 23%, specificity of 97%, PPV of 25%, NPV of 96%

Tocolytics for Preterm Premature Rupture of Membranes
Cochrane OB Syst Rev 2014;2:CD007062
- Purpose: To assess the potential benefits and harms of tocolysis in women with PPROM.
- Selection Criteria: Pregnant women with singleton pregnancies and PPROM (23-36 wk and 6-7 GA).
- Results: 8 studies with 408 women total.
  - Prophylactic tocolysis with PPROM was associated with increased overall latency, without additional benefits for maternal/neonatal outcomes. For women with PPROM before 34 wk, there was a significantly increased risk of chorioamniotitis in women who received tocolysis. Neonatal outcomes were not significantly different.
  - Conclusion: Although there are limitations to the studies, there is currently insufficient evidence to support tocolytic therapy for women with PPROM as there was an increase in maternal chorioamniotitis without significant benefits to the infant.

Cerclage for Short Cervix on Ultrasonography in Women With Singleton Gestations and Previous Preterm Birth
Obstet Gynecol 2011;117:663-671
- Purpose: To determine if cerclage prevents preterm birth (<35 wk gestation) and perinatal mortality and morbidity among women with previous spontaneous preterm birth, asymptomatic singleton gestation, and short cervical length (<25 mm before 24 wk gestation) on transvaginal ultrasonography.
- Methods: Meta-analysis of randomized trials identified using searches on MEDLINE, PUBMED, EMBASE, and the Cochrane Library.
- Results: 5 trials included. Preterm birth was significantly lower among women receiving cerclage vs. those not receiving (RR = 0.70, 95% CI 0.55-0.89). Cerclage also significantly reduced preterm birth before 24, 28, 32, and 37 wk gestation. Perinatal mortality and morbidity were significantly lower in the cerclage group (RR = 0.64, 95% CI 0.45-0.91).
- Conclusions: Cerclage significantly prevents preterm birth and perinatal mortality and morbidity in this specific group of women.

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery
- Purpose: This was a randomized controlled trial comparing betamethasone (n = 1428) to placebo (n = 1420) in the treatment of women with a singleton pregnancy at 34 to 36 + 5/7 wk that were at high risk of delivery. Composite endpoints assessed the need for respiratory support within 72 h of birth were used to measure treatment effectiveness. Specifically, these endpoints included: supplemental oxygen, extrapulmonary membrane oxygenation (ECMO), mechanical ventilation, and CPAP or high-flow nasal canula.
- Results: The primary outcome occurred less frequently in those who received betamethasone (11.6% vs. 14.4%, RR 0.8, p = 0.02). Treatment with betamethasone also significantly reduced additional respiratory complications, bronchopulmonary dysplasia, transient tachypnea of the newborn, and surfactant use.
- Conclusion: Treating women (GA 34 to 36 + 5/7 wk) who are at risk of delivery with betamethasone reduces the risk of neonatal complications.
**Obstetrics**

**Obstetrical Complications**

**Prognosis**
- Prematurity is the leading cause of perinatal morbidity and mortality
- 30 wk or 1,500 g (3.3 lb) = 90% survival
- 33 wk or 2,000 g (4.4 lb) = 99% survival
- Morbidity due to asphyxia, hypoxia, sepsis, RDS, intraventricular cerebral hemorrhage, thermal instability, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis

**Prevention of Preterm Labour**
- Currently there are no agents approved by Health Canada to arrest preterm labour
- Preventative measures: good prenatal care, identify pregnancies at risk, treat silent vaginal infection or UTIs, patient education
- Transvaginal ultrasound of cervical length is recommended only for high-risk pregnancies and only before 30 weeks GA

**Premature Rupture of Membranes**

**Definitions**
- PROM: pre-labour rupture of membranes at any GA
- Prolonged ROM: >24 h elapsed between rupture of membranes and onset of labour
- Preterm ROM: ROM occurring before 37 wk gestation
- PPROM: preterm (before 37 wk) AND pre-labour rupture of membranes

**Risk Factors**
- Maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STI, UTI), family history of PROM, low socioeconomic class/poor nutrition
- Fetal: congenital anomaly, multiple gestation
- Other risk factors associated with PTL

**Clinical Features**
- History of fluid gush or continued leakage

**Investigations**
- Sterile speculum exam (avoid introduction of infection)
- Pooling of fluid in the posterior fornix
- May observe fluid leaking out of cervix on cough/Valsalva ("cascade")
- Nitrazine (basic amniotic fluid turns nitrazine paper blue)
- Low specificity as it can also be positive with blood, urine, or semen
- Ferning (high salt in amniotic fluid evaporates, looks like ferns under microscope)
- U/S to rule out fetal anomalies; assess GA, presentation, and BPP

**Management**
- Admit for expectant management and monitor vitals q4h, daily BPP and WBC count
- Avoid introducing infection by minimizing examinations
- Consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <34 wk and up to 36-6 weeks if no evidence of infection
- Consider tocolysis for 48 h to permit administration of steroids if PPROM induces labour
- Screen women for UTIs, STIs, GBS infection and treat with appropriate antibiotics if positive (treat GBS at time of labour)
- If not in labour or labour not indicated, consider antibiotics: penicillins or macrolide antibiotics are the antibiotics of choice
- Deliver urgently if evidence of fetal distress and/or chorioamnionitis

**Table 11. PROM Management**

<table>
<thead>
<tr>
<th>Degree of Prematurity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 wk</td>
<td>Consider termination (poor outcome due to pulmonary hypoplasia)</td>
</tr>
<tr>
<td>24-25 wk</td>
<td>Individual consideration with counselling of parents regarding risks to preterm infants</td>
</tr>
<tr>
<td>26-34 wk</td>
<td>Expectant management as prematurity complications are significant</td>
</tr>
<tr>
<td>34-36 wk</td>
<td>“Grey zone” where risk of death from RDS and neonatal sepsis is the same</td>
</tr>
<tr>
<td>≥37 wk</td>
<td>Induction of labour since the risk of death from sepsis is greater than RDS</td>
</tr>
</tbody>
</table>

**Prognosis**
- Varies with gestational age
- 90% of women with PROM at 28-34 wk GA go into spontaneous labour within 1 wk
- 50% of women with PROM at <26 wk GA go into spontaneous labour within 1 wk
- Complications: cord prolapse, intrapartum infection (chorioamnionitis), premature delivery, limb contracture
Postterm Pregnancy

Definition
- pregnancy >42 wk GA

Epidemiology
- 41 wk GA: up to 27%
- >42 wk GA: 5.5%

Etiology
- most cases idiopathic
- anencephalic fetus with no pituitary gland
- placental sulfatase deficiency (X-linked recessive condition in 1/2,000-1/6,000 infants) – rare

Clinical Features
- postmaturity syndrome (10-20% of post-term pregnancies): fetal weight loss, reduced subcutaneous fat, scaling, dry skin from placental insufficiency, long thin body, open-eyed, alert and worried look, long nails, palms and soles wrinkled
- with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental aging and infarction, macrosomia, dystocia, fetal distress, operative deliveries, pneumonia, seizures, and requirement of NICU admission, stillbirth

Management
- GA 39 wk with advanced maternal age (>40yo): consideration should be given to IOL due to increased risk of stillbirth
- GA 40-41 wk: expectant management
  - no evidence to support IOL or C/S unless other risk factors for morbidity are present (see prognosis)
- GA >41 wk: offer IOL if vaginal delivery is not contraindicated
  - IOL shown to decrease C/S, fetal heart rate changes, meconium staining, macrosomia, and death when compared with expectant management
- GA >41 wk and expectant management elected: serial fetal surveillance
  - fetal movement count by the mother
  - BPP q3-4d
  - if AFI is decreased, labour should be induced

Prognosis
- if >42 wk, perinatal mortality 2-3x higher (due to progressive uteroplacental insufficiency)
- morbidity increased with HTN in pregnancy, DM, abruption, IUGR, and multiple gestation

Intrauterine Fetal Death (Demise)

Definition
- fetal death in utero after 20 wk GA (before 20 wk GA called spontaneous abortion)

Epidemiology
- occurring in 1% of pregnancies

Etiology
- 50% idiopathic
- 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, APS

Clinical Features
- decreased perception of fetal movement by mother
- SFH and maternal weight not increasing
- absent fetal heart tones on Doppler (not diagnostic)
- high MSAFP
- on U/S: no fetal heart rate. Depending on timing of death, may see skull collapse, brain tissue retraction, empty fetal bladder, non-filled aorta, poor visualization of midline flax

Management
- diagnosis: absent cardiac activity and fetal movement on U/S required for diagnosis
- determine secondary cause
  - maternal: HbA1c, fasting glucose, TSH, Kleihauer-Betke, VDRL, ANA, CBC, anticardiolipins, antibody screens INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, TORCH screen
  - fetal: karyotype, cord blood, skin biopsy, genetics evaluation, autopsy, amniotic fluid culture for CMV, parvovirus B19, herpes
  - placenta: pathology, bacterial cultures

 DIC: Generalized Coagulation and Fibrinolysis Leading to Depletion of Coagulation Factors

Obstetrical Causes
- Abruption
- Gestational HTN
- Fetal demise
- PPH

DIC-specific Blood Work
- Platelets
- aPTT and PT
- FDP
- Fibrinogen

Treatment
- Treat underlying cause
- Supportive
- Fluids
- Blood products
- FFP, platelets, cryoprecipitate
- Consider anti-coagulation as VTE prophylaxis
Treatment

- <12 wk: dilation and curettage
- 13–20 wk: dilation and evacuation or sometimes IOL
- >20 wk: induction of labour
- monitor for maternal coagulopathy (10% risk of DIC)
- parental psychological care/bereavement support as per hospital protocol
- comprehensive discussion within 3 mo about final investigation and post-mortem results, help make plans for future pregnancies

### Intrauterine Growth Restriction

#### Definition
- infant weight <10th percentile for GA or <2,500 g at term

#### Etiology/Risk Factors
- 50% unknown
- maternal causes
  - malnutrition, smoking, drug abuse, alcoholism, cyanotic heart disease, type 1 DM, SLE, pulmonary insufficiency, previous IUGR (25% risk, most important risk factor), chronic HTN
- maternal fetal
  - any disease causing placental insufficiency
  - includes gestational HTN, chronic renal insufficiency, gross placental morphological abnormalities (infarction, hemangiomas, placenta previa, abnormal cord insertion), prolonged gestation fetal causes
  - TORCH infections, multiple gestation, congenital anomalies/chromosomal abnormalities (10%)

#### Clinical Features
- symmetric/type I (25-30%): occurs early in pregnancy
  - reduced growth of both head and abdomen
  - head:abdomen ratio may be normal (>1 up to 32 wk; =1 at 32-34 wk; <1 after 34 wk GA)
  - usually associated with congenital anomalies or TORCH infections
- asymmetric/type II (70%): occurs late in pregnancy
  - fetal abdomen is disproportionately smaller than fetal head
  - brain is spared, therefore head:abdomen ratio increased
  - usually associated with placental insufficiency
  - more favourable prognosis than type I
- complications
  - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, hypocalcemia, hyrophosphatemia, hyponatremia, and mental retardation
  - greater risk of perinatal morbidity and mortality

#### Investigations
- SFH measurements at every antepartum visit
- if mother at high risk or SFH lags >2 cm behind GA
  - U/S for biparietal diameter, head and abdominal circumference ratio, femur length, fetal weight, and AFV (decrease associated with IUGR), decrease in the rate of growth
  - ± BPP
  - Doppler analysis of umbilical cord blood flow

#### Management
- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition, and treat maternal illness
- bed rest in LLDP
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if GA >34 wk
- liberal use of C/S since IUGR fetus withstands labour poorly

### Macrosomia

#### Definition
- infant weight >90th percentile for a particular GA or >4,000 g

#### Etiology/Risk Factors
- maternal obesity, GDM, past history of macrosomic infant, prolonged gestation, multiparity

#### Clinical Features
- increased risk of perinatal mortality
- CPD and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labour (see Table 15, OB27)
Investigations
- serial SFH
- further investigations if mother at high risk or SFH > 2 cm ahead of GA
- U/S predictors
  - polyhydramnios
  - third trimester AC > 1.5 cm/wk
  - HC/AC ratio < 10th percentile
  - FL/AC ratio < 20th percentile

Management
- prophylactic C/S is a reasonable option where EFW > 5,000 g in non-diabetic woman and EFW > 4,500 g in diabetic woman
- no evidence that prophylactic C/S improves outcomes
- risks and benefits of early induction (risk of C/S vs. risk of dystocia) must be weighed in diabetic mothers, as current research is unclear

**Polyhydramnios/Oligohydramnios**

<table>
<thead>
<tr>
<th>Polyhydramnios</th>
<th>Oligohydramnios</th>
</tr>
</thead>
</table>
| **Definition** | AFI > 25 cm  
U/S: single deepest pocket > 8 cm | AFI < 5 cm  
U/S: single deepest pocket ≤ 2 cm |
| **Etiology** | Idiopathic most common  
Maternal  
Type 1 DM: abnormalities of transchorionic flow  
Maternal-fetal  
Chorioangiomas  
Multiple gestation  
Fetal hydrops (increased erythroblastosis)  
Fetal  
Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios)  
Respiratory: cystic adenomatoid malformation lung  
CNS: anencephaly, hydrocephalus, meningocoele  
GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfere with swallowing) | Idiopathic most common  
Maternal  
Uteroplacental insufficiency (preeclampsia, nephropathy)  
Medications (ACEI)  
Fetal  
Congenital urinary tract anomalies (renal agenesis, obstruction, posterior urethral valves)  
UGR  
Ruptured membranes: prolonged amniotic fluid leak  
Amniotic fluid normally decreases after 35 wk |
| **Epidemiology** | Occur in 0.2-1.6% of all pregnancies | Occur in ~ 4.5% of all pregnancies  
Severe form in < 0.7%  
Common in pregnancies > 41 wk (~ 12%) |
| **Clinical Features and Complications** | Uterus large for dates, difficulty palpating fetal parts and hearing FHR  
Maternal complications  
Pressure symptoms from overstretched uterus (dyspnea, edema, hydrocephrosis)  
Obstetrical complications  
Cord prolapse, placental abruption, malpresentation, preterm labour, uterine dysfunction, and PPH | Uterus small for dates  
Fetal complications  
15-25% have fetal anomalies  
Amniotic fluid bands (T1) can lead to Potter’s facies, limb deformities, abdominal wall defects  
Obstetrical complications  
Cord compression  
Increased risk of adverse fetal outcomes  
Pulmonary hypoplasia (late-onset)  
Marker for infants who may not tolerate labour well |
| **Management** | Determine underlying cause  
Screen for maternal disease/infection  
Complete fetal U/S evaluation  
Depends on severity  
Mild to moderate cases require no treatment  
If severe, hospitalize and consider therapeutic amniocentesis | Always warrants admission and investigation  
Rule out ROM  
Fetal monitoring (NST, BPP)  
U/S Doppler studies (umbilical cord and uterine artery)  
Maternal hydration with oral or IV fluids to help increase amniotic fluid  
Injection of fluid via amniocentesis will improve condition for ~ 1 wk – may be most helpful for visualizing any associated fetal anomalies  
Consider delivery if term  
Amnio-infusion may be considered during labour via intrauterine catheter |
| **Prognosis** | 2-5 fold increase in risk of perinatal mortality | Poorer with early onset  
High mortality related to congenital malformations and pulmonary hypoplasia when diagnosed during T2 |
Multi-Fetal Gestation and Malpresentation

Epidemiology
- incidence of twins is 1/80 and triplets 1/6,400 in North America
- 2/3 of twins are dizygotic (fraternal)
  - risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, ethnicity (e.g. certain African regions)
- monozygous twinning occurs at a constant rate worldwide (1/250)
- determine zygosity by number of placentas, thickness of membranes, sex, blood type

Clinical Features

### Table 13. Complications Associated with Multiple Gestation

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Uteroplacental</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>Increased PROM/PTL</td>
<td>Prematurity*</td>
</tr>
<tr>
<td>GDM</td>
<td>Polyhydramnios</td>
<td>IUGR</td>
</tr>
<tr>
<td>Gestational HTN</td>
<td>Placental previa</td>
<td>Malpresentation</td>
</tr>
<tr>
<td>Anemia</td>
<td>Placental abruption</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Increased physiological stress on all systems</td>
<td>PPPI (uterine atony)</td>
<td>Twin-twin transfusion</td>
</tr>
<tr>
<td>Increased compressive symptoms</td>
<td>Umbilical cord prolapse</td>
<td>Increased perinatal morbidity and mortality</td>
</tr>
<tr>
<td>C/S</td>
<td>Cord anomalies (velamentous insertion, 2 vessel cord)</td>
<td>Twin interlocking (twin A breech twin B vertex)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single fetal demise</td>
</tr>
</tbody>
</table>

Management
- U/S determination of chorionicity must be done within first trimester (ideally 8-12 wk GA)
- increased antenatal surveillance
  - serial U/S q 2-3wk from 24 wk GA to assess growth (uncomplicated diamniotic dichorionitic)
  - increased frequency of ultrasounds in monochorionic diamniotic and monochorionic monoamniotic twins
  - Doppler flow studies weekly if discordant fetal growth (>30%)
  - BPP as needed
- may attempt vaginal delivery if twin A presents as vertex, otherwise C/S (40-50% of all twin deliveries, 15% of cases have twin A delivered vaginally and twin B delivered by C/S)
- mode of delivery depends on fetal weights, GA, presentation

### The Ps of Multiple Gestation Complications

- increased rates of
  - Puking
  - Pallor (anemia)
  - Preclampsia/PIH
  - Pressure (compressive symptoms)
  - PTL, PROM, PPH
  - Polyhydramnios
  - Placenta previa/abruption
  - PP/H/A
  - Prolonged labour
  - Cord prolapse
  - Prematurity
  - Malpresentation
  - Perinatal morbidity and mortality
  - Parental distress
  - Postpartum depression

### Figure 4. Classification of twin pregnancies

- *Indicates time of cleavage

---

- Monoamnionic Monochorionic (forked cord)
- Monoamnionic Monochorionic *9-12 d*
- Monoamnionic Monochorionic (one cord)
- Diamnionic Dichorionic (fused) *0-72 h*
- Diamnionic Dichorionic (separated)
- Diamnionic Monochorionic *4-8 d*
**Twin-Twin Transfusion Syndrome**

**Definition**
- formation of placental intertwin vascular anastomoses causes arterial blood from donor twin to pass into veins of the recipient twin

**Epidemiology**
- 10% of monochorionic twins
- concern if >30% discordance in estimated fetal weight

**Clinical Features**
- donor twin: IUGR, hypovolemia, hypotension, anemia, oligohydramnios
- recipient twin: hypervolemia, HTN, CHF, polycythemia, edema, polyhydramnios, kernicterus in neonatal period

**Investigations**
- detected by U/S screening, Doppler flow analysis

**Management**
- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary
- laparoscopic occlusion of placental vessels
- fetoscopic laser ablation of placental vascular anastomoses when indicated and if available

---

**Breech Presentation**

**Definition**
- fetal buttocks or lower extremity is the presenting part as determined on U/S
- complete (10%): hips and knees both flexed
- frank (60%): hips flexed, knees extended, buttocks present at cervix
  - most common type of breech presentation
  - most common breech presentation to be delivered vaginally
- incomplete (30%): both or one hip flexed and both or one knee present below the buttocks, feet or knees present first (footling breech, kneeling breech)

**Epidemiology**
- occurs in 3-4% of pregnancies at term (25% <28 wk)

**Risk Factors**
- maternal: pelvis (contracted), uterus (shape abnormalities, intrauterine tumours, fibroids, previous breech), pelvic tumours causing compression, grand multiparity
- maternal-fetal: placenta (previa), amniotic fluid (poly-/oligohydramnios)
- fetal: prematurity, multiple gestation, congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations), abnormalities in fetal tone and movement, aneuploidy, hydrocephalus, anencephalus

**Management**
- ECV: repositioning of singleton fetus within uterus under U/S guidance
  - overall success rate of 65%
  - criteria: >36 wk GA, singleton, unengaged presenting part, reactive NST, not in labour
  - contraindications: previous T3 bleed, prior classical C/S, previous myomectomy, oligohydramnios, PROM, placenta previa, abnormal U/S, suspected IUGR, HTN, uteroplacental insufficiency, nuchal cord
  - risks: abruption, cord compression, cord accident, ROM, labour, fetal bradycardia requiring C/S (<1% risk), alloimmunization, fetal death (1:5,000)
  - method: tocometry, followed by U/S guided transabdominal manipulation of fetus with constant fetal heart monitoring
  - if patient Rh negative, give Rhogam® prior to procedure
  - better prognosis if multiparous, good fluid volume, small baby, skilled obstetrician, posterior placenta
  - pre- or early-labour ultrasound to assess type of breech presentation, fetal growth, estimated weight, placenta position, attitude of fetal head (flexed is preferable); if ultrasound unavailable, recommend C/S
  - ECV and elective C/S should be presented as options with the risks and benefits outlined; obtain informed consent

---

Criteria for Vaginal Breech Delivery
- Frank or complete breech, GA >36 wk
- EFW 2,500-3,800 g based on clinical and U/S assessment (5.5–8.5 lb)
- Fetal head flexed
- Continuous fetal monitoring
- 2 experienced obstetricians, assistant, and anesthetist present
- Ability to perform emergency C/S within 30 min if required
Hypertensive Disorders of Pregnancy

**Hypertensive Disorders of Pregnancy**

- hypertensive disorders of pregnancy are classified as either pre-existing or gestational HTN

**PRE-EXISTING HYPERTENSION**

**Definition**
- BP >140/90 prior to 20 wk GA, persisting >7 wk postpartum
- essential HTN is associated with an increased risk of gestational HTN, abruptio placentae, IUGR, and IUFD

**GESTATIONAL HTN**

**Definition**
- sBP >140 or dBP >90 developing after 20th wk GA in the absence of proteinuria in a woman known to be normotensive before pregnancy

**Risk Factors**
- maternal factors
  - primigravida (80-90% of gestational HTN), first conception with a new partner, PMHx or FHx of gestational HTN
  - DM, chronic HTN, or renal insufficiency
  - obesity
  - antiphospholipid syndrome
  - extremes of maternal age (<18 or >35 yr)
  - previous stillbirth or IUFD
- fetal factors
  - IUGR or oligohydramnios
  - GTN
  - multiple gestation
  - fetal hydrops “mirror syndrome”

**Clinical Evaluation of HTN in Pregnancy**
- in general, clinical evaluation should include the mother and fetus
- **evaluation of mother**
  - body weight
  - central nervous system
    - presence and severity of headache
    - visual disturbances – blurring, scotomata
    - tremulousness, irritability, somnolence
    - hyperreflexia
  - hematologic
    - bleeding, petechiae
  - hepatic
    - RUQ or epigastric pain
    - severe N/V
  - renal
    - urine output and colour
    - non-dependent edema (i.e. hands and face)

- method for vaginal breech delivery
  - encourage effective maternal pushing efforts
  - at delivery of head (after feet), assistant must apply suprapubic pressure to flex and engage fetal head
  - delivery can be spontaneous or assisted; avoid fetal traction
  - apply fetal manipulation only after spontaneous delivery to level of umbilicus
- C/S recommended if: the breech has not descended to the perineum in the second stage of labour after 2 h, in the absence of active pushing, or if vaginal delivery is not imminent after 1 h of active pushing
- contraindications to vaginal breech delivery
  - cord presentation
  - clinically inadequate maternal pelvis
  - fetal factors incompatible with vaginal delivery (e.g. hydrocephalus, macrosomia, fetal growth restriction)

**Prognosis**
- regardless of route of delivery, breech infants have lower birth weights and higher rates of perinatal mortality, congenital anomalies, abruption, and cord prolapse

**Ominous Symptoms of HTN in Pregnancy**
- RUQ pain, headache, and visual disturbances

**Hypertension in Pregnancy**

**Adverse Maternal Conditions**
- sBP >160 mmHg
- dBP >100 mmHg
- HELLP
- Cerebral hemorrhage
- Renal dysfunction: oliguria <500 mL/d
- Left ventricular failure, pulmonary edema
- Placental abruption, DIC
- Symptoms
- Abdominal pain, N/V
- Headaches, visual prob ems
- SOB, chest pain
- Eclampsia: convulsions

**Adverse Fetal Conditions**
- IUGR
- Oligohydramnios
  - Absent/reversed umbilical artery end diastolic flow
  - Can result in:
    - Fetal disability and/or death

**Vaginal Delivery of Breech Presentation**

**SOGC Clinical Practice Guidelines**
2009;226:557-566.

**Objective**: To discuss risks and benefits of trial of labour versus planned CS, with selection criteria, management, and delivery techniques for trial of vaginal breech birth.

**Evidence**: Randomized trials, prospective cohort studies and select cohort studies from Medline search for long-term outcomes and epidemiology of vaginal breech delivery.

**Summary**: Higher risk of perinatal mortality and short-term neonatal morbidity can be associated with vaginal breech birth as compared to elective C/S. However, careful case selection (including term singleton breech fetuses and clinically adequate maternal pelvis) and labour management may achieve a similar safety level as elective C/S (—2 per 1,000 births perinatal mortality, ~2% short-term neonatal morbidity). Specific protocols for vaginal breech delivery should be followed: continuous fetal heart monitoring, assessment for adequate progress in labour, no induction of labour recommended, emergency C/S available if required, and health care providers with requisite skills and experience. Informed consent for the preferred delivery method should be obtained.
• evaluation of fetus
  - fetal movement
  - fetal heart rate tracing – NST
  - ultrasound for growth
  - BPP
  - Doppler flow studies

Laboratory Evaluation of Gestational Hypertension
• CBC
• PT, INR, fibrinogen – if abnormal LFTs or bleeding
• ALT, AST
• creatinine, uric acid
• 24 h urine collection for protein or albumin:creatinine ratio

Complications
• maternal
  - liver and renal dysfunction
  - seizure "eclampsia"
  - abruptio placentae
  - left ventricular failure/pulmonary edema
  - DIC (release of placental thromboplastin consumptive coagulopathy)
  - HELLP syndrome
  - hemorrhagic stroke (50% of deaths)
  - fetal (2nd to placental insufficiency)
  - IUGR, prematurity, abruptio placentae, IUFD

Management
• for non-severe HTN (149-159/90-105) target a BP of 130-155/80-105 in women without comorbidities or <140/90 in women with comorbidities
• for both pre-existing and gestational HTN, labetalol 100-400 mg PO bid-tid, nifedipine XL preparation 20-60 mg PO od, or a-methyldopa 250-500 mg PO bid-qid
• for severe HTN (BP>160/110), give one of:
  - labetalol 20 mg IV then 20-80 mg IV q30min (max 300 mg) (then switch to oral)
  - nifedipine 5-10 mg capsule q30min
  - hydralazine 5 mg IV, repeat 5-10 mg IV q30min or 0 5 to 10 mg/hr IV, to a maximum of 20 mg IV (or 30 mg IM)
• no ACEI, ARBs, diuretics, prazosin, or atenolol
• pre-existing HTN and gestational HTN without any deterioration can be followed until 37 wk, then decide to induce shortly thereafter

PREECLAMPSIA

Definition
• pre-existing or gestational HTN with new onset proteinuria or adverse conditions

Risk Factors
• nulliparity
• preeclampsia in a previous pregnancy
• age >40 yr or <18 yr
• FHx of preeclampsia
• chronic HTN
• chronic renal disease
• antiphospholipid antibody syndrome or inherited thrombophilia
• vascular or connective tissue disease
• DM (pre-gestational and gestational)
• obesity
• hydrops fetalis “mirror syndrome”
• unexplained fetal growth restriction
• abruptio placentae
• there is a potential for further deterioration to severe preeclampsia as defined above

Management
• depends on GA, possible threat of seizures
• if stable and no adverse factors, may admit and follow, ± decide to deliver as approaching 34-36 wk
  (must weigh risks of fetal prematurity vs. risks of developing severe preeclampsia/eclampsia)
• for severe preeclampsia, stabilize and deliver
• if severe preeclampsia during labour, increase maternal monitoring: hourly input and output, urine dip q12h, hourly neurological vitals, and increase fetal monitoring (continuous FHR monitoring)
• antihypertensive therapy
  - labetalol 20 mg IV, then 20-80 mg IV q30min (max 300 mg) (then switch to oral)
  - nifedipine 5-10 mg capsule q30min
  - hydralazine 5 mg IV, repeat 5-10 mg IV q30min or 0.5 to 10 mg/hr IV, to a maximum of 20 mg IV (or 30 mg IM)

I-A Evidence-Recommendation Highlights of SOGC Clinical Practice Guidelines
Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy
• For BP measurement, Korotkoff phase V should be used to designate the dBP.
• Calcium supplementation (if at least 1g/d, orally) is recommended for women with low dietary intake of calcium (<800 mg/d). (I-A)
• For preeclampsia prevention among increased risk women, low-dose “spironolactone” (75-100 mg/d) is recommended until delivery.
• Umbilical artery Doppler velocimetry should be part of the antenatal fetal surveillance in preeclampsia.
• Initial antihypertensive therapy for severe HTN (sBP >160 or dBP >110) should be with labetalol, nifedipine, or hydralazine.
• Initial antihypertensive therapy for non-severe HTN (BP 140-159/90-109 mmHg) should be with methyldopa, β-blockers, or calcium channel blockers.
• Antenatal corticosteroids for fetal lung maturation should be considered for all women with preeclampsia before 34 wk gestation.
• In a planned vaginal delivery with an unfavourable cervix, cervical ripening should be used.
• Oxytocin 5 units IV or 10 units IM should be used as part of the management during the third stage of labour, particularly in the presence of thrombocytopenia or coagulopathy.
• MgSO4 is the recommended first-line treatment for eclampsia.
• MgSO4 is the recommended eclampsia prophylaxis in severe preeclampsia.
• seizure prevention
  ■ MgSO₄
• postpartum management
• risk of seizure highest in first 24 h postpartum – continue MgSO₄ for 12-24 h after delivery
• watch for HELLP syndrome
• most return to a normotensive BP within 2 wk

ECLAMPSIA

Definition
• the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions

Epidemiology
• an eclamptic seizure occurs in approximately 0.5% of mildly preeclamptic women and 2-3% of severely preeclamptic women

Risk Factors
• same as risk factors for preeclampsia

Clinical Manifestations
• eclampsia is a clinical diagnosis
• typically tonic-clonic and lasting 60-75 s
• symptoms that may occur before the seizure include persistent frontal or occipital headache, blurred vision, photophobia, right upper quadrant or epigastric pain, and altered mental status
• in up to one third of cases, there is no proteinuria or blood pressure <140/90 mmHg prior to the seizure
• in general, women with typical eclamptic seizures who do not have focal neurologic deficits or prolonged coma do not require diagnostic evaluation including imaging

Management
• ABCs
• roll patient into LLDP
• supplemental O₂ via face mask to treat hypoxemia due to hypoventilation during convulsive episode
• aggressive antihypertensive therapy for sustained diastolic pressures ≥105 mmHg or systolic blood pressures ≥160 mmHg with hydralazine or labetalol
• prevention of recurrent convulsions: to prevent further seizures and the possible complications of repeated seizure activity (e.g. rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, etc.)
• MgSO₄ is now the drug of choice, with previously used agents including diazepam and phenytoin
• the definitive treatment of eclampsia is DELIVERY, irrespective of gestational age, to reduce the risk of maternal morbidity and mortality from complications of the disease
• mode of delivery is dependent on clinical situation and fetal-maternal condition

Medical Complications of Pregnancy

Iron and Folate Deficiency Anemia

Table 14. Iron Deficiency and Folate Deficiency Anemia

<table>
<thead>
<tr>
<th>Iron Deficiency Anemia</th>
<th>Folate Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>See Hematology, H15</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Responsible for 80% of causes of non-physiologic anemia during pregnancy</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>See Hematology, H15</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>See Hematology, H15</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Prevention (non-anemic): 30 mg elemental iron/d (net by most prenatal vitamins)</td>
</tr>
<tr>
<td>Treatment (anemic): 30-120 mg elemental iron/d</td>
<td></td>
</tr>
<tr>
<td>325 mg ferrous fumarate = 106 mg elemental Fe²⁺</td>
<td></td>
</tr>
<tr>
<td>325 mg ferrous sulfate = 65 mg elemental Fe²⁺</td>
<td></td>
</tr>
<tr>
<td>325 mg ferrous gluconate = 36 mg elemental Fe²⁺</td>
<td></td>
</tr>
<tr>
<td>Polysaccharide-Iron Complex = 150 mg elemental Fe/capsule</td>
<td></td>
</tr>
<tr>
<td>Prevention: 0.4-1 mg folic acid PO daily for 1-3 mg preconceptionally and throughout T1, or 5 mg folic acid per day with past history of ONTD, DM, or antiepileptic medication use</td>
<td></td>
</tr>
</tbody>
</table>

| **Complications**              | Maternal: increased blood volume, N/V, anorexia |
| Fetal: neural tube defects in T1, low birth weight, prematurity |
| **Notes**                      | Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake |
| Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg) and losses (200 mg) – more needed for multiple gestations |
| **Minimum daily requirement is 0.4 mg** |
| Most often associated with iron deficiency anemia |
| Folic acid is necessary for closure of neural tube during early fetal development (by day 28 of gestation) |
Diabetes Mellitus

Epidemiology
- 2-4% of pregnancies are complicated by DM

Classification of Diabetes Mellitus
- type 1 and type 2 DM (see Endocrinology, E7)
- GDM: onset of DM during pregnancy (usually tested for around 24-28 wk GA)

Etiology
- type 1 and type 2 DM
- GDM: anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → leading to GDM and/or exacerbating pre-existing DM

MANAGEMENT

A. TYPE 1 and TYPE 2 DM

Preconception
- pre-plan and refer to high-risk clinic
- optimize glycemic control
- counsel patient on potential risks and complications
- evaluate for diabetic retinopathy, neuropathy, CAD

Pregnancy
- if already on oral medication, generally switch to insulin therapy
  - continuing glyburide or metformin controversial
  - teratogenicity unknown for other oral anti-hyperglycemics
  - tight glycemic control
  - insulin dosage may need to be adjusted in T2 due to increased demand and increased insulin resistance
  - monitor as for normal pregnancy, plus initial 24 h urine protein and creatinine clearance, retinal exam, HbA1c
    - HbA1c: >140% of pre-pregnancy value associated with increased risk of spontaneous abortion and congenital malformations
  - increased fetal surveillance (BPP, NST), consider fetal ECHO (if high Hgb A1c in first trimester or just prior to pregnancy) to look for cardiac abnormalities

Labour
- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose, and blood pressure control)
- can wait for spontaneous labour if blood glucose well-controlled and BPP normal
- induce by 38-39 wk
- type of delivery
  - increased risk of cephalopelvic disproportion (CPD) and shoulder dystocia with babies >4,000 g (8.8 lbs)
  - consider elective C/S for predicted birthweight >4,500 g (9.9 lbs) (controversial)
  - monitoring
    - during labour, monitor blood glucose q1h with patient on insulin and dextrose drip
    - aim for blood glucose between 3.5-6.5 mmol/L to reduce the risk of neonatal hypoglycemia

Postpartum
- insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
- no insulin is required for 48-72 h postpartum in most type 1 DM
- monitor glucose q6h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >8 mmol/L

B. GESTATIONAL DM

Screening and Diagnosis
- all pregnant women between 24-28 wk GA (or at any stage if high risk)
- 2 screening options
  - 1-step screening with fasting 75 g OGTT; GDM if ≥1 of:
    - FPG ≥ 5.1 mmol/L
    - 1h PG ≥ 10.0 mmol/L
    - 2h PG ≥ 8.5 mmol/L
  - 2-step screening (recommended by the Canadian Diabetes Association)
    - Step 1: Perform a random non-fasting 50 g OGCT
      - 1h PG < 7.8 mmol/L is normal
      - 1h PG ≥ 11.1 mmol/L is GDM
    - if 1h PG 7.8-11.0 mmol/L, proceed to Step 2
    - Step 2: Perform a fasting 75 g OGTT, GDM if ≥1 of:
      - FPG ≥ 5.3 mmol/L
      - 1h PG ≥ 10.6 mmol/L
      - 2h PG ≥ 9.0 mmol/L

Monitoring Glucose Levels
- Frequent measurements of blood glucose during pregnancy are advised for women with type 1 or 2 DM to help prevent or treat both hypoglycemia and hyperglycemia, and also improves neonatal outcome
- Aim for:
  - FPG < 5.3 mmol/L (95 mg/dL)
  - 1 h post prandial PG < 7.8 mmol/L (140 mg/dL), 2 h post prandial PG < 6.7 mmol/L (120 mg/dL)
- Most women can be followed with monthly HbA1c determinations

Risk Factors for GDM
- Age > 25 yr
- Obesity
- Ethnicity (Aboriginal, Hispanic, Asian, African)
- FHx of DM
- Previous history of GDM
- Previous child with birthweight > 4.0 kg
- Polycystic ovarian syndrome
- Current use of glucocorticoids
- Essential HTN or pregnancy-related HTN

Post-prandial blood glucose values seem to be the most effective at determining the likelihood of macrosomia or other adverse pregnancy outcomes
Management
- first line is management through diet modification and increased physical activity
- initiate insulin therapy if glycemic targets not achieved within 2 wk of lifestyle modification alone
- glycemic targets: FPG <5.3 mmol/L, 1h PG <7.8 mmol/L, 2h PG <6.7 mmol/L
- oral agents can be used in pregnancy but is off-label and should be discussed with patient
- stop insulin and diabetic diet postpartum
- follow-up with 75 g OGGT by 3 months postpartum, counsel about lifestyle modifications, and perform glucose challenge test q3yr

Prognosis
- most maternal and fetal complications are related to hyperglycemia and its effects

Long-Term Maternal Complications
- type 1 and type 2 DM: risk of progressive retinopathy and nephropathy
- GDM: 50% risk of developing type 2 DM in next 20 yr

Table 15. Complications of DM in Pregnancy

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric</td>
<td>Growth Abnormalities</td>
</tr>
<tr>
<td>HTN/preeclampsia (especially if pre-existing nephropathy/proteinuria): insulin resistance is implicated in etiology of HTN</td>
<td>Macrosomia: maternal hyperglycemia leads to fetal hyperinsulinism resulting in accelerated anabolism</td>
</tr>
<tr>
<td>Polyhydramnios: maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal polyuria (a major source of amniotic fluid)</td>
<td>IUGR: due to placental vascular insufficiency</td>
</tr>
<tr>
<td>Diabetic Emergencies</td>
<td>Delayed Organ Maturity</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Fetal lung immaturity: hyperglycemia interferes with surfactant synthesis (respiratory distress syndrome)</td>
</tr>
<tr>
<td>Ketonacidosis</td>
<td></td>
</tr>
<tr>
<td>Diabetic coma</td>
<td></td>
</tr>
<tr>
<td>End-Organ Involvement or Deterioration (occur in type 1 DM and type 2 DM, not in GDM)</td>
<td>Congenital Anomalies (occur in type 1 DM and type 2 DM, not in GDM)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>2.7x increased risk of cardiac (VSD), NTD, GU (cystic kidneys), GI (anal atresia), and MSK (sacral agenesis) anomalies due to hyperglycemia</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Note: Preganancies complicated by GDM do not manifest an increased risk of congenital anomalies because GDM develops after the critical period of organogenesis (in T1)</td>
</tr>
<tr>
<td>Other</td>
<td>Labour and Delivery</td>
</tr>
<tr>
<td>Pyelonephritis/UTI: glucosuria provides a culture medium for E. coli and other bacteria</td>
<td>Preterm labour/prematurity: most commonly in patients with HTN/preeclampsia</td>
</tr>
<tr>
<td>Increased incidence of spontaneous abortion (in type 1 DM and type 2 DM, not in GDM): related to pre-conception glycemic control</td>
<td>Preterm labour is associated with poor glycemic control but the exact mechanism is unknown</td>
</tr>
<tr>
<td></td>
<td>Increased incidence of stillbirth</td>
</tr>
<tr>
<td></td>
<td>Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia</td>
</tr>
<tr>
<td>Neonatal</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia and jaundice: due to prematurity and polycythemia</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia: exact pathophysiology not understood, may be related to functional hypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Polycythemia: hyperglycemia stimulates fetal erythropoietin production</td>
<td></td>
</tr>
</tbody>
</table>

Group B Streptococcus

Epidemiology
- 15-40% vaginal carrier rate

Risk Factors (for neonatal disease)
- GBS bacteriuria during current pregnancy, even if treated
- previous infant with invasive GBS disease
- preterm labour <37 wk
- ruptured membranes >18 h before delivery
- intrapartum maternal temperature ≥38°C
- positive GBS screen between 35-37 weeks GA in current pregnancy

Clinical Features
- not harmful to mother
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia, and death)
Investigations
• offer screening to all women at 35-37 wk with vaginal and anorectal swabs for GBS culture

Treatment
• treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
• indications for antibiotic prophylaxis: positive GBS screen, GBS in urine, or previous infant with GBS
disease or GBS status unknown and one of the other risk factors
antibiotics for GBS prophylaxis
  ■ penicillin G 5 million units IV, then 2.5 million units IV q4h until delivery
  ■ penicillin allergic but not at risk for anaphylaxis: cefazolin 2 g IV then 1 g q8h
  ■ penicillin allergic and at risk for anaphylaxis: vancomycin 1 g IV q12h until delivery
• if fever, broad spectrum antibiotic coverage is advised

Urinary Tract Infection

Epidemiology
• most common medical complication of pregnancy
• asymptomatic bacteriuria in 2-7% of pregnant women, more frequently in multiparous women
• note: asymptomatic bacteriuria should be treated in pregnancy due to increased risk of pyelonephritis
  and preterm labour

Etiology
• increased urinary stasis from mechanical and hormonal (progesterone) factors
• organisms include GBS as well as those that occur in non-pregnant women

Clinical Features
• may be asymptomatic
• dysuria, urgency, and frequency in cystitis
• fever, flank pain, and costovertebral angle tenderness in pyelonephritis

Investigations
• urinalysis, urine C&S
• cystoscopy and renal function tests in recurrent infections

Management
• uncomplicated UTI
  ■ first line: amoxicillin (250-500 mg PO q8h x 7 d)
  ■ alternatives: nitrofurantoin (100 mg PO bid x 7 d)
  ■ follow with monthly urine cultures
• pyelonephritis
  ■ hospitalization and IV antibiotics

Prognosis
• complications if untreated: acute cystitis, pyelonephritis, and possible preterm labour
• recurrence is common
# Infections During Pregnancy

## Table 16. Infections During Pregnancy

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent</th>
<th>Source of Transmission</th>
<th>Greatest Transmission Risk to Fetus</th>
<th>Effects on Fetus</th>
<th>Effects on Mother</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken Pox</td>
<td>Varicella zoster virus</td>
<td>To mom: direct, respiratory To baby: transplacental</td>
<td>13-30 wk GA, and 5 d pre- to 2 d post-delivery</td>
<td>Congenital varicella syndrome (limb aplasia, chorioretinitis, cataracts, cutaneous scars, cortical atrophy, IU5R, hydrops), preterm labour</td>
<td>Fever, malaise, vesicular pruritic lesions</td>
<td>Clinical, ± vesicle fluid culture, ± serology</td>
<td>VZIG for mother if exposed, decreases congenital varicella syndrome Note: do not administer vaccine during pregnancy (live attenuated vaccine)</td>
</tr>
<tr>
<td>*CMV</td>
<td>DNA virus (herpes family)</td>
<td>To mom: blood/organ transfusion, sexual contact To baby: transplacental, during delivery, breast milk</td>
<td>T1-T3</td>
<td>5-10% develop CNS involvement (mental retardation, cerebral calcification, hydrocephalus, microcephaly, deafness, chorioretinitis)</td>
<td>Asymptomatic or flu-like</td>
<td>Serologic screen; isolate virus from urine or secretion culture</td>
<td>No specific treatment; maintain good hygiene and avoid high risk situations</td>
</tr>
<tr>
<td>Erythema Infectiosum (Fifth Disease)</td>
<td>Parvovirus B19</td>
<td>To mom: respiratory, infected blood products To baby: transplacental</td>
<td>10-20 wk GA</td>
<td>Spontaneous abortion (SA), stillbirth, hydrops in utero</td>
<td>Flu-like, rash, arthritis; often asymptomatic</td>
<td>Serologic screening for all pregnancies</td>
<td>Rx neonate with HBIG and vaccine (at birth, 1, 6 mo); 90% effective</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>DNA virus</td>
<td>To mom: blood saliva, semen, vaginal secretions To baby: transplacental, breast milk</td>
<td>T3</td>
<td>10% vertical transmission if asymptomatic and HBSAg + ve; 85-90% if HBSAg and HBeAg + ve</td>
<td>Prematurity, low birth weight, neonatal death</td>
<td>Fever, N/V, fatigue, jaundice, elevated liver enzymes</td>
<td>Serologic screening for all pregnancies</td>
</tr>
<tr>
<td>*Herpes Simplex Virus</td>
<td>DNA virus</td>
<td>To mom: intimate mucocutaneous contact To baby: transplacental, during delivery</td>
<td>Delivery (if genital lesions present); less commonly in utero</td>
<td>Disseminated herpes (20%); CNS sequelae (35%); self-limited infection</td>
<td>Painful vesicular lesions</td>
<td>Clinical diagnosis</td>
<td>Acyclovir for symptomatic women, suppressive therapy at 36 wk controversial Suggested C/S if active genital lesions, even if remote from vulva</td>
</tr>
<tr>
<td>HIV</td>
<td>RNA retrovirus</td>
<td>To mom: blood, semen, vaginal secretions To baby: in utero, during delivery breast milk</td>
<td>1/3 in utero, 1/3 at delivery, 1/3 breastfeeding</td>
<td>U5R, preterm labour; PROM</td>
<td>See Infectious Diseases, ID27</td>
<td>Serology, viral PCR; All pregnant women are offered screening</td>
<td>Triple anti-retroviral therapy decreases transmission to &lt;1% Elective C/S: no previous antiviral Rx or monotherapy only, viral load unknown or &gt;500 RNA copies/mL, unknown perinatal care, patient request</td>
</tr>
<tr>
<td>*Rubella</td>
<td>ssRNA togavirus</td>
<td>To mom: respiratory droplets (highly contagious) To baby: transplacental</td>
<td>T1</td>
<td>SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, MR, JUGR, hepatitis, CNS defects, cossos changes)</td>
<td>Rash (50%), fever, posterior auricular or occipital lymphadenopathy, arthralgia</td>
<td>Serologic testing; all pregnant women screened (immune if titer ≥ 1:16); infection if IgM present or &gt;4x increase in IgG</td>
<td>No specific treatment; offer vaccine following pregnancy Do not administer during pregnancy (live attenuated)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Spirochete (Treponema pallidum)</td>
<td>To mom: sexual contact To baby: transplacental</td>
<td>T1-T3</td>
<td>Risk of preterm labour, multisystem involvement, fetal death</td>
<td>See Infectious Diseases, ID25</td>
<td>VDRL screening for all pregnancies; if positive, requires confirmatory testing</td>
<td>Pen G 2.4 million U IM x 1 dose if early syphilis, 3 doses if late syphilis, monitor VDRL monthly If Pen G allergic: Cindamycin 900 mg IV q4h</td>
</tr>
<tr>
<td>*Toxoplasmosis</td>
<td>Protozoa (toxoplasma gondii)</td>
<td>To mom: raw meat, unpasteurized goat’s milk, cat feces/urine To baby: transplacental</td>
<td>T3 (but most severe if infected in T1); only concern if primary infection during pregnancy</td>
<td>Congenital toxoplasmosis (choorioretinitis, hydrocephaly intracranial calcification, MR, microcephaly) NB: 75% initially asymptomatic at birth</td>
<td>Majority subclinical; may have flu-like symptoms</td>
<td>IgM and IgG serology; PCR of amniotic fluid</td>
<td>Self-limiting in mother; spiramycin decreases fetal morbidity but not rate of transmission</td>
</tr>
</tbody>
</table>

* Indicates TORCH infection
Venous Thromboembolism

Epidemiology
- incidence of 12.1/10,000 (DVT), and 5.4/10,000 (PE)
- increased risk of VTE throughout pregnancy with highest risk of DVT in third trimester and postpartum period; highest risk of PE post-partum (first 6 weeks)

Risk Factors
- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, thrombophilias (see Hematology, H35)

Table 17. Risk Factors for VTE Specific to Pregnancy

<table>
<thead>
<tr>
<th>Hypercoagulability</th>
<th>Stasis</th>
<th>Endothelial</th>
</tr>
</thead>
<tbody>
<tr>
<td>II, V, VII, IX, X, XII, fibrinogen</td>
<td>Increased Factors</td>
<td>Vascular damage at delivery (C/S or SVD)</td>
</tr>
<tr>
<td>Increased platelet aggregation</td>
<td>Increased resistance to activated protein C</td>
<td>Uterine instrumentation</td>
</tr>
<tr>
<td>Decreased protein S</td>
<td>Antithrombin can be normal or reduced</td>
<td>Peripartum pelvic surgery</td>
</tr>
<tr>
<td>tPA Factors XI, XII</td>
<td>Increased venous distensibility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased venous tone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% decrease in venous flow in lower extremity by T3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uturus is mechanical impediment to venous return</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a pulmonary embolism are non-specific (as in non-pregnant women)
- unexplained spontaneous fetal loss

Investigations
- duplex venous Doppler sonography for DVT
- CXR and V/Q scan or spiral CT for PE

Management
- before initiating treatment, obtain a baseline CBC including platelets and aPTT
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- unfractionated heparin
  - bolus of 5,000 IU followed by an infusion of ~30 000 IU/24h
  - measure aPTT 6 h after the bolus
  - maintain aPTT at a therapeutic level (1.5-2x normal)
  - repeat q24h once therapeutic
  - heparin-induced thrombocytopenia (HIT) uncommon (3%), but serious complication
  - LMWH can also be used in pregnancy
- compression stockings
- poor evidence to support a recommendation for or against avoidance of prolonged sitting
- VTE prophylaxis
  - women on long-term anticoagulation: full therapeutic anticoagulation throughout pregnancy and for 6-12 wk postpartum
  - women with a non-active PMHx of VTE: unfractionated heparin regimens suggested
  - insufficient evidence in pregnancy to recommend routine use of LMWH for all patients
  - current prophylaxis regimens for acquired thrombophilias (e.g. APS syndrome) include low dose Aspirin® in conjunction with prophylactic heparin

Normal Labour and Delivery

Definition of Labour
- true labour: regular, painful contractions of increasing intensity associated with progressive dilatation and effacement of cervix and descent of presenting part, or progression of station
  - preterm (>20 to <36+6 wk GA)
  - term (37-41+6 wk GA)
  - postterm (>42 wk GA)
- false labour (Braxton-Hicks contractions): irregular contractions, with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any cervical dilatation, effacement, or descent
  - often relieved by rest or sedation
The Cervix

- dilatation: latent phase (0-4 cm, variable time); active phase (4-10 cm)
- effacement: thinning of the cervix by percentage or length of cervix (cm)
- consistency: firm vs. soft
- position: posterior, mid, or anterior
- application: contact between the cervix and presenting part (i.e. well or poorly applied)
- see Bishop Score (Table 22, OB36)

The Fetus

- fetal lie: orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, oblique)
- fetal presentation: fetal body part closest to the birth canal
  - breech (complete, frank, incomplete) (see Figure 5, OB22)
  - cephalic (vertex/occiput, face, asynclitc, brow)
  - transverse (shoulder)
  - compound (fetal extremity prolapses along with presenting part)
  - all ex. ept vertex are considered malpresentations (see Obstetrical Complications, OB15)
- fetal position: position of presenting part of the fetus relative to the maternal pelvis
  - OA: most common presentation (“normal”) – left OA most common
  - OP: most rotate spontaneously to OA; may cause prolonged second stage of labour
  - OT: leads to arrest of dilatation
    - normally, fetal head enters maternal pelvis and engages in OT position
    - subsequently rotates to OA position (or OP in a small percentage of cases)
- attitude: flexion/extension of fetal head relative to shoulders
  - brow presentation: head partially extended (requires C/S)
  - face presentation: head fully extended
  - mentum posterior always requires C/S, mentum anterior can deliver vaginally
- station: position of presenting bony part relative to ischial spines – determined by vaginal exam
  - at ischial spines = station 0 = engaged
  - -5 to -1 cm above ischial spines or
  - +1 to +5 cm below ischial spines

Maternal Triage Assessment

ID: Age, GPA, EDC, GA, GBS, Rh, Ser CC
HPI: 4 key questions:
- Contractions: Since when, how close (q x min), how long (x s), how painful
- Bleeding: Since when, how much (pads), colour (pink/purplish show vs. brownish vs. bright red = clots), pain?, last U/S, trauma/intercourse? (CDM)
- Fluid (ROM): Since when, large gush vs. trickle, soaked pants? clear vs. green vs. red?, continuous?
- FM: As much as usual?, When last movement?, Kick counts (ie still for 1-2 h, cold juice, feel FM – should have 6 movements in 2 h)

Pregrift: Any complications (HTN, GDM, infections), IPI/FTS screening, last U/S (BPP score, growth/estimated fetal weight, position), last vaginal exam
POBax: Every previous pregnancy and outcome: Year, SVD/CS/miscarriage/abortion, baby size, length of labour, use of vacuum or forceps, complications
PMH, Meds, Allergies, Stx
O/E: Maternal vitals, fetal heart tracing (baseline, variability, presence of accelerations/decelerations), Leopold’s, vaginal exam, U/S

Reference Point for Describing Fetal Position

- Occiput for cephalic presentation
- Sacrum for breech presentation
- Mentum for face presentation

Figure 6. Fetal positions
Four Stages of Labour

First Stage of Labour (0 – 10 cm cervical dilation)
- latent phase
  - uterine contractions typically infrequent and irregular
  - slow cervical dilatation (usually to 4 cm) and effacement
- active phase
  - rapid cervical dilatation to full dilatation (nulliparous ≥1.0 cm/h, multiparous ≥1.2 cm/h)
  - phase of maximum slope on cervical dilatation curve
  - painful, regular contractions q2-3min, lasting 45-60 s
  - contractions strongest at fundus

Second Stage of Labour (10 cm dilation – delivery of the baby)
- from full dilatation to delivery of the baby; duration varies based on parity, contraction quality, and type of analgesia
- mother feels a desire to bear down and push with each contraction
- women may choose a comfortable position that enhances pushing efforts and delivery
  - upright (semi-sitting, squatting) and LLDP are supported in the literature
- progress measured by descent

Third Stage of Labour (delivery of the baby – delivery of the placenta)
- from baby’s birth to separation and expulsion of the placenta
- can last up to 30 min before intervention is indicated
- demonstrated by gush of fresh blood, umbilical cord lengthening, uterine fundus changing shape (firm and globular) and rising upward
- active management: start oxytocin IV drip, or give 10 U IM or 5 mg IV push after delivery of anterior shoulder in anticipation of placental delivery, otherwise give after delivery of placenta
- routine oxytocin administration in third stage of labour can reduce the risk of PPH by >40%

Fourth Stage of Labour
- first postpartum hour
- monitor vital signs and bleeding, repair lacerations
- ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
- inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
- 3rd and 4th stages of labour most dangerous to the mother (i.e. hemorrhage)

The Cardinal Movements of the Fetus During Delivery

1. Head floating, before engagement
2. Engagement, descent, flexion
3. Further descent, internal rotation
4. Complete rotation, beginning extension
5. Complete extension
6. Restitution (external rotation)
7. Delivery of anterior shoulder
8. Delivery of posterior shoulder

Course of Normal Labour*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Nulliparous</th>
<th>Multiparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>6-18 h</td>
<td>2-10 h</td>
</tr>
<tr>
<td>Second</td>
<td>30 min-1 h</td>
<td>5-30 min</td>
</tr>
<tr>
<td>Third</td>
<td>5-30 min</td>
<td>5-30 min</td>
</tr>
</tbody>
</table>

*without epidural

Signs of Placental Separation
- Gush of blood
- Lengthening of cord
- Uterus becomes globular
- Fundus rises

Continuous Support for Women During Childbirth
Cochrane DB Syst Rev 2011;16:CD003766
Study: Systematic review of 21 RCTs from 11 countries, 15,061 women in labour.
Intervention: Continuous support during labour vs. usual care.
Outcome: Effects on mothers and their babies.
Results: Continuous intrapartum support increased likelihood of shorter labour, spontaneous vaginal birth, decrease in analgesia use, and a decrease in dissatisfaction with childbirth experience. Greatest benefit when provider is not a healthcare professional. Continuous support was also associated with decreased likelihood to have a Caesarean or instrumental vaginal birth, regional analgesia, or a baby with a low 5 min APGAR score.

Figure 7. Cardinal movements of fetus during delivery
Adapted from illustration in Williams Obstetrics, 19th ed
Analgesic and Anesthetic Techniques in Labour and Birth

• pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

Non-Pharmacologic Pain Relief Techniques
• reduction of painful stimuli
  • maternal movement, position change, counter-pressure, abdominal compression
• activation of peripheral sensory receptors
  • superficial heat and cold
  • immersion in water during labour
  • touch and massage, acupunture, and acupressure
  • TENS
  • intradermal injection of sterile water
  • aromatherapy
• enhancement of descending inhibitory pathways
  • attention focusing and distraction
  • hypnosis
  • music and audio analgesia
  • biofeedback

Pharmacologic Methods (see Anesthesia and Perioperative Medicine, A26)
• nitrous oxide (e.g. self-administered Entonox®)
• narcotics (usually combined with anti-emetic)
• pudendal nerve block
• perineal infiltration with local anesthetic
• regional anesthesia (epidural block, combined spinal-epidural, spinal)

Fetal Monitoring in Labour

• see online Fetal Heart Rate Tutorial

Vaginal Exam
• membrane status, as indicated by amniotic fluid (clear, pink, bloody, meconium)
• cervical effacement (thinning), dilatation, consistency position, application
• fetal presenting part, position, station
• bony pelvis size and shape
• monitor progress of labour at regular intervals and document in a partogram

Intrapartum Fetal Monitoring
• intermittent fetal auscultation with Doppler device q15-30min for 1 min in first stage active phase following a contraction, q5min during second stage when pushing has begun
• continuous electronic FHR monitoring reserved for abnormal auscultation, prolonged labour, labour which is induced or augmented, meconium present, multiple gestation/fetal complication
  • use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate when used routinely in all patients (i.e. no risk factors)
  • techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
• fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (CTG) to resolve the interpretation of abnormal or atypical patterns

Electronic FHR Monitoring
• FHR measured by Doppler; contractions measured by tocometer
• described in terms of baseline FHR, variability (short-term, long-term), and periodicity (accelerations, decelerations)
• Baseline FHR
  • normal range is 110-160 bpm
  • parameter of fetal well-being vs. distress
• Variability
  • physiologic variability is a normal characteristic of FHR
  • variability is measured over a 15 min period and is described as: absent, minimal (<6 bpm), moderate (6-25 bpm), marked (>25 bpm)
  • normal variability indicates fetal acid-base status is acceptable
  • can only be assessed by electronic fetal monitoring (CTG)
  • variability decreases intermittently even in healthy fetus
  • see Table 19, OB34

Approach to the Management of Abnormal FHR

POISON – ER
Position (left lateral decubitus position)
O₂ (100% by mask)
IV fluids (corrects maternal hypotension)
Fetal scalp stimulation
Fetal scalp electrode
Fetal scalp pH
Stop oxytocin
Notify MD
Vaginal exam to rule out cord prolapse
Rule out fever, dehydration, drug effects, prematurity
• If above fails, consider C/S
• Periodicity
  • accelerations: increase of ≥15 bpm for ≥15 s, in response to fetal movement or uterine contraction (or ≥10 bpm for ≥10 s if <32 wk GA)
  • decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability

Table 18. Factors Affecting Fetal Heart Rate

<table>
<thead>
<tr>
<th>Fetal Tachycardia (FHR &gt;160 bpm)</th>
<th>Fetal Bradycardia (FHR &lt;110 bpm)</th>
<th>Decreased Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Factors</td>
<td>Fetal Factors</td>
<td>Drugs</td>
</tr>
<tr>
<td>Fever, hyperthyroidism, anemia,</td>
<td>Hypothermia, hypotension, hypoglycemia, position, umbilical cord occlusion</td>
<td>Sympathomimetics, β-blockers, narcotics, sedatives</td>
</tr>
<tr>
<td>dehydration</td>
<td>Infection</td>
<td>Magnesium sulphate, β-blockers</td>
</tr>
<tr>
<td>Fetal Factors</td>
<td>Rapid descent, dysrhythmia, heart block, hypoxia, vaginal stimulation (head compression), hypothermia, acidosis</td>
<td>Chorioamnionitis, Early hypoxia (abruption, HTN)</td>
</tr>
<tr>
<td>Arrhythmia, anemia, infection,</td>
<td>CNS anomalies</td>
<td>Late hypoxia (abruption HTN)</td>
</tr>
<tr>
<td>prolonged activity, chronic</td>
<td>Dysrhythmia</td>
<td>Acute cord prolapse</td>
</tr>
<tr>
<td>hypoxemia, congenital anomalies</td>
<td>Inactivity/sleep cycle, preterm</td>
<td>Hypercontractility</td>
</tr>
<tr>
<td>Drugs</td>
<td>Obstructive</td>
<td>Uteroplacental</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Early hypoxia</td>
<td>Early hypoxia (abruption, HTN)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Brachial</td>
<td>Late hypoxia (abruption HTN)</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Hypertension</td>
<td>Acme of contraction</td>
</tr>
<tr>
<td>Narcotics, sedatives</td>
<td>Hypotension</td>
<td>FHR (baseline)</td>
</tr>
<tr>
<td>Magnesium sulphate, β-blockers</td>
<td>Hypoglycemia</td>
<td>Nadir of deceleration</td>
</tr>
<tr>
<td>Uteroplacental</td>
<td>acidosis</td>
<td>Onset of deceleration</td>
</tr>
<tr>
<td>Early hypoxia (abruption, HTN)</td>
<td></td>
<td>Early Deceleration</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td></td>
<td>End of contraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine contraction</td>
</tr>
<tr>
<td></td>
<td>Variable Deceleration</td>
<td>(baseline)</td>
</tr>
</tbody>
</table>

Variable Decelerations

- Variable in shape, onset, and duration
- Most common type of periodicity seen during labour
- Often with abrupt drop in FHR >15 bpm below baseline (>15 s, <2 min); usually no effect on baseline FHR or variability
- Due to cord compression or, in second stage, forceful pushing with contractions

Complicated Variable Decelerations

- FHR drop <70 bpm for >60 s
- Loss of variability or decrease in baseline after deceleration
- Biphasic deceleration
- Slow return to baseline
- Baseline tachycardia or bradycardia
- May be associated with fetal acidemia

Late Decelerations

- Uniform shape with onset, nadir, and recovery occurring after peak of contraction, slow return to baseline
- May cause decreased variability and change in baseline FHR
- Due to fetal hypoxia and acidemia, maternal hypotension, or uterine hypertonus
- Usually a sign of uteroplacental insufficiency (an ominous sign)

Table 19. Comparison of Decelerations

<table>
<thead>
<tr>
<th>Early Deceleration</th>
<th>Variable Deceleration</th>
<th>Complicated Variable Deceleration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of contraction</td>
<td>Variable in duration, intensity, and timing</td>
<td>FHR &gt;60 bpm at baseline</td>
</tr>
<tr>
<td>Nadir of deceleration</td>
<td>End of contraction</td>
<td>&gt;60 s in duration with slow return to baseline</td>
</tr>
<tr>
<td>FHR (baseline)</td>
<td>Onset of deceleration</td>
<td>Onset of contraction</td>
</tr>
<tr>
<td>FHR (baseline)</td>
<td>Nadir of deceleration</td>
<td>30 seconds of lag time</td>
</tr>
<tr>
<td>FHR</td>
<td>Acme of contraction</td>
<td></td>
</tr>
</tbody>
</table>
Table 20. Classification of Intrapartum EFM Tracings

<table>
<thead>
<tr>
<th>Category</th>
<th>Normal Tracing (Category 1)</th>
<th>Atypical Tracing* (Category 2)</th>
<th>Abnormal Tracing* (Category 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>110-160 bpm</td>
<td>Bradycardia 100-110 bpm</td>
<td>Bradycardia &lt; 100 bpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia &gt; 160 for 30-80 min</td>
<td>Tachycardia &gt; 160 for &gt;80 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rising baseline</td>
<td>Erratic baseline</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td>6-25 bpm, ≤5 bpm for &lt; 40 min</td>
<td>≤5 bpm for 40-80 min</td>
<td>&lt;5 bpm for &gt; 80 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥25 bpm for &gt; 10 min</td>
</tr>
<tr>
<td><strong>Decelerations</strong></td>
<td>None</td>
<td>Repetitive (≥3) uncomplicated</td>
<td>Repetitive (≥3) complicated variable decelerations</td>
</tr>
<tr>
<td></td>
<td>Early decelerations</td>
<td>variable decelerations</td>
<td>Any prolonged deceleration</td>
</tr>
<tr>
<td></td>
<td>Occasional uncomplicated</td>
<td>Occasional late decelerations</td>
<td>Any prolonged deceleration</td>
</tr>
<tr>
<td></td>
<td>variable decelerations</td>
<td>Any prolonged deceleration</td>
<td>Any prolonged deceleration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2-3 min)</td>
</tr>
<tr>
<td><strong>Accelerations</strong></td>
<td>Accelerations spontaneous</td>
<td>Absent with scalp stimulation</td>
<td>Nearly absent</td>
</tr>
<tr>
<td></td>
<td>or during scalp stimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>EFM may be interrupted for</td>
<td>Further assessment required</td>
<td>Action required: review clinical situation, obtain scalp pH, prepare for possible delivery</td>
</tr>
<tr>
<td></td>
<td>≤30 min if mother/fetus stable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from SOGC Guidelines, September 2008
*Previous classification was “reassuring” vs. “non-reassuring”, but distinction is now made between tracings that have some concerning changes but do not require immediate action (atypical) versus those with major concerns requiring immediate intervention (abnormal)

Fetal Scalp Blood Sampling
- cervix must be adequately dilated
- indicated when atypical or abnormal fetal heart rate is suggested by clinical parameters including heavy meconium or moderately to severely abnormal FHR patterns (including unexplained low variability, repetitive late decelerations, complex variable decelerations, fetal cardiac arrhythmias)
- done by measuring pH or more recently fetal lactate
  - pH ≥7.25, lactate <4.2 mmol/L: normal, repeat if abnormal FHR persists
  - pH 7.21-7.24, lactate 4.2-4.8 mmol/L: repeat assessment in 30 min or consider delivery if rapid fall since last sample
  - pH ≤7.20, lactate >4.8 mmol/L: indicates fetal acidosis, delivery is indicated
- contraindications
  - known or suspected fetal blood dyscrasia (hemophilia, von Willebrand disease)
  - active maternal infection (HIV, genital herpes)

Fetal Oxygenation
- uterine contractions during labour decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow and have no adverse effects
- distribution of oxygen to the fetus depends on maternal, uteroplacental, and fetal factors
- fetal response to hypoxia/asphyxia:
  - decreased movement, tone, and breathing activities
  - anaerobic metabolism (decreased pH)
  - transient fetal bradycardia followed by fetal tachycardia
  - redistribution of fetal blood flow
    - increased flow to brain, heart, and adrenals
    - decreased flow to kidneys, lungs, gut, liver, and peripheral tissues
    - increase in blood pressure

Table 21. Factors Affecting Fetal Oxygenation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Decreased maternal oxygen carrying capacity</td>
<td>Significant anemia (iron deficiency, hemoglobinopathies), carboxyhemoglobin (smokers)</td>
</tr>
<tr>
<td></td>
<td>Decreased uterine blood flow</td>
<td>Hypotension (blood loss, sepsis), regional anesthesia, maternal positioning</td>
</tr>
<tr>
<td></td>
<td>Chronic maternal conditions</td>
<td>Vasculopathies (SLE, type 1 DM, chronic HTN), antiphospholipid syndrome, cyanotic heart disease, COPD</td>
</tr>
<tr>
<td>Uteroplacental</td>
<td>Uterine hypertonus</td>
<td>Placental abruption, hyperstimulation secondary to oxytocin, prostaglandins, or normal labour</td>
</tr>
<tr>
<td></td>
<td>Uteroplacental dysfunction</td>
<td>Placental abruption, placental infarction (dysfunction marked by IUUG, oligohydramnios, abnormal Doppler studies), chooroamnionitis, placental edema (DM, hydrops), placental senescence (post-dates)</td>
</tr>
<tr>
<td>Fetal</td>
<td>Cord compression</td>
<td>Oligohydramn os, cord prolapse, or entanglement</td>
</tr>
<tr>
<td></td>
<td>Decreased fetal oxygen carrying capacity</td>
<td>Significant anemia (isoimmunization, feto-maternal bleed), carboxyhemoglobin (exposure to smokers)</td>
</tr>
</tbody>
</table>
Induction of Labour

Definition
- artificial initiation of labour in a pregnant woman prior to spontaneous initiation to deliver the fetus and placenta

Prerequisites for Labour Induction
- capability for C/S if necessary
- maternal
  - inducible/ripe cervix: short, thin, soft, anterior cervix with open os
  - if cervix is not ripe, use p ostaglandin vaginal insert (Cervidil*), prostaglandin gel (Prepidil*), misoprostol (Cytotec*) or Foley catheter
- fetal
  - normal fetal heart tracing
  - cephalic presentation
  - adequate fetal monitoring available
  - likelihood of success determined by Bishop score
    - cervix considered unfavourable if <6
    - cervix favourable if ≥6
    - score of 9-13 associated with high likelihood of vaginal delivery

Table 22. Bishop Score

<table>
<thead>
<tr>
<th>Cervical Characteristic</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>Mid</td>
<td>Anterior</td>
<td>–</td>
</tr>
<tr>
<td>Consistency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Firm</td>
<td>Medium</td>
<td>Soft</td>
<td>–</td>
</tr>
<tr>
<td>Effacement (%)</td>
<td>0-30</td>
<td>40-50</td>
<td>60-70</td>
<td>≥80</td>
</tr>
<tr>
<td>Dilatation (cm)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
<td>≥5</td>
</tr>
<tr>
<td>Station of Fetal Head</td>
<td>-3</td>
<td>-2</td>
<td>-1, 0</td>
<td>+1, +2, +3</td>
</tr>
</tbody>
</table>

Indications
- post-dates pregnancy (generally >41 wk) = most common reason for induction
- maternal factors
  - DM = second most common reason for induction
  - gestational HTN
  - other maternal medical problems, e.g. renal or lung disease, chronic hypertension, cholestasis
  - maternal age over 40
- maternal-fetal factors
  - isoimmunization, PROM, chorioamnionitis, post-term pregnancy
- fetal factors
  - suspected fetal jeopardy as evidenced by biochemical or biophysical indications
  - fetal demise, IUGR, oligo/polyhydraminos, anomalies requiring surgical intervention, twins
  - previous stillbirth, low PAPP-A

Risks
- failure to achieve labour and/or vaginal birth
- uterine hyperstimulation with fetal compromise or uterine rupture
- maternal side effects to medications
- uterine atony and PPH

Contraindications
- maternal
  - prior classical or inverted T-incision C/S or uterine surgery (e.g. myomectomy)
  - unstable maternal condition
  - active maternal genital herpes
  - invasive cervical carcinoma
  - pelvic structure deformities
- maternal-fetal
  - placenta previa or vasa previa
  - cord presentation
- fetal
  - fetal distress, malpresentation/abnormal lie, preterm fetus without lung maturity
CERVICAL RIPENING

Definition
- use of medications or other means to soften, efface, and dilate the cervix; increases likelihood of successful induction
- ripening of an unfavourable cervix (Bishop score <6) is warranted prior to induction of labour

Methods
- intravaginal prostaglandin PGE2 gel (Prostin® gel): long and closed cervix
  - recommended dosing interval of prostaglandin gel is every 6-12 h up to 3 doses
  - continuous release; can be removed if needed
  - controlled release PGE2
- intravaginal PGE1 Misoprostol (Cytotec®): long and closed cervix
  - inexpensive, stored at room temperature
  - more commonly used in 2nd trimester termination of pregnancy
- Foley catheter placement to mechanically dilate the cervix

INDUCTION OF LABOUR

Amniotomy
- artificial rupture of membranes (amniotomy) to stimulate prostaglandin synthesis and secretion; may try this as initial measure if cervix is open and soft, the membranes can be felt, and if the head is present at the cervix
- few studies address the value of amniotomy alone for induction of labour
- amniotomy plus intravenous oxytocin: more women delivered vaginally at 24 h than amniotomy alone (relative risk = 0.03) and had fewer instrumental vaginal deliveries (relative risk = 5.5)

Oxytocin
- oxytocin (Pitocin®): 10 U in 1L NS, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60min to a max of 36-48 mU/min
- reduces rate of unsuccessful vaginal deliveries within 24 h when used alone (8.3% vs. 54%, RR 0.16)
- ideal dosing regimen of oxytocin is not known
- current recommendations: use the minimum dose to achieve active labour and increase q30min as needed
- reassessment should occur once a dose of 20 mU/min is reached
- potential complications:
  - hyperstimulation/tetanic contraction (may cause fetal distress or rupture of uterus)
  - uterine muscle fatigue, uterine atony (may result in PPH)
  - vasopressin-like action causing anti-diuresis

Augmentation of Labour
- augmentation of labour is used to promote adequate contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur
- oxytocin

Abnormalities and Complications of Labour and Delivery

Abnormal Progression of Labour (Dystocia)

Definition
- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labour
- during active phase: >4 h of <0.5 cm/h
- during 2nd stage: >1 h with no descent during active pushing

Etiology
- Power (leading cause): contractions (hypotonic, uncoordinated), inadequate maternal expulsive efforts
- Passenger: fetal position, attitude, size, anomalies (hydrocephalus)
- Passage: pelvic structure (CPD), maternal soft tissue factors (tumours, full bladder or rectum, vaginal septum)
- Psyche: hormones released in response to stress may contribute to dystocia; psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed
Management
- confirm diagnosis of labour (rule out false labour)
- search for factors of CPD
- diagnosed if adequate contractions measured by intrauterine pressure catheter (IUPC) with no descent/dilatation for >2 h
- management: if CPD ruled out, IV oxytocin augmentation ± amniotomy

Risks of Dystocia
- inadequate progression of labour is associated with an increased incidence of:
  - maternal stress
  - maternal infection
  - postpartum hemorrhage
  - need for neonatal resuscitation
  - fetal compromise (from uterine hyperstimulation)
  - uterine rupture
  - hypotension

Shoulder Dystocia

Definition
- fetal anterior shoulder impacted above symphysis pubis after fetal head has been delivered
- life threatening emergency

Etiology/Epidemiology
- incidence 0.15-1.4% of deliveries
- occurs when breadth of shoulders is greater than biparietal diameter of the head

Risk Factors
- maternal: obesity, DM, multiparity, previous shoulder dystocia
- fetal: prolonged gestation, macrosomia (especially if associated with GDM)
- labour
  - prolonged 2nd stage
  - instrumental midpelvic delivery

Presentation
- "turtle sign": head delivered but retracts against inferior portion of pubic symphysis
- complications
  - fetal
    - hypoxic ischemic encephalopathy (chest compression by vagina or cord compression by pelvis can lead to hypoxia)
    - brachial plexus injury (Erbi's palsy C5-C7; Klumpke's palsy: C8-T1), 90% resolve within 6 mo
    - fracture (clavicle, humerus, cervical spine)
    - death
  - maternal
    - perineal injury
    - PPH (uterine atony lacerations)
    - uterine rupture

Treatment
- goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved
- other options
  - cleidotomy (deliberate fracture of neonatal clavicle)
  - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent C/S
  - symphysiotomy

Prognosis
- 1% risk of long-term disability for infant

Umbilical Cord Prolapse

Definition
- descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

Etiology/Epidemiology
- increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, CPD
- incidence: 1/200-1/400 deliveries

Umbilical Cord Accident Causes
- Nuchal cord
- Type A (looped)
- Type B (hitched)
- Body loop
- Single artery
- True knot
- Torsion
- Velamentous
- Short cord <35 cm
- Long cord >80 cm
**Abnormalities and Complications of Labour and Delivery**

**Presentation**
- visible or palpable cord
- FHR changes (variable decelerations, bradycardia, or both)

**Treatment**
- emergency C/S
- O2 to mother, monitor fetal heart
- alleviate pressure of the presenting part on the cord by elevating fetal head with a pelvic exam (maintain this position until C/S)
- keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
- roll mom onto all fours
- position mother in Trendelenburg or knee-to-chest position
- if fetal demise or too premature (<22 wk), allow labour and delivery

**Uterine Rupture**

**Etiology/Epidemiology**
- associated with previous uterine scar (in 40% of cases), hyperstimulation with oxytocin, grand multiparity, and previous intrauterine manipulation
- generally occurs during labour, but can occur earlier with a classical incision
- 0.5-0.8% incidence, up to 12% with classical incision

**Presentation**
- prolonged fetal bradycardia – most common presentation
- acute onset of constant lower abdominal pain, may not have pain if receiving epidural analgesia
- hyper/hypotonic uterine contractions
- vaginal bleeding
- intra-abdominal hemorrhage
- sudden loss of fetal descent

**Risk Factors**
- uterine scarring (i.e. previous uterine surgeries including Cesarean (especially classical incision), perforation with D&C, myomectomy)
- excessive uterine stimulation (i.e. protracted labour, oxytocin, prostaglandins)
- uterine trauma (i.e. operative equipment, ECV)
- multiparity
- uterine abnormalities
- placenta accreta

**Treatment**
- rule out placental abruption
- immediate delivery for fetal survival
- maternal stabilization (may require hysterectomy), treat hypovolemia

**Complications**
- maternal mortality 1-10%
- maternal hemorrhage, shock, DIC
- amniotic fluid embolus
- hysterectomy if uncontrollable hemorrhage
- fetal distress, associated with 50% fetal mortality

**Amniotic Fluid Embolus**

**Definition**
- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

**Etiology/Epidemiology**
- rare intrapartum or immediate postpartum complication
- 60-80% maternal mortality rate, accounts for 10% of all maternal deaths
- leading cause of maternal death in induced abortions and miscarriages
- 1/8,000-1/80,000 births

**Risk Factors**
- placental abruption
- rapid labour
- multiparity
- uterine rupture
- uterine manipulation
Differential Diagnosis
- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruption, chronic coagulopathy

Presentation
- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia), and coagulopathy
- seizure in 10%
  ARDS and left ventricular dysfunction seen in survivors

Management
- supportive measures (high flow O₂, ventilation support, fluid resuscitation, inotropic support, ± intubation), coagulopathy correction
- ICU admission

Chorioamnionitis

Definition
- infection of the chorion, amnion, and amniotic fluid typically due to ascending infection by organisms of normal vaginal flora

Etiology/Epidemiology
- incidence 1-5% of term pregnancies and up to 25% in preterm deliveries
- predominant microorganisms include: GBS, Bacteroides and Prevotella species, E. coli, and anaerobic Streptococcus
- ascending from vagina

Risk Factors
- prolonged ROM, long labour, multiple vaginal exams during labour, internal monitoring
- bacterial vaginosis and other vaginal infections

Clinical Features
- maternal fever, maternal or fetal tachycardia, uterine tenderness, foul and purulent cervical discharge

Investigations
- CBC: leukocytosis
- amniotic fluid: leukocytes or bacteria

Treatment
- IV antibiotics
  - ampicillin 2 g IV q6h and gentamicin 1.5 mg/kg IV q8h
  - anaerobic coverage (i.e. clindamycin 900 mg IV q8h)
  - expedient delivery regardless of gestational age

Complications
- bacteremia of mother or fetus, wound infection if C/S, pelvic abscess, infant meningitis

Meconium

Epidemiology
- present early in labour in 10% of pregnancies, more common in postdate pregnancies
- in general, meconium may be present in up to 25% of all labours, usually NOT associated with poor outcome, but extra care is required at time of delivery to avoid aspiration. Concern if fluid changes from clear to meconium-stained. Always abnormal if seen in preterm fetus

Etiology
- likely cord compression ± uterine hypertonia
- may indicate undiagnosed breech
- increasing meconium during labour may be a sign of fetal distress

Features
- may be watery or thicker (particulate)
- light yellow/green or dark green-black in colour

Treatment
- call respiratory therapy, neonatology, or pediatrics to delivery room
- closely monitor FHR for signs of fetal distress

Clinical Features of Chorioamnionitis
- Temperature
- Tachycardia (maternal or fetal)
- Tenderness (uterine)
- Foul discharge

Clinical Features of Meconium
- Temperature
- Tachycardia (maternal or fetal)
- Tenderness (uterine)
- Foul discharge

Particulate (thickened) meconium is associated with lower APGARs, an increased risk of meconium aspiration, and perinatal death. Particulate meconium generally has a darker green or black colour, whereas thin meconium is usually yellow to light green.
Operative Obstetrics

Operative Vaginal Delivery

Definition
• forceps or vacuum extraction

Indications
• fetal
  • atypical or abnormal fetal heart rate tracing, evidence of fetal compromise
  • consider if second stage is prolonged, as this may be due to poor contractions or failure of fetal head to rotate
• maternal
  • need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
  • exhaustion, lack of cooperation, and excessive analgesia may impair pushing effort

Contraindications
• non-vertex cephalic presentation (i.e. brow or face)
• unengaged head
• cervix incompletely dilated

Forceps

Outlet Forceps Position
• head visible between labia in between contractions
• sagittal suture in or close to AP diameter
• rotation cannot exceed 45°

Low Forceps Position
• presenting part at station +2 or greater
• subdivided based on whether rotation less than or greater than 45 degrees

Mid Forceps Position
• presenting part below spines but above station +2

Types of Forceps
• Simpson or Tucker-McLane forceps for OA presentations
• Kielland (rotational) forceps when rotation of head is required
• Piper forceps for breech

Vacuum Extraction

• traction instrument used as alternative to forceps delivery; aids maternal pushing
• contraindications: <34 wk GA (<2500 g), fetal head deflexed, fetus requires rotation, fetal condition (e.g. bleeding disorder)

| Table 23. Advantages and Disadvantages of Forceps versus Vacuum Extraction |
|---------------------------------|---------------------------------|
| **Forces** | **Vacuum Extraction** |
| Advantages | Higher overall success rate for vaginal delivery |
| | Decreased incidence of fetal morbidity |
| | Easier to apply |
| | Less anesthesia required |
| | Less maternal soft-tissue injury compared to forceps |
| Disadvantages | Greater incidence of maternal injury |
| | Contraindicated if fetus at risk for coagulation defect |
| | Suitable only for vertex presentations |
| | Maternal pushing required |
| | Contraindicated in preterm delivery |

Complications
• Maternal: anesthesia risk, lacerations, injury to bladder, uterus, or bone, pelvic nerve damage, PPH, infections
• Fetal: fractures, facial nerve palsy, trauma to face/scalp, intracerebral hemorrhage, cephalohematoma, cord compression
• Increased incidence of cephalohematoma and retinal hemorrhages, and jaundice compared to forceps
• Subgaleal hemorrhage
• Subaponeurotic hemorrhage
• Soft tissue trauma

Limits for Trial of Vacuum
• After 3 pulls over 3 contractions with no progress
• After 3 pop-offs with no obvious cause
• 20 min and delivery is not imminent
Lacerations

- first degree: involves skin and vaginal mucosa but not underlying fascia and muscle
- second degree: involves fascia and muscles of the perineal body but not the anal sphincter
- third degree: involves the anal sphincter (partial IIIa or complete IIIb)
- fourth degree: extends through the anal sphincter into the rectal mucosa

Episiotomy

Definition
- incision in the perineal body at the time of delivery
- essentially a controlled second degree laceration
- midline: incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernous muscle
- mediolateral: incision through bulbocavernous, superficial transverse perineal muscle, and levator ani

Indications
- to relieve obstruction of the unyielding perineum
- to expedite delivery (e.g. abnormal FHR pattern)
- instrumental delivery
- controversial between practitioners as to whether it is preferable to make a cut or let the perineum tear as needed
- current evidence suggests letting perineum tear and then repair as needed (restricted use)

Complications
- infection, hematoma, extension into anal musculature or rectal mucosa, fistula formation, incontinence

Cesarean Delivery

Epidemiology
- incidence 20-25%

Indications
- maternal: obstruction, active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery (past C/S is most common), underlying maternal illness (eclampsia, HELLP syndrome, heart disease) maternal-fetal: failure to progress, placental abruption or previa, vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, certain congenital anomalies

Types of Cesarean Incisions
- skin
  - transverse (i.e. Pfannenstiel)
    - decreased exposure and slower entry
    - improved strength and cosmesis
  - vertical midline
    - rapid peritoneal entry and increased exposure
    - increased dehiscence
- uterine
  - low transverse (most common): in noncontractile lower segment
    - decreased chance for rupture in subsequent pregnancies
  - low vertical
  - used for very preterm infants, poorly developed maternal lower uterine segment
  - classical (rare): in thick, contractile segment
    - used for transverse lie, preterm b ee, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid, morbidly obese patients

Risks/Complications
- complications related to general anesthesia* (e.g. aspiration)
- hemorrhage (average blood loss ~1,000 cc)
- infection (UTI, wound, endometritis)
  - single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g)
- injury to surrounding structures (bowel, bladder, ureter, uterus)
- thromboembolism (DVT, PE)
- increased recovery time/hospital stay
- maternal mortality (<0.1%)
**Trial of Labour after Cesarean Section (TOLAC)**

- should be recommended if no contraindications after previous low transverse incision
- success rate varies with indication for previous C/S (generally 60-80%)
- risk of uterine rupture (<1% with low transverse incision), increased by interval <18 months and one layer closure

**Contraindications**
- previous classical, inverted T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
- history of uterine surgery (e.g. myomectomy) or previous uterine rupture
- multiple gestation
- non-vertex presentation or placenta previa
- inadequate facilities or personnel for emergency C/S

---

**Puerperal Complications**

- puerperium: 6 wk period of adjustment after pregnancy when pregnancy-induced anatomic and physiologic changes are reversed

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**Postpartum Hemorrhage**

**Definition**
- loss of >500 mL of blood at the time of vaginal delivery, or >1,000 mL with C/S
- early (immediate) – within first 24 h postpartum
- late (delayed) – after 24 h but within first 6 wk

**Epidemiology**
- incidence 5-15%

**Etiology (4 Ts)**

1. **Tone** (uterine atony)
   - most common cause of PPH
   - avoid by giving oxytocin with delivery of the anterior shoulder or placenta occurs within first 24 h
   - due to:
     - overdistended uterus (polyhydramnios, multiple gestations, macrosomia)
     - uterine muscle exhaustion (prolonged or rapid labour, grand multiparity, oxytocin use, general anesthetic)
     - uterine distortion (fibroids, placenta previa, placental abruption)
     - intra-amniotic infection (fever, prolonged ROM)

2. **Tissue**
   - retained placental products (membranes, cotyledon or succenturiate lobe)
   - retained blood clots in an atonic uterus
   - gestational trophoblastic neoplasia
   - abnormal placentation

3. **Trauma**
   - laceration (vagina, cervix, uterus), episiotomy, hematoma (vaginal, vulvar, retroperitoneal), uterine rupture, uterine inversion

4. **Thrombin**
   - coagulopathy (pre-existing or acquired)
   - most identified prior to delivery (low platelets increases risk)
   - includes hemophilia, DIC, Aspirin® use, ITP, TTP, vWD (most common)
   - therapeutic anti-coagulation

**Investigations**
- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of tone, tissue, or trauma
- may be helpful to observe red-topped tube of blood – no clot in 7-10 min indicates coagulation problem

**Management**
- ABCs, call for help
- 2 large bore IVs, run crystalloids wide open
- CBC, coagulation profile, cross and type pRBCs
- treat underlying cause
- Foley catheter to empty bladder and monitor urine output

---

**VBAC**
- Rate of successful VBAC ranges from 60-82%
- No significant difference in maternal deaths or hysterectomies between VBAC or C/S
- Uterine rupture more common in VBAC group
- Evidence regarding fetal outcome is lacking


---

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- Rate of successful VBAC ranges from 60-82%
- No significant difference in maternal deaths or hysterectomies between VBAC or C/S
- Uterine rupture more common in VBAC group
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---

**DDx of Early PPH – 4 Ts**
- Tone (atony)
- Tissue (retained placenta, clots)
- Trauma (laceration, inversion)
- Thrombin (coagulopathy)

**DDx of Late PPH**
- Retained products
- ± endometritis
- Sub involution of uterus
**Medical Therapy**
- oxytocin 5 U IV bolus (20-40 U/250 mL crystalloid) with delivery of anterior shoulder or infusion of 20 U in 1000 mL crystalloid at 50 mL/h or can give 10 U IM if CV collapse or IV access not possible
- methylergonovine maleate (ergotamine) 0.25 mg IM/IMM q15min up to 1.25 mg; can be given as IV bolus of 0.125 mg (may exacerbate HTN)
- carbo-prost (Hemabate®), a synthetic PGF-1α analog, 250 µg IM/IMM q15min to max 2 mg (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary, renal, and hepatic dysfunction)
- misoprostol 600-800 µg PO/SL (faster) or PR/PV (side effect: pyrexia if >600 µg)
- tranexamic acid (Cyklokapron®), an antifibrinolytic, 1 g IV

**Local Control**
- bimanual massage: elevate the uterus and massage through patient's abdomen
- uterine packing (mesh with antibiotic treatment)
- Bakri Balloon for tamponade: may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR

**Surgical Therapy (Intractable PPH)**
- D&C (beware of vigorous scraping which can lead to Asherman's syndrome)
- embolization of uterine artery or internal iliac artery by interventional radiologist
- laparotomy with bilateral ligation of uterine artery (may be effective), internal iliac artery (not proven), ovarian artery, or hypogastric artery, compression sutures (B-Lynch or Cho sutures)
- hysterectomy last option, with angiographic embolization if post-hysterectomy bleeding

---

### Retained Placenta

**Definition**
- placenta undelivered after 30 min postpartum

**Etiology**
- placenta separated but not delivered
- abnormal placental implantation (placenta accreta, placenta increta, placenta percreta)

**Risk Factors**
- placenta previa, prior C/S, post-pregnancy curettage, prior manual placental removal, uterine infection

**Clinical Features**
- risk of postpartum hemorrhage and infection

**Investigations**
- explore uterus
- assess degree of blood loss

**Management**
- 2 large bore IVs, type and screen
- Brant maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure cephalad to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL NS into umbilical vein
- manual removal if above fails
- D&C if required
- Ancef 2 g IV if manual removal or D&C

---

### Uterine Inversion

**Definition**
- inversion of the uterus through cervix ± vaginal introitus

**Etiology/Epidemiology**
- often iatrogenic (excess cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous (lax uterine ligaments)
- 1/1,500-1/2,000 deliveries

**Clinical Features**
- can cause profound vasovagal response with bradycardia, vasodilation, and hypovolemic shock
- shock may be disproportionate to maternal blood loss

**Management**
- urgent management essential, call anesthesia
- ABCs: initiate IV crystalloids
Puerperal Complications

• can use tocolytic drug (see Management of Preterm Labour, OB16) or nitroglycerin IV to relax uterus and aid replacement
• replace uterus without removing placenta
• remove placenta manually and withdraw slowly
• IV oxytocin infusion (only after uterus replaced)
• re-explore uterus
• may require general anesthetic ± laparotomy

Postpartum Pyrexia

Definition
• fever >38°C on any 2 of the first 10 d postpartum, except the first day

Etiology
• endometritis
• wound infection (check C/S and episiotomy sites)
• mastitis/engorgement
• UTI
• atelectasis
• pneumonia
• DVT, pelvic thrombophlebitis

Investigations
• detailed history and physical exam, relevant cultures
• for endometritis: blood and genital cultures

Treatment
• depends on etiology
  • infection: empiric antibiotics, adjust when sensitivities available
    • endometritis: clindamycin + gentamycin IV
    • mastitis: clindamycin or cephalaxin
    • wound infection: cephalaxin, frequent sitz baths for episiotomy site infection
    • DVT: anticoagulants
  • prophylaxis against post-C/S endometritis: administer 2g of Cephazolin IV 30 minutes prior to skin incision

ENDOMETRITIS
• definition: infection of uterine myometrium and parametrium
• clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling discharge, or lochia
• treatment: depends on infection severity; oral antibiotics if well, IV with hospitalization in moderate to severe cases

VENOUS THROMBOEMBOLISM
• see Venous Thromboembolism, OB30

Mastitis

• definition: inflammation of mammary glands
• must rule out inflammatory carcinoma, as indicated
• differentiate from mammary duct ectasia: mammary duct(s) beneath nipple clogged and dilated ± ductal inflammation ± nipple discharge (thick, grey to green), often postmenopausal women

Table 24 Lactational vs. Non-Lactational Mastitis

<table>
<thead>
<tr>
<th></th>
<th>Lactational</th>
<th>Non-Lactational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>More common than non-lactational</td>
<td>Periductal mastitis most common</td>
</tr>
<tr>
<td></td>
<td>Often 2-3 wk postpartum</td>
<td>Mean age 32 yr</td>
</tr>
<tr>
<td>Etiology</td>
<td>S. aureus</td>
<td>May be sterile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be infected with S. aureus or other anaerobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking is risk factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be associated with mammary duct ectasia</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Unilateral localized pain</td>
<td>Subareolar pain</td>
</tr>
<tr>
<td></td>
<td>Tenderness</td>
<td>May have subareolar mass</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>Discharge (variable colour)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nipple inversion</td>
</tr>
<tr>
<td>Treatment</td>
<td>Heat or ice packs, continued nursng/pumping</td>
<td>Broad-spectrum antibiotics and I&amp;D</td>
</tr>
<tr>
<td></td>
<td>Antibiotics (clindamycin/cephalexin) (erythromycin if pen-allergic)</td>
<td>Total duct excision (definitive)</td>
</tr>
<tr>
<td>Abscess</td>
<td>Fluctuant mass</td>
<td>If mass does not resolve, FNA to exclude cancer and US to assess presence of abscess</td>
</tr>
<tr>
<td></td>
<td>Purulent nipple discharge</td>
<td>Treatment includes antibiotics, aspiration, or I&amp;D (tends to recur)</td>
</tr>
<tr>
<td></td>
<td>Fever, leukocytosis</td>
<td>May develop mammary duct fistula</td>
</tr>
<tr>
<td></td>
<td>Discontinue nursing, IV antibiotics (nafcillin/oxacillin), I&amp;D usually required</td>
<td>A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually S. aureus)</td>
</tr>
</tbody>
</table>
Postpartum Mood Alterations

POSTPARTUM BLUES
- 40-80% of new mothers, onset day 3-10; extension of the “normal” hormonal changes and adjustment to a new baby
  - self-limited, should resolve by 2 wk
  - manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness, fatigue, irritability, poor concentration/despondency, anxiety, insomnia

POSTPARTUM DEPRESSION
- definition: major depression occurring in a woman within 6 mo of childbirth (see Psychiatry, PS12)
- epidemiology: 10-15%, risk of recurrence 50%
- risk factors
  - personal or family history of depression (including PPD)
  - prenatal depression or anxiety
  - stressful life situation
  - poor support system
  - unwanted pregnancy
  - colicky or sick infant
- clinical features: suspect if the “blues” last beyond 2 wk, or if the symptoms in the first 2 wk are severe (e.g., extreme disinterest in the baby, suicidal or homicidal/infanticidal ideation)
  - assessment: Edinburgh Postnatal Depression Scale or other
  - treatment: antidepressants, psychotherapy, supportive care, ECT if refractory
- prognosis: interferes with bonding and attachment between mother and baby, so it can have long-term effects

POSTPARTUM PSYCHOSIS
- definition: onset of psychotic symptoms over 24-72 h within first month postpartum, can present in the context of depression
- epidemiology: rare (0.2%)

Postpartum Care

Postpartum Office Visit at 6 Weeks

Care of Mother (The 10 Bs)
- Be careful: do not use douches or tampons for 4-6 wk post-delivery
- Be fit: encourage gradual increases in walking, Kegel exercises
- Birth control: assess for use of contraceptives; breastfeeding is NOT an effective method of birth control (see Gynecology, GY17, for more detail about different contraceptive options postpartum)
- Bladder: assess for urinary incontinence, maintain high fluid intake
- Blood pressure: especially if gestational HTN
- Blood tests: CBC (for anemia if had PPH)
- Blues: (see Postpartum Mood Alterations)
- Bowel: fluids and high-fibre foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain meds, doughnut cushion, Sitz baths, ice compresses
- Breast and pelvic exam: watch for Staphylococcal or Streptococcal mastitis/abscess, ± Pap smear at 6 wk

Physiological Changes Postpartum
- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains firmness
  - should involute ~1 cm below umbilicus per day in first 4-5 d, reaches non-pregnant state in 4-6 wk postpartum
- ovulation resumes in ~45 d for non-lactating women and within 3-6 mo for lactating women and sometimes later
- lochia: normal vaginal discharge postpartum, uterine decidual tissue sloughing
  - decreases and changes in colour from red (lochia rubra; presence of erythrocytes, 3-4 d) → pale (lochia serosa) → white/yellow (lochia alba; residual leukorrhoea) over 3-6 wk
  - foul-smelling lochia suggests endometritis

Breastfeeding Problems
- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisture cream, topical steroid if needed
- mastitis: treat promptly (see Postpartum Pyrexia, OB45)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see Breastfeeding and Drugs)
Bladder Dysfunction
- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management: pelvic floor retraining with Kegel exercises/pelvic physiotherapy, vaginal cone or pessaries, lifestyle modifications (e.g. limit fluid, caffeine intake)
- surgical management: minimally invasive procedures (tension-free vaginal tape, transobturator tape, midurethral sling)

Puerperal Pain
- "after pains" common in first 3 d due to uterine contractions; encourage simple analgesia
- ice packs can be used on perineum if painful
- encourage regular analgesia and stool softener

Breastfeeding and Drugs

Table 25. Drug Safety During Breastfeeding

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics (e.g. acetaminophen, NSAIDs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants (e.g. heparin)</td>
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<tr>
<td>Antidepressants (e.g. sertraline, fluoxetine, TCAs)</td>
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<td></td>
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<tr>
<td>Anxiolytics</td>
<td></td>
<td></td>
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<tr>
<td>Antihistamines</td>
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<td></td>
</tr>
<tr>
<td>Antibiotics (e.g. penicillin, carbapenem, vancomycin)</td>
<td></td>
<td></td>
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<tr>
<td>Antihypertensives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antivirals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiepileptics (e.g. phenytoin, carbamazepine, valproic acid)</td>
<td></td>
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<tr>
<td>Antimalarials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigout</td>
<td></td>
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<tr>
<td>Antiemetics</td>
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<tr>
<td>Antihyperlipidemics</td>
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<tr>
<td>Antineoplastics</td>
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<tr>
<td>Psychotropic drugs</td>
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<td></td>
</tr>
<tr>
<td>OCP (low dose) – although may decrease breast milk production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Common Medications

Table 26. Common Medications

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Dosing Schedule</th>
<th>Indications/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone valerate (Celestone®)</td>
<td>12 mg IM q24h x 2 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>Carbetapentol (Hemabate®)</td>
<td>0.25 mg IM/MM q15min; max 2 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2 g IV then 1 g q8h</td>
<td>GBS prophylaxis (penicillin allergic and not at risk for anaphylaxis)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>900 mg q8h</td>
<td>Used in endometritis</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>6 mg IM q12h x 4 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>Dinoprostone (Cervidil®, PGE2 impregnated thread)</td>
<td>10 mg PV (remove after 12 h) Max 3 doses</td>
<td>Induction of labour</td>
</tr>
<tr>
<td>Doxylamine succinate</td>
<td>2 tabs qhs + 1 tab qAM + 1 tab qPM Max 8 tabs/d</td>
<td>Each tablet contains 10 mg doxylamine succinate with vitamin B6 Used for hyperemesis gravidarum</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td></td>
<td></td>
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<tr>
<td>Diltiazem hydrochloride</td>
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<td></td>
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<tr>
<td>Doxycycline</td>
<td></td>
<td></td>
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<tr>
<td>Erythromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td>0.4-1 mg PO OD x 1-3 mo preconception and T1-2 5 mg PO OD with past Hx of NTD or risks for NTD</td>
<td>Prevention of ONTD</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>50 mg/m² IM or 50 mg PO x 1 dose</td>
<td>For ectopic pregnancy or medical abortion</td>
</tr>
<tr>
<td>Methylergonovine maleate (Ergotamine®)</td>
<td>0.125 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>Misoprostol (Cytotec®)</td>
<td>600-1000 µg PR x 1 dose 400 µg PO/SI x 1 dose or 800 µg PV x 1 dose 3-7 d after methotrexate</td>
<td>For treatment of PPH For medical abortion/retained products of conception Also used for NSAID-induced ulcers (warn patients of contraindications)</td>
</tr>
<tr>
<td>Oxytocin (Pitocin®)</td>
<td>0.5-2.0 mU/ml IV or 10 U/L NS increase by 1.2 mU/ml q20-60 min Max 38-48 mU/ml 10 U IM at delivery of anterior shoulder and of placenta 20 U/L NS or RL IV continuous infusion</td>
<td>Augmentation of labour (also induction of labour) Prevention of uterine atony Treatment of uterine atony</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>5 million U IV, then 2.5 million U IV q4h until delivery</td>
<td>GBS prophylaxis</td>
</tr>
<tr>
<td>PGE2 gel (Prostin® gel)</td>
<td>0.5 mg PV q8-12h; max 3 doses</td>
<td>Induction of labour</td>
</tr>
<tr>
<td>Rh IgG (Rhogam®)</td>
<td>300 µg IM x 1 dose</td>
<td>Given to Rh negative women Routinely at 28 wk GA Within 72 h of birth of Rh+ fetus Positive Kleihauer-Betke test With any invasive procedure in pregnancy Ectopic pregnancy A therapeutic abortion Miscarriage or therapeutic abortion (dose: 50 µg IM only)</td>
</tr>
</tbody>
</table>
References

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Acronyms ............................................. 2
Basic Anatomy Review .......................... 2
Differential Diagnoses of Common Presentations .................. 3
Loss of Vision
Red Eye
Ocular Pain
Floaters
Flashes of Light (Photopsia)
Photophobia (Severe Light Sensitivity)
Diplopia (Double Vision)
Ocular Problems in the Contact Lens Wearer
Acute Painless Vision Loss

Ocular Emergencies ................................ 5
The Ocular Examination .......................... 5

Optics ............................................. 7
The Orbit ................................. 9
Globe Displacement
Orbital Cellulitis
Preseptal Cellulitis

Lacrimal Apparatus ......................... 10
Dry Eye Syndrome (Keratoconjunctivitis Sicca)
Epiphora (Excessive Tearing)
Dacryocystitis
Dacryoadenitis

Lids and Lashes ............................... 11
Lid Swelling .......................... Entropion
Ptosis .............................. Ectropion
Trichiasis

Conjunctiva ................................... 13
Pinguecula .......................... Subconjunctival Hemorrhage
Pterygium .......................... Conjunctivitis
Trichiasis

Sclera ......................................... 15
Episcleritis .......................... Scleritis

Cornea .......................................... 16
Foreign Body .......................... Herpes Zoster
Corneal Abrasion ........................ Ophthalmicus
Recurrent Erosions ........................ Keratoconus
Corneal Ulcer .......................... Arcus Senilis
Herpes Simplex Keratitis ........................ Kayser-Fleischer Ring

The Uveal Tract ................................ 19
Uveitis

Lens ............................................. 20
Cataracts .......................... Dislocated Lens (Ectopia Lentis)

Vitreous ...................................... 21
Posterior Vitreous Detachment
Vitreous Hemorrhage
Endophthalmitis and Vitritis

Retina ........................................... 22
Central/Branch Retinal Artery Occlusion
Central/Branch Retinal Vein Occlusion
Retinal Detachment
Retinitis Pigmentosa
Age-Related Macular Degeneration

Glaucoma ...................................... 25
Primary Open-Angle Glaucoma
Normal Tension Glaucoma
Secondary Open Angle Glaucoma
Primary Angle-Closure Glaucoma
Secondary Angle Closure Glaucoma

Pupils ......................................... 28
Pupillary Light Reflex
Pupil Abnormalities
Dilated Pupil (Mydriasis)
Constricted Pupil (Miosis)
Relative Afferent Pupillary Defect

Malignancies .................................... 31
Lid Carcinoma
Metastases
Uveal Melanoma

Ocular Manifestations of Systemic Disease ........................... 32
HIV/AIDS
Other Systemic Infections
Diabetes Mellitus
Hypertension
Multiple Sclerosis
TIA/Amaurosis Fugax
Graves’ Disease
Connective Tissue Disorders
Giant Cell Arteritis/Temporal Arteritis
Sarcoidosis

Pediatric Ophthalmology ...................................... 36
Strabismus
Amblyopia
Leukocoria
Retinoblastoma
Retinopathy of Prematurity
Nasolacrimal System Defects
Ophthalmitis Neonatorum
Congenital Glaucoma

Ocular Trauma ..................................... 39
Blunt Trauma
Penetrating Trauma
Hyphema
Blow-Out Fracture
Chemical Burns

Ocular Drug Toxicity .................................. 41
Common Medications ................................ 42

References ...................................... 44
**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>AION</td>
<td>anterior ischemic optic neuropathy</td>
</tr>
<tr>
<td>AMD</td>
<td>age-related macular degeneration</td>
</tr>
<tr>
<td>BCVA</td>
<td>best corrected visual acuity</td>
</tr>
<tr>
<td>BRAO</td>
<td>branch retinal artery occlusion</td>
</tr>
<tr>
<td>BRVO</td>
<td>branch retinal vein occlusion</td>
</tr>
<tr>
<td>C/D</td>
<td>cup to disc ratio</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CRAO</td>
<td>central retinal artery occlusion</td>
</tr>
<tr>
<td>D</td>
<td>diopter</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>DR</td>
<td>diabetic retinopathy</td>
</tr>
<tr>
<td>EOM</td>
<td>extraocular movement</td>
</tr>
<tr>
<td>FML</td>
<td>fluoromethalone</td>
</tr>
<tr>
<td>GAT</td>
<td>Goldmann applanation tonometry</td>
</tr>
<tr>
<td>GCA</td>
<td>giant cell arteritis</td>
</tr>
<tr>
<td>GPC</td>
<td>giant papillary conjunctivitis</td>
</tr>
<tr>
<td>HRT</td>
<td>Heidelberg retinal tomography</td>
</tr>
<tr>
<td>INX</td>
<td>intranuclear ophtalmoplegia</td>
</tr>
<tr>
<td>IOL</td>
<td>intraocular lens</td>
</tr>
<tr>
<td>IOP</td>
<td>intraocular pressure</td>
</tr>
<tr>
<td>LASIK</td>
<td>laser-assisted in situ keratomileusis</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RAPD</td>
<td>relative afferent pupillary defect</td>
</tr>
<tr>
<td>RD</td>
<td>retinal detachment</td>
</tr>
<tr>
<td>RGP</td>
<td>retinopathy of prematurity</td>
</tr>
<tr>
<td>RPE</td>
<td>retinal pigment epithelium</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SPK</td>
<td>superficial punctate keratitis</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>YAG</td>
<td>yttrium aluminium garnet</td>
</tr>
</tbody>
</table>

**Basic Anatomy Review**

**Lateral View**
- Tendon of superior rectus muscle
- Tendon of inferior rectus muscle
- Meibomian gland
- Eyelash
- Cornea
- Palpebral conjunctiva
- Bulbar conjunctiva

**Superior View**
- Anterior chamber
- Iris
- Bulbar conjunctiva
- Retinal blood vessels
- Optic nerve
- Retinal vessels
- Ciliary muscle and body
- Conjunctival fornix

**Figure 1. Anatomy of the eye**

**Figure 2. Layers of the retina**

**Retinal Layers (10)**
1. Inner limiting membrane
2. Nerve fibre layer
3. Ganglion cell layer
4. Inner plexiform layer
5. Outer plexiform layer
6. Inner nuclear layer
7. Outer nuclear layer
8. Outer limiting membrane
9. Photoreceptor layer
10. Retinal pigmented epithelium

**Cell Types**
- Vitreous humour
- Optic nerve fibres
- Ganglion fibres
- Amacrine cells
- Bipolar cells
- Horizontal cells
- Rod nuclei
- Cone nuclei
- Rod cells
- Cone cells
- Pigmented cells
- Bruch’s membrane
- Choroid

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Differential Diagnoses of Common Presentations

Loss of Vision

Top 3 Differential Diagnosis of Acute Loss of Vision
- Vitreous hemorrhage
- Retinal artery/vein occlusion
- Retinal detachment

Top 3 Differential Diagnosis of Chronic Loss of Vision
Reversible
- Cataract
- Refractive error
- Corneal dystrophy
- Glaucoma

Irreversible
- AMD
- DR

Note: Anti-VEGF treatment for exudative AMD and diabetic macular edema may reverse some vision loss

Red Eye

Table 1. Common Causes of Red Eye

<table>
<thead>
<tr>
<th>Lids/orbit/lacrimal system</th>
<th>Cornea</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hordeolum/chaeton</td>
<td>Foreign body (including contact lens)</td>
<td>Trauma</td>
</tr>
<tr>
<td>Scleritis</td>
<td>Keratitis</td>
<td>Post-operative endophthalmitis</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>Abrasion, laceration</td>
<td>Pharmacologic (e.g. prostaglandin analogs)</td>
</tr>
<tr>
<td>Entropion/ectropion</td>
<td>Ulcer</td>
<td></td>
</tr>
<tr>
<td>Foreign body/laceration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dacryocystitis/dacryoadenitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conjunctiva/sclera</th>
<th>Anterior chamber</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subconjunctival hemorrhage</td>
<td>Anterior uveitis (iritis, iridocyclitis)</td>
<td>Trauma</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Acute glaucoma</td>
<td>Post-operative endophthalmitis</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>Hyphema (blood in anterior chamber)</td>
<td>Pharmacologic (e.g. prostaglandin analogs)</td>
</tr>
<tr>
<td>Pterygium</td>
<td>Hypopyon (pus in anterior chamber)</td>
<td></td>
</tr>
<tr>
<td>Episcleritis/scleritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preseptal/orbital cellulitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Loss of vision
Ocular Pain

- differentiate from eye fatigue (asthenopia)
- ocular surface disease
- herpes zoster prodrome
- trauma/foreign body
- blepharitis
- keratitis
- corneal abrasion/ulcer
- acute glaucoma
- acute uveitis
- scleritis
- episcleritis
- optic neuritis

Floaters

- PVD (often secondary to age-related vitreous syneresis)
- vitreous hemorrhage
- retinal tear/detachment
- intermediate uveitis (pars planitis)
- posterior uveitis (chorioretinitis)

Flashes of Light (Photopsia)

- PVD (often secondary to age-related vitreous syneresis)
- retinal tear/detachment
- migraine with aura

Photophobia (Severe Light Sensitivity)

- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis/encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

Diplopia (Double Vision)

<table>
<thead>
<tr>
<th>Binocular Diplopia</th>
<th>Monocular Diplopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurs with both eyes open, eliminated with occlusion of either eye</td>
<td>Occurs with one eye open, remains with occlusion of unaffected eye</td>
</tr>
</tbody>
</table>

Table 2 Common Causes of Diplopia

- Disease of eye muscle: congenital strabismus syndromes
- Ocular motor nerve dysfunction: III IV VI Nerve Palsy
- Neuromuscular junction disease: myasthenia gravis, botulism
- Mechanical process: muscle restriction/entrapment, thyroid ophthalmopathy
- Optical factors: refractive error/astigmatism
- Mechanical process: dislocated lens, postoperative sequelae (cataract surgery, peripheral laser iridotomy)
- Other: strands of mucus in tear film (keratoconus)

Supranuclear Causes

INO (multiple sclerosis, brainstem infarct)

Ocular Problems in the Contact Lens Wearer

- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis/contact lens allergy
- SPK from dry eyes
- limbal stem cell deficiency
- corneal neovascularization
- sterile corneal infiltrates (immunologic)
- infected ulcers (Pseudomonas, Acanthamoeba)

Acute Painless Vision Loss

- vitreous hemorrhage
- retinal artery/vein occlusion
- RD
- AION
- optic neuritis
- amaurosis fugax/TIA/stroke
Table 3. Common Differential Diagnoses of Red Eye

<table>
<thead>
<tr>
<th></th>
<th>Conjunctivitis</th>
<th>Acute Iritis</th>
<th>Acute Glaucoma</th>
<th>Keratitis (Corneal Abrasion/Ulcer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>Bacterial: purulent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral: serous/mucoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic: mucoid</td>
<td>No</td>
<td>No</td>
<td>Profuse tearing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>±</td>
<td>+ (dull/achy)</td>
<td>+ + (nausea)</td>
<td>+ + (sharp)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>No</td>
<td>+ +</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>No</td>
<td>+ +</td>
<td>+ + +</td>
<td>Varies</td>
</tr>
<tr>
<td>Pupil</td>
<td>Normal</td>
<td>Smaller</td>
<td>Fixed in mid dilation</td>
<td>Same or smaller</td>
</tr>
<tr>
<td>Injection</td>
<td>Diffuse conjunctival injection involving the bulbar conjunctiva for 360° of palpebral or tarsal conjunctiva</td>
<td>Ciliary flush (peri-limbal)</td>
<td>Conjunctival injection</td>
<td>±</td>
</tr>
<tr>
<td>Limbal Palle</td>
<td>Ciliary flush</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>No</td>
</tr>
<tr>
<td>Cornea</td>
<td>Normal</td>
<td>Keratic precipitates</td>
<td>Cloudy</td>
<td>Infiltrate, edema, and may have keratic precipitates</td>
</tr>
<tr>
<td>IOP</td>
<td>Normal</td>
<td>Varies</td>
<td>Increased markedly</td>
<td>Normal or slightly decreased</td>
</tr>
<tr>
<td>Anterior Chamber</td>
<td>Normal</td>
<td>+ + + Cells and flare</td>
<td>Shallow</td>
<td>Cells and flare or normal</td>
</tr>
<tr>
<td>Other</td>
<td>Large, tender pre auricular node(s) if viral</td>
<td>Posterior synchiae</td>
<td>Coloured halos</td>
<td></td>
</tr>
</tbody>
</table>

Nausea and vomiting

Ocular Emergencies

These require urgent ophthalmology consultation for management

Sight Threatening
- lid/globe lacerations
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute glaucoma
- CRAO
- intraocular foreign body
- RD (especially when macula threatened)
- endophthalmitis
- GCA

Life-Threatening
- proptosis (rule out cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or externally compressive neoplastic lesion)
- papilledema (elevated increased intracranial pressure workup)
- orbital cellulitis
- leukocoria: white reflex (absent red reflex, must rule out retinoblastoma)

The Ocular Examination

Visual Acuity – Distance
- Snellen Acuity (Figure 5) = testing distance (usually 20 ft or 6 m)
  smallest line patient can read on the chart
- e.g. 20/40 = what the patient can see at 20 feet (numerator), what a “normal” person can see at 40 feet (denominator)
- distance visual acuity should be tested with distance glasses on in order to obtain best corrected visual acuity
- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
• legal blindness is BCVA that is ≤20/200 in best eye
• minimum visual requirements to operate a non-commercial automobile in Ontario are: 20/50 BCVA with both eyes open and examined together, 120° continuous horizontal visual field, and 15° continuous visual field above and below fixation

Visual Acuity – Near
• use pocket vision chart (Rosenbaum Pocket Vision Screener)
• record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
• conversion to distance visual acuity possible (e.g. immobile patient, no distance chart available)

Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics
• newborns
  • VA cannot be tested conventionally
• 3 mo-3 yr (can only assess visual function, not acuity)
• test each eye for fixation symmetry using an interesting object
• normal function noted as “CSM” = central, steady, and maintained
• 3 yr until alphabet known
• pictures or letter cards/charts such as HOTV or Sheridan-Gardner test (children point to optotypes on a provided matching card)
• tumbling “E” chart

Colour Vision
• test with Ishihara pseudoisochromatic plates
• record number of correctly identified plates presented to each eye, specify incorrect plates
• important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
• note: red-green colour blindness is sex-linked and occurs in 7-10% of males

VISUAL FIELDS
• test “visual fields by confrontation” (4 quadrants, each eye tested separately) for estimation of visual field loss
• accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
• use Amsler grid (each eye tested separately) to check for central or paracentral scotomas (blindspots) in patients with AMD

PUPILS
• use reduced room illumination with patient focusing on distant, fixed object to prevent near reflex
• examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
• test for RAPD with swinging flashlight test, check by reverse RAPD if one pupil non-reactive
• test pupillary constriction portion of near reflex by bringing object close to patient’s nose
• “normal” pupil testing often noted as PERRLA (pupils equal, round, reactive to light and accommodation)

ANTERIOR CHAMBER DEPTH
• shine light tangentially from temporal side
• if >2/3 of nasal side of iris in shadow → shallow anterior chamber

The van Herick Method (Slit Lamp technique)
• shine thin-angled slit beam onto the peripheral cornea of each eye, view at a 60° angle from the beam
• estimate depth between the posterior surface of the cornea and the iris as a proportion of corneal thickness
• ratios ≤1/4 implies risk of occludable angle; however, if >1/4, this does not rule out risk
• gonioscopy, as performed by an ophthalmologist, is gold-standard for assessing anterior chamber depth

EXTRAOCULAR MUSCLES
Alignment
• Hirschberg corneal reflex test
  • examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  • shine light into patient’s eyes from ~30 cm away
  • corneal light reflex should be at the same position on each cornea
  • strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see Strabismus, OP50)

Movement
• examine movement of eyeball through six cardinal positions of gaze
• ask patient if diplopia or pain is present in any position of gaze
• observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
• resolving horizontal nystagmus at end-gaze is usually normal

Diplopia
• see Neurology – Neuro-ophthalmology Diplopia
SLIT-LAMP EXAMINATION

Ocular Adnexa
- lids, lashes, lacrimal system

Anterior Segment
- conjunctiva / sclera
- cornea
  - fluorescein dye: stains de-epithelialized cornea; dye appears fluorescent green with cobalt blue filtered light
  - Rose Bengal dye: stains devitalized corneal epithelium
- anterior chamber/angle (Van Herick)
- iris/pupil
- lens (assess for cataract)
- anterior vitreous

Posterior Segment (requires 78D or 90D lens)
- vitreous
- optic disc (colour, C:D ratio, sharpness of disc margin)
- macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
- retinal vessels
- retinal background

TONOMETRY
- measurement of IOP
- normal range is 9-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by:
  - GAT: clinical gold standard, performed using the slit-lamp with special tip (prism)
  - Tono-Pen*: benefit is portability and use of disposable probe tips; use when cornea is scarred/ asymmetric (GAT inaccurate)
  - air puff (non-contact and least reliable)
- use topical anesthetic for GAT and Tono-Pen*; apply fluorescein dye when using GAT

DIRECT OPHTHALMOSCOPY
- best performed with pupils dilated (for list of mydriatics and cycloplegics see Table 13, OP58)
  1. assess red reflex
     - light reflected off the retina produces a "red reflex" when viewed from ~1 foot away
     - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract, retinoblastoma)
  2. examine the posterior segment of the eye
     - vitreous
     - optic disc (colour, C:D ratio, sharpness of disc margin)
     - macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
     - retinal vessels
     - retinal background
     - contraindications to pupillary dilatation
     - shallow anterior chamber – can precipitate acute angle-closure glaucoma
     - iris-supported anterior chamber lens implant
     - potential neurologic abnormality requiring pupil evaluation
     - use caution with cardiovascular disease – mydriatics may cause tachycardia and hypertension

REFRACTION
- two techniques used
  - flash/streak retinoscopy: refractive error determined objectively by the examiner using lenses and retinoscope
  - manifest: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
    - cycloplegic: manifest refraction with accommodation temporarily paralyzed with cycloplegics
  - a typical lens prescription would contain
    - sphere power in dioptre (measurement of refractive power of lens, equal to reciprocal of focal length in metres)
    - cylinder power in dioptre to correct astigmatism
    - axis of cylinder in degrees
    - "add" (bifocal/progressive reading lens) for presbyopes
    - e.g. -1.50 + 1.00 x 120 degrees, add +2.00

Optics

Aqueous Flare
- Resembles dust particles in a beam of light
- Results from protein leaking from blood vessels
- Distinguish from aqueous cells (individual cells in anterior chamber)

Figure 8. Diagnostic positions of gaze for isolated primary actions of extraocular muscles

Figure 9. Slit-lamp examination note

Figure 10. Tonometry
REFRACTIVE EYE SURGERY
- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK and LASIK
- potential risks/side-effects: infection, under/overcorrection, increased glare/halo perception at night, corneal haze (PRK only), dry eyes (more common in LASIK than PRK), regression, and flap complications such as free cap (loss of flap), traumatic flap dislocations, buttonhole flap, and epithelial in growth (LASIK only)

Table 4. Optics

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmetropia</td>
<td>Image of distant objects focus exactly on the retina</td>
<td>No refractive error</td>
<td></td>
</tr>
<tr>
<td>Myopia</td>
<td>Globe too long relative to refractive mechanisms, or refractive mechanisms too strong</td>
<td>“Nearsightedness” Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with DM or cataracts Blurring of distance vision; near vision usually unaffected Prevalence: 30-40% in U.S. population</td>
<td>Correct with negative dioptr/concave/“negative” lenses to diverge light rays Refractive eye surgery</td>
</tr>
<tr>
<td>Hyperopia</td>
<td>Globe too short relative to refractive mechanisms, or refractive mechanisms too weak</td>
<td>“Farsightedness” Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia (see Strabismus, OP36)</td>
<td>When symptomatic, correct with positive dioptr/convex/“plus” lenses to converge light rays Refractive eye surgery</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped) Two types Regular – curvature uniformly different in meridians at right angles to each other Irregular – distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye Affects ~30% of population, with prevalence increasing with age Mild astigmatism unnoticeable Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches</td>
<td>Correct with cylindrical lens (if regular Try contact lens (if irregular) Refractive eye surgery</td>
<td></td>
</tr>
<tr>
<td>Presbyopia</td>
<td>Normal aging process (&gt;40 yr) Hardening/reduced deformability of lens results in decreased accommodative ability Accommodative power is 14D at age 10, diminishes to 3.5D by age 40 yr Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia) If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected If initially myopic, person removes distance glasses to read If initially hyperopic, symptoms of presbyopia occur earlier</td>
<td>Correct with positive dioptr/convex/“plus” lenses for reading</td>
<td></td>
</tr>
<tr>
<td>Anisometropia</td>
<td>Difference in refractive errors between eyes</td>
<td>Second most common cause of amblyopia in children</td>
<td></td>
</tr>
</tbody>
</table>
The Orbit

Globe Displacement

Table 5. Exophthalmos (Proptosis) and Enophthalmos

<table>
<thead>
<tr>
<th>Exophthalmos (Proptosis)</th>
<th>Enophthalmos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>Anterior displacement (protrusion) of the globe</td>
<td>Posterior displacement (retraction) of the globe</td>
</tr>
<tr>
<td>Exophthalmos generally refers to an endocrine etiology or protrusion of &gt;18 mm (as measured by a Hertel exophthalmometer) Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of &gt;18 mm</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>CT/MRI head/orbits ultrasound orbits, thyroid function tests</td>
<td>CT/MRI orbits</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Note: rule out pseudoexophthalmos (e.g. lid retraction) Graves’ disease (unilateral or bilateral, most common cause in adults) Orbital cellulitis (unilateral, most common cause in children) 1° or 2° orbital tumours Orbital/retrobulbar hemorrhage Cavernous sinus thrombosis or fistula</td>
<td>“Blow-out” fracture (see Ocular Trauma, OP39) Orbital fat atrophy Congenital abnormality Metastatic disease</td>
</tr>
</tbody>
</table>

Preseptal Cellulitis

infection of soft tissue anterior to orbital septum

Etiology
- usually follows periorbital trauma or dermal infection

Clinical Features

Table 6. Clinical Features of Preseptal and Orbital Cellulitis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Preseptal Cellulitis</th>
<th>Orbital Cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>May be present</td>
<td>Present</td>
</tr>
<tr>
<td>Lid edema</td>
<td>Moderate to severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Chemosis</td>
<td>Absent or mild</td>
<td>Marked</td>
</tr>
<tr>
<td>Proptosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Pain on eye movement</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Ocular mobility</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Vision</td>
<td>Normal</td>
<td>Diminished ± diplopia</td>
</tr>
<tr>
<td>RAPD</td>
<td>Absent</td>
<td>May be seen if severe</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>ESR</td>
<td>Normal or elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Additional findings</td>
<td>Skin infection</td>
<td>Sinusitis, dental abscess</td>
</tr>
</tbody>
</table>

Treatment
- systemic antibiotics (suspect H. influenzae in children; S. aureus or Streptococcus in adults)
  - e.g. amoxicillin-clavulanic acid
  - if severe or child <1 yr, treat as orbital cellulitis

Orbital Cellulitis

- OCULAR and MEDICAL EMERGENCY
- inflammation of orbital contents posterior to orbital septum
  - common in children, elderly, and immunocompromised

Etiology
- usually secondary to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

Clinical Features (see Table 6)

Treatment
- admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
- surgical drainage of abscess with close follow-up, especially in children

Complications
- optic nerve inflammation, cavernous sinus thrombosis, meningitis, brain abscess with possible loss of vision, and death
Lacrical Apparatus

- tear film made up of three layers
  - outer oily layer (reduces evaporation): secreted by the Meibomian glands
  - middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  - inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
- tears drain from the eyes through the upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrinal duct → nasal cavity behind inferior concha (Figure 3)

Dry Eye Syndrome (Keratoconjunctivitis Sicca)

Etiology
- aqueous-deficient
  - Sjögren syndrome (autoimmune etiology e.g. RA, SLE)
  - non-Sjögren syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy, anticholinergics, antihistamines, diuretics, β blockers)
- evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  - Meibomian gland dysfunction (posterior blepharitis)
  - vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  - eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  - topical ocular medications with preservatives
  - contact lenses, allergic conjunctivitis
- mixed etiologies are common

Clinical Features
- dry eyes, red eyes, foreign body sensation, blurred vision, tearing
- slit-lamp exam: decreased tear meniscus, decreased tear break-up time (normally should be 10 s), punctate staining of cornea with fluorescein

Investigations
- surface damage observed with fluorescein/Rose Bengal staining
- decreased distance in Schirmer's test

Complications
- erosions and scarring of cornea

Treatment
- medical: preservative-free artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used more than 4-6x/day), short course of mild topical corticosteroid, omega-3 fatty acids orally, and eyelid hygiene for blepharitis
  - for moderate cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) can be used
- procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
- treat underlying cause

Epiphora (Excessive Tearing)

Etiology
- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, dacryoadenitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex (crocodile tears)

Investigations
- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

Treatment
- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation (dilation and irrigation)
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy – forming a new connection between the lacrimal sac and the nasal cavity

Long-term use of artificial tears with preservatives should be avoided when treating dry eyes
Excessive tearing can be caused by dry eyes – if the tear quality is insufficient, “reflex tearing” may occur
Dacryocystitis

• acute or chronic infection of the lacrimal sac
• most commonly due to obstruction of the nasolacrimal duct
• commonly associated with *S. aureus, S. pneumoniae, Pseudomonas* species

Clinical Features

• pain, swelling, redness over lacrimal sac at medial canthus
• epiphora, crusting, ± fever
• digital pressure on the lacrimal sac may extrude pus through the punctum
• in the chronic form, epiphora may be the only symptom

Treatment

• warm compresses, nasal decongestants, systemic and topical antibiotics
• if chronic, obtain cultures by aspiration
• once infection resolves, consider dacryocystorhinostomy

Dacryoadenitis

• inflammation of the lacrimal gland (outer third of upper eyelid)
• acute causes: *S. aureus, mumps, EBV, herpes zoster, N. gonorrhoeae*
• chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

Clinical Features

• pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
• chronic form is more common and may present as painless enlargement of the lacrimal gland

Treatment

• supportive: warm compresses, oral NSAIDs
• systemic antibiotics if bacterial cause
• if chronic, treat underlying disorder

Lids and Lashes

Lid Swelling

Etiology

• commonly due to allergy, with shriveling of skin between episodes
• dependent edema on awakening (e.g. CHF, renal or hepatic failure)
• orbital venous congestion due to mass or cavernous sinus fistula
• dermatochalasis (loose skin due to aging or heredity)
• lid cellulitis, thyroid disease (e.g. myxedema), trauma, chemosis

Ptosis

• drooping of upper eyelid

Etiology

• aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
  • associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
• mechanical
  • incomplete opening of eyelid due to mass or scarring
• neuromuscular
  • myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  • CN III palsy
  • Horner’s syndrome (see *Constricted Pupil, Horner’s Syndrome, OP30*)
• congenital
• pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)
• drugs (e.g. high dose opioids, heroin abuse, pregabalin)

Treatment

• surgery (e.g. blepharoplasty, levator resection, Müller’s muscle resection, frontalis sling)
**Trichiasis**

- eyelashes turned inwards
- may result from entropion, involutional age change, chronic inflammatory lid diseases (e.g. blepharitis), trauma, burns
- patient complains of red eye, foreign body sensation, significant discomfort, tearing
- may result in corneal ulceration and scarring

**Treatment**

- topical lubrication, repeat eyelash epilation, electrolysis, cryotherapy

**Entropion**

- lid margin turns in towards globe causing tearing, foreign body sensation, and red eye
- most commonly affects lower lid
- may cause corneal abrasions with secondary corneal scarring

**Etiology**

- involutonal (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital

**Treatment**

- lubricants, evert lid with tape, surgery

**Ectropion**

- lid margin turns outward from globe causing tearing and possibly exposure keratitis

**Etiology**

- involutonal (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, surgery)
- mechanical (lid edema, tumour, herniated fat)
- congenital

**Treatment**

- topical lubrication, eyelid taping overnight, surgery

**Hordeolum (Stye)**

- acute inflammation of eyelid gland: either Meibomian glands (internal lid), glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)
- infectious agent is usually *S. aureus*
- painful, red swelling of lid

**Treatment**

- warm compresses, lid care, gentle massage
- topical antibiotics are typically ineffective
- usually resolves within 2 wk, but may require incision and drainage

**Chalazion**

- chronic granulomatous inflammation of Meibomian gland often preceded by an internal hordeolum
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, Meibomian gland carcinoma

**Treatment**

- warm compresses
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy

Testing for Entropion

Forced lid closure: Ask patient to tighten lid then open. In entropion, lid rolls inwards

Testing for Ectropion

Snapback test: Pull eyelid inferiorly. In ectropion, lid remains away from globe

Hordeolum vs. Chalazion

Hordeolums are due to an infectious etiology, whereas chalazions are granulomatous inflammation
Blepharitis

- inflammation of lid margins

**Etiology**
- Anterior blepharitis
  - staphylococcal (S. aureus): ulcerative, dry scales
  - seborrheic: no ulcers, greasy scales
- Posterior blepharitis
  - Meibomian gland dysfunction

**Clinical Features**
- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids (“toothpaste sign”)

**Complications**
- recurrent hordeola
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

**Treatment**
- warm compresses, lid massages, and lid washing using commercially available eyelid scrub solution
- topical or systemic antibiotics as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids, omega-3 fatty acids

Xanthelasma

- eyelid xanthoma (lipid deposits in dermis of lids)
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (~50% of patients)
- common in the elderly, more concerning in the young

**Treatment**
- excision for cosmesis only, commonly recurs

Conjunctiva

thin, vascular mucous membrane
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

Pinguecula

- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea
- associated with sun and wind exposure, aging
- benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops

Pterygium

- fibrovascular, triangular, wing-like encroachment of epithelial tissue onto the cornea
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (~5%)

Subconjunctival Hemorrhage

- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, HTN, anticoagulation
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- 360 degree involvement should be highly suspicious for globe rupture if trauma history
- if recurrent, consider medical/hematologic workup
Conjunctivitis

Etiology
- infectious
  - bacterial, viral, chlamydial, gonococcal, fungal, parasitic
- non-infectious
  - allergic, atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
  - secondary to another disorder: dacryocystitis, dacyroadenitis, cellulitis, systemic inflammatory disease

Clinical Features
- red eye (conjunctival injection often with limbal pallor), chemosis, corneal subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, lid edema
- ± preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva, overlain by vessels
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)

ALLERGIC CONJUNCTIVITIS
- associated with rhinitis, asthma, dermatitis, hay fever
- ocular pruritus, small papillae, chemosis, redness, thickened and erythematous lids
- seasonal (pollen, grasses, plant allergens)

Treatment
- allergen avoidance, cool compresses, non-preserved artificial tears, topical or oral antihistamine, topical mast cell stabilizer (e.g. cromolyn, ketotifen, olopatadine), topical corticosteroids

Atopic Conjunctivitis
- onset late adolescence and early adulthood with peak between 30-50 years old
- intense ocular pruritus (perennially), tearing, burning, clear mucus discharge, redness, blurry vision, photophobia, and foreign body sensation
- thickened and intermittent swelling of the eyelids, conjunctival chemosis, conjunctival hyperemia, and tarsal papillary hypertrophy

Treatment
- calcineurin inhibitor ointment (e.g. tacrolimus and pimecrolimus), and topical corticosteroid (clobetasone)

Giant Papillary Conjunctivitis
- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva

Treatment
- clean, change or discontinue use of contact lens, topical corticosteroids

Vernal Conjunctivitis
- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 yr then resolves

Treatment
- non-preserved artificial tears, consider topical steroid, topical cyclosporine (by ophthalmologist)

VIRAL CONJUNCTIVITIS (pink eye)
- presents with itchiness, pain and swelling
- serous discharge, lid edema, follicles, pseudomembranes
- subepithelial corneal infiltrates
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye within a few days
- mainly due to adenovirus – highly contagious for up to 12 d

Treatment
- cool compresses, topical lubrication.
- usually self-limiting (7-12 d)
- proper hygiene is important to prevent transmission

BACTERIAL CONJUNCTIVITIS
- purulent discharge, lid swelling, papillae, conjunctival injection, chemosis
- common agents include S. aureus, S. pneumoniae, H. influenzae and M. catarrhalis
- in neonates or if sexually active must consider N. gonorrhoeae (invades cornea to cause keratitis)
- C. trachomatis is the most common cause in neonates

Treatment
- topical broad-spectrum antibiotic, systemic antibiotics if indicated (especially in neonates and children)
- usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment
OP15 Ophthalmology

GONOCOCCAL AND CHLAMYDIAL CONJUNCTIVITIS
- caused by N. gonorrhoeae and C. trachomatis, respectively
- affects sexually active individuals, neonates (ophthalmia neonatorum) in first 5 d of life when caused by gonorrhea (shorter incubation period) and d 3-14 of life when caused by chlamydia (longer incubation period)
- newborn prophylaxis with 0.5% erythromycin ointment no longer recommended
- chlamydia causes trachoma and inclusion conjunctivitis (different serotypes)

Trachoma
- leading infectious cause of blindness in the world
- severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
- initially, follicles on superior palpebral conjunctiva and later palpebral scarring (Arlt’s line)

Treatment
- oral azithromycin and topical tetracycline

Inclusion Conjunctivitis
- chronic conjunctivitis with follicles and subepithelial infiltrates
- most common cause of conjunctivitis in newborns
- newborn prophylaxis with 0.5% erythromycin ointment no longer recommended

Treatment
- oral azithromycin, tetracycline, doxycycline

Sclera
- white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

Episcleritis
- immunologically mediated inflammation of episclera
- 1/3 bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

Etiology
- mostly idiopathic
- associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, syphilis), inflammatory bowel disease, rosacea, atopy

Clinical Features
- may have discomfort and pain associated with red eye (often interpalpebral)
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial vessels)

Treatment
- generally self-limited, recurrent in 2/3 of cases
- topical steroid (prescribed and monitored by ophthalmologist)
- oral NSAID

Scleritis
- usually unilateral: can be classified as anterior or posterior and diffuse, nodular, necrotizing with inflammation, or necrotizing without inflammation (scleromalacia perforans)
- anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing
- posterior scleritis: rapidly progressive blindness, may cause exudative RD
- more common in women and elderly

Etiology
- may be a manifestation of systemic disease
- collagen vascular disease, e.g. SLE, RA, GCP, ankylosing spondylitis
- granulomatous, e.g. tuberculosis, sarcoidosis, syphilis
- metabolic, e.g. goit, thyrotoxicosis
- infectious, e.g. S. aureus, S. pneumoniae, P. aeruginosa, herpes zoster
- chemical or physical agents, e.g. thermal, alkali, or acid burns
- idiopathic

Clinical Features
- severe “deep” or “boring” pain, photophobia, red eye, decreased vision
- pain is 1 st indicator of disease progression
- inflammation of scleral, episcleral, and conjunctival vessels

To differentiate between episcleritis and scleritis, place a drop of phenylephrine 2.5% (Mydristine®; Alcon) in the affected eye. Re-examine the vascular pattern 10-15 min later; if episcleritis the episcleral vessels should blanch with phenylephrine.

Scleromalacia Perforans
- Asymptomatic anterior necrotizing scleritis without inflammation
- Strongly associated with RA
- May result in scleral thinning
- Traumatic perforation can easily occur – examine eye very gently

Preventing Ophthalmia Neonatorum
Paediatr Child Health 2015;20(2):93-96
The use of silver nitrate as prophylaxis for neonatal ophthalmia was instituted in the late 1800s to prevent the devastating effects of neonatal ocular infection with Neisseria gonorrhoeae. At that time – during the preantibiotic era – many countries made such prophylaxis mandatory by law. Today, neonatal gonococcal ophthalmia is rare in Canada, but ocular prophylaxis for this condition remains mandatory in some provinces/territories. Silver nitrate drops are no longer available and erythromycin, the only ophthalmic antibiotic eye ointment currently available for use in newborns, is of questionable efficacy. Ocular prophylaxis is not effective in preventing chlamydial conjunctivitis. Applying medication to the eyes of newborns may result in mild eye irritation and has been perceived by some parents as interfering with mother-infant bonding. Physicians caring for newborns should advocate for rescinding mandatory ocular prophylaxis laws. More effective means of preventing ophthalmia neonatorum include screening all pregnant women for gonorrhea and chlamydia infection, and treatment and follow-up of those found to be infected. Mothers who were not screened should be tested at delivery. Infants of mothers with untreated gonococcal infection at delivery should receive ceftriaxone. Infants exposed to chlamydia at delivery should be followed closely for signs of infection.
• may have anterior chamber cells and flare, corneal infiltrate, scleral thinning, scleral edema
• sclera may have a purple or “violaceous” hue (best seen in natural light), due to rearranged scleral fibres
• failure to blanch with topical phenylephrine

**Treatment**
• vision threatening – needs to be referred to ophthalmology
• life threatening- indicator of poor systemic disease control with an increased 5 year mortality rate (not from scleritis) without treatment of underlying untreated or unrecognized autoimmune condition
• systemic NSAID, systemic steroid, and systemic immunomodulation
• treat underlying etiology

---

**Cornea**

• function
  ■ transmission of light
  ■ refraction of light (2/3 of total refractive power of eye)
  ■ barrier against infection, foreign bodies
  ■ transparency due to avascularity, uniform collagen structure and deturgescence (relative dehydration)
  ■ 5 layers (anterior to posterior): epithelium, Bowman's layer, stroma, Descemet's membrane, and the endothelium (dehydrates the cornea; dysfunction leads to corneal edema). Some have argued the existence of a 6th layer, “Du’s layer”, although it is debated if this is a truly unique and additional layer. extensive sensory fibre network (V1 distribution) therefore abrasions are very painful

---

**Foreign Body**

• foreign material in or on cornea
• may have associated rust ring if metallic
• patients may note pain, tearing, photophobia, foreign body sensation, red eye
• signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, anterior chamber cells/flare

**Complications**
• abrasion, infection, ulcer, scarring, rust ring, secondary iritis

**Treatment**
• remove under magnification using local anesthetic and sterile needle or refer to ophthalmology for removal under magnification (depending on depth and location)
• treat as per cornea abrasion

---

**Corneal Abrasion**

• epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (Figure 14)

**Clinical Features (Table 7)**
• pain, redness, tearing, photophobia, foreign body sensation
• de-epithelialized area stains with fluorescein dye
• pain relieved with topical anesthetic (DO NOT use for treatment- risk of corneal melt or infection)

**Complications**
• infection, ulceration, recurrent erosion, secondary iritis

**Treatment**
• topical antibiotic (drops or ointment), abrasion from organic material should be covered against pseudomonas
• consider topical NSAID (caution due to risk of corneal melt with prolonged use), cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch
• most abrasions clear spontaneously within 24-48 h

---

**Recurrent Erosions**

• recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
• usually occurs upon awakening
• associated with improper adherence of epithelial cells to the underlying basement membrane

**Etiology**
• previous traumatic corneal abrasion
• corneal dystrophy
• idiopathic
Treatment
• same as corneal abrasion until re-epithelialization occurs
• topical hypertonic saline ointment at bedtime for 6-12 mo, topical lubrication
• bandage contact lens, anterior stromal puncture or photo therapeutic keratectomy for chronic recurrences

Corneal Ulcer

Etiology
• local necrosis of corneal tissue due to infection
  • infection is usually bacterial; rarely viral, fungal, or protozoan (Acanthamoeba)
  • secondary to corneal exposure, abrasion, foreign body, contact lens use (50% of ulcers)
  • also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

Clinical Features
• pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
• corneal opacity that necroses and forms an excavated ulcer with infiltrative base
• overlying corneal epithelial defect that stains with fluorescein
• may develop corneal edema, conjunctival injection, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
• bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

Complications
• decreased vision, corneal perforation, iritis, endophthalmitis

Investigations
• Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect leaking penetrating lesions; any aqueous leakage will dilute the green stain at site of wound

Treatment
• urgent referral to ophthalmology
• culture prior to treatment
• topical antibiotics every hour
• must treat vigorously to avoid complications

Table 7. Corneal Abrasion vs. Corneal Ulcer

<table>
<thead>
<tr>
<th></th>
<th>Abrasion</th>
<th>Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Course</td>
<td>Acute (instantaneous)</td>
<td>Subacute (days)</td>
</tr>
<tr>
<td>History of Trauma</td>
<td>Commonly</td>
<td>Rare</td>
</tr>
<tr>
<td>Cornea</td>
<td>Clear</td>
<td>White, necrotic area</td>
</tr>
<tr>
<td>Iris Detail</td>
<td>Clear</td>
<td>Obscured</td>
</tr>
<tr>
<td>Corneal Thickness</td>
<td>Normal</td>
<td>May have crater/thinning</td>
</tr>
<tr>
<td>Extent of Lesion</td>
<td>Limited to epithelium</td>
<td>Extension into stroma</td>
</tr>
</tbody>
</table>

Herpes Simplex Keratitis

• usually HSV type 1 (90% of population are carriers)
• may be triggered by stress, fever, sun exposure, immunosuppression

Clinical Features
• pain, tearing, foreign body sensation, red eye, may have decreased vision, eyelid edema
• corneal hypoesthesia
• classic form of HSV infectious epithelial keratitis is a dendritic (thin and branching) lesion with terminal end bulbs in epithelium that stains with fluorescein
• HSV may cause other forms of infectious epithelial keratitis, as well as stromal keratitis (which may be infectious or immune-mediated), and endotheliitis (presumably immune-mediated but possible role of live virus)

Complications
• corneal scarring (can lead to loss of vision)
• chronic interstitial keratitis due to penetration of virus into stroma
• secondary iritis, secondary glaucoma

Treatment
• topical antiviral such as trifluridine, or systemic antiviral such as acyclovir
• debridement of dendrite
• NO STEROIDS initially – may exacerbate condition
• ophthalmologist must exercise caution if adding topical steroids for stromal keratitis, endotheliitis or iritis, and patients covered with antiviral prophylaxis
Herpes Zoster Ophthalmicus

- dermatitis in the dermatomal distribution of CN V1 that is typically unilateral and respects the midline
- Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then globe will be involved in ~75% of cases
  if no nasal involvement, eye is involved in 1/3 of patients

Clinical Features
- pain, tearing, photophobia, red eye
- corneal edema, pseudodendritis, SPK
- corneal hypoesthesia

Complications
- keratitis, ulceration, perforation and scarring
- secondary iritis, secondary glaucoma, cataract
- muscle palsies (rare) due to CNS involvement
- occasionally severe post-herpetic neuralgia

Treatment
- oral antiviral (acyclovir, valcyclovir, or famciclovir) immediately
- topical steroids, cycloplegia as indicated for immune-mediated keratitis, iritis
- erythromycin ointment if conjunctival involvement

Keratoconus

- bilateral thinning and bulging (ectasia) of the cornea resulting in a conical shape
- usually sporadic but can be associated with Down's syndrome, atopy, contact lens use and vigorous eye rubbing
- associated with breaks in Descemet's membrane and Bowman's layer
- results in decreased vision from irregular astigmatism, scarring and stromal edema

Treatment
- attempt correction with spectacles and/or rigid gas permeable contact lens
- corneal collagen cross-linking treatment to halt disease progression
- intrastromal corneal ring segments can help flatten the corneal cone
- penetrating keratoplasty or deep anterior lamellar keratoplasty (partial-thickness corneal transplant) as last resort

Arcus Senilis

- hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
- common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
- may be associated with hypercholesterolemia if age <40 yr, check lipid profile
- no associated visual symptoms, complications or treatment necessary

Kayser-Fleischer Ring

- brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
- due to deposition of copper pigment in Descemet's membrane
- associated with Wilson's disease
- no associated symptoms or complications of ring
- treat underlying disease
The Uveal Tract

- uveal tract (from anterior to posterior) = iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina

Uveitis

- uveal inflammation which may involve one, two, or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, malignant causes
- should be managed by an optometrist or ophthalmologist
- anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis based on primary site of inflammation

Table 8. Anatomic Classification of Uveitis

<table>
<thead>
<tr>
<th>Location</th>
<th>Anterior Uveitis (Iritis)</th>
<th>Intermediate Uveitis</th>
<th>Posterior Uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), both = iridocyclitis</td>
<td>The vitreous is the major site of the inflammation</td>
<td>Inflammation of the choroid and/or retina</td>
</tr>
<tr>
<td>Etiology</td>
<td>Usually idiopathic</td>
<td>Mostly idiopathic, secondary causes include sarcoidosis, Lyme disease, and multiple sclerosis</td>
<td>Bacterial: syphilis, tuberculosis</td>
</tr>
<tr>
<td>Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster</td>
<td></td>
<td></td>
<td>Fungal: histoplasmosis, candidiasis</td>
</tr>
<tr>
<td>Other: sarcoidosis, trauma, large abrasion, post ocular surgery</td>
<td></td>
<td></td>
<td>Parasitic: toxoplasmosis (most common cause) toxocara</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Photophobia (due to reactive spasm of inflamed iris (ciliary muscle spasm), decreased VA, lacrimation Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle)</td>
<td>Insidious onset of blurred vision, accompanied by vitreous floaters Initial symptoms are usually unilateral but inflammatory changes are usually bilateral and asymmetric</td>
<td>Painless as choroid has no sensory innervation</td>
</tr>
<tr>
<td>Anterior chamber &quot;cells&quot; (WBC in anterior chamber due to anterior segment inflammation) and &quot;flare&quot; (protein precipitates in anterior chamber secondary to inflammation), hypopyon (collection of neutrophilic exudates inferiorly in the anterior chamber)</td>
<td></td>
<td>Associated with anterior uveitis, most severe cases of secondary intermediate uveitis</td>
<td>Often no conjunctival or scleral injection present</td>
</tr>
<tr>
<td>Occasionally keratic precipitates (clumps of cells on corneal endothelium) Iritis typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis or iritis from herpetic encephalitis and zoster may cause an inflammatory glaucoma (trabectitis)</td>
<td></td>
<td>Vitreous cells, condensations, and snowballs (vitreous aggregates of inflammatory cells) Posterior segment 'snowbank' = grey-white fibrovascular plaque at the pars plana</td>
<td>Decreased VA</td>
</tr>
<tr>
<td>Complications</td>
<td>Inflammatory glaucoma Posterior synechiae Adhesions of posterior iris to anterior lens capsule Indicated by an irregularly shaped pupil If occurs 360°, can lead to angle closure glaucoma Peripheral anterior synechiae (rare): adhesions of iris to cornea → secondary angle closure glaucoma Cataracts Band keratopathy (with chronic iritis) Superficial corneal calcification keratopathy Macular edema with chronic iritis</td>
<td>Cystoid macular edema (30% of cases), cataract, and glaucoma</td>
<td>Macular edema Vitriris Neovascularization Visual field loss/scotoma</td>
</tr>
<tr>
<td>Treatment</td>
<td>Mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm Steroids: topical, sub-tenon, or systemic Systemic analgesia If recurrent episodes, extensive medical workup may be indicated to rule out secondary causes</td>
<td>Systemic or sub-tenon/intravitreal steroids and immunosuppressive agents Vitrectomy, cryotherapy, or laser photoagulation to the &quot;snowbank&quot;</td>
<td>Steroids: sub-tenon, intravitreal, or systemic if indicated (e.g. threat of vision loss)</td>
</tr>
</tbody>
</table>
Lens

• consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

Cataracts

• any opacity of the lens, regardless of etiology
• most common cause of reversible blindness worldwide
• types: nuclear sclerosis, cortical, posterior subcapsular

Etiology

• acquired
  • age-related (over 90% of all cataracts)
  • cataract associated with systemic disease (may have juvenile onset)
    • DM
    • meabolic disorders (e.g. Wilson's disease, galactosemia, homocystinuria)
    • hypocalcemia
  • traumatic (may be rosette shaped)
  • intraocular inflammation (e.g. uveitis)
  • toxic (steroids, phenothiazines)
  • radiation
• congenital
  • high myopia
  • present with altered red reflex or leukocoria
  • treat promptly to prevent amblyopia

Clinical Features

• gradual, painless, progressive decrease in VA
• glare, dimness, halos around lights at night, monocular diplopia
• "second sight" phenomenon: patient is more myopic than previously noted, due to increased refractive power of the lens in nuclear sclerosis only
  • patient may read without previously needed reading glasses
• diagnosis by slit-lamp exam
• may impair view of retina during fundoscopy

Treatment

• medical: no role for medical management
• surgical: definitive treatment
  • indications for surgery
    • to improve visual function in patients whose vision loss leads to functional impairment
    • to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
    • congenital or traumatic cataracts
  • phacoemulsification (phaco = lens)
  • most commonly used surgical technique
  • post-operative complications: RD, endophthalmitis, dislocated IOL, macular edema, glaucoma, posterior capsular opacification

Dislocated Lens (Ectopia Lentis)

Etiology

• associated with Marfan's Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
• traumatic

Clinical Features

• decreased VA
• may get monocular diplopia
• iridodonesis (quivering of iris with movement)
• phacodonesis (observed movement of the lens)
• direct ophthalmoscopy may elicit abnormal red reflex

Complications

• cataract, glaucoma, uveitis

Treatment

• surgical lens replacement
**Vitreous**

- clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, pars plana, and along major retinal blood vessels

**Posterior Vitreous Detachment**

**Etiology**
- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, molecules that hold water condense causing vitreous floaters
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

**Clinical Features**
- floaters, flashes of light

**Complications**
- traction at sites of firm adhesion may result in a retinal tear with or without subsequent rhegmatogenous retinal detachment
- retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
- complications more common in high myopes and following ocular trauma (blunt or perforating)

**Treatment**
- acute onset of PVD requires a dilated fundus exam to rule out retinal tears/detachment
- no specific treatment available for floaters/flashes of light

**Vitreous Hemorrhage**

- bleeding into the vitreous cavity

**Etiology**
- PDR
- retinal tear/detachment
- PVD
- retinal vein occlusion
- trauma

**Clinical Features**
- sudden loss of VA
- may be preceded by “shower” of many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

**Treatment**
- ultrasound (B-scan) to rule out RD
- expectant: in non-urgent cases (e.g. no RD), blood usually resorbs in 3-6 mo
- surgical: vitrectomy ± RD repair ± retinal endolaser to possible bleeding sites/vessels

**Endophthalmitis and Vitritis**

- intraocular infection: acute, subacute, or chronic

**Etiology**
- most commonly a post-operative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal

**Clinical Features**
- painful, red eye, photophobia, discharge
- severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased IOP, etc.)

**Treatment** *(see Ocular Trauma, OP39)*
- OCULAR EMERGENCY: presenting vision best indicates prognosis
- LP or worse: admission, immediate vitrectomy, and intravitreal antibiotics to prevent loss of vision
- HM or better: vitreous tap for culture and intravitreal antibiotics
- topical fortified antibiotics

**Weiss Ring**: formed by glial tissue around the optic disc that remains attached to the detached posterior vitreous

**Floaters**: “bugs”, “cobwebs”, or “spots” of vitreous condensation that move with eye position

**Although most floaters are benign, new or markedly increased floaters or flashes of light require a dilated fundus exam to rule out retinal tears/detachment**

**Any time a vitreous or retinal hemorrhage is seen in a child, must rule out child abuse**

Remember to inquire about tetanus status in post-traumatic endophthalmitis
Retina

- composed of two parts (Figure 2)
  - neurosensory retina: comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
  - retinal pigment epithelium (RPE) layer: external to neurosensory retina
- macula: rich in cones (for colour vision); most sensitive area of retina
- fovea: centre of macula; responsible for detail, fine vision, lacks retinal vessels
- optic disc: collection of retinal nerve fibre layers forming optic nerve (CN2)
- ora serrata: irregularly-shaped, anterior margin of the retina (cannot be visualized with direct ophthalmoscope)

Central/Branch Retinal Artery Occlusion

Etiology
- occlusion of blood flow from following causes results in loss of vision due to oxygen starvation of the retinal tissues and eventual cell death
  - emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
  - thrombus
  - temporal arteritis

Clinical Features
- sudden, painless (except in GCA), severe monocular loss of vision
- RAPD
- patient may have experienced transient episodes in the past (amaurosis fugax)

fundoscopy
- “cherry-red spot”
- retinal pallor
- cotton wool spots (retinal infarcts)
- cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations

Treatment
- OCULAR EMERGENCY: attempt to restore blood flow within 2 h (irreversible retinal damage if >90 min of complete CRAO)
- massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
- decrease IOP
  - topical β-blockers
  - IV acetazolamide
  - IV mannitol (draws fluid from eye)
  - drain aqueous fluid – anterior chamber paracentesis (carries risk of infection, lens puncture)
- Nd:YAG laser embololysis
- intra-arterial or intra-venous thrombolysis

Central/Branch Retinal Vein Occlusion

- second most frequent “vascular” retinal disorder after DR
- usually a manifestation of a systemic disease (e.g. HTN, DM)
- thrombus occurs within the lumen of the central retinal vein/arteriovenous crossing point

Predisposing Factors
- arteriosclerotic vascular disease
- HTN
- DM
- glaucoma
- hyperviscosity (e.g. polycythemia rubra vera, sickle-cell disease, lymphoma, leukemia)
- drugs (e.g. oral contraceptive pill, diuretics)

Clinical Features
- painless, monocular, gradual or sudden vision loss
- ± RAPD
- fundoscopy
  - “blood and thunder” appearance
  - diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - no RAPD, VA ~ 20/80
    - mild hemorrhage, few cotton wool spots
    - resolves spontaneously over weeks to months
    - may regain normal vision if macula intact
  - ischemic retinopathy
    - RAPD, VA < 20/200
    - dark or orange macula
    - severe vision loss
    - may have retinal neovascularization

Intravitreal Aflibercept injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One Year results of Phase 3 GAULIEO study
Ophthalmology 2014; 121(1) 202-8
Treatment with intravitreal aflibercept provided significant functional and anatomic benefits after 52 weeks as compared with sham. The improvement achieved after 6 monthly doses at week 24 were maintained until week 52 with prn dosing.
Retina

Complications
- neovascularization of retina and iris (secondary rubeosis), leading to secondary glaucoma
- vitreous hemorrhage
- macular edema

Treatment
- treatment available for complications of CRVO/BRVO, including retinal laser photoacoagulation, anti-VEGF and/or corticosteroid injection

Retinal Detachment
- cleavage in the plane between the neurosensory retina and the RPE
  - three types
    - rhegmatogenous (most common)
      - caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - tractional
      - caused by vitreal, epiretinal, or subretinal membrane pulling the neurosensory retina away from the underlying RPE
    - exudative
      - caused by damage to the RPE resulting in fluid accumulation in the subretinal space
      - main causes are intraocular tumours, posterior uveitis, central serous retinopathy

Clinical Features
- sudden onset
- flashes of light
  - due to mechanical stimulation of the retinal photoreceptors
- floaters
- hazy spots in the line of vision which move with eye position due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/peripheral field loss
  - darkness in one field of vision when the retina detaches in that area
- loss of central vision (if macula “off”)
- decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
- ophthalmoscopy: detached retina is grey-white with surface blood vessels, loss of red reflex
- ± RAPD

Treatment
- prophylactic: symptomatic tear (flashes or floaters) can be sealed off with laser/cryotherapy
  - therapeutic
    - rhegmatogenous
      - scleral buckle procedure
    - pneumatic retinopexy
    - vitrectomy plus injection of gas (injection of silicone oil in cases of recurrent detachment)
    - tractional
      - vitrectomy ± membrane removal/scleral buckling/injection of intraocular gas or silicone oil as necessary
    - exudative
    - management is nonsurgical; any underlying disease should be treated if possible

Complications
- loss of vision, vitreous hemorrhage, recurrent RD
- a RD is an emergency, especially if the macula is still attached (macula “on”)
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

Retinitis Pigmentosa
- hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy
- many forms of inheritance, most commonly autosomal recessive (60%)
Clinical Features
- night blindness, decreased peripheral vision ("tunnel vision"), decreased central vision (macular changes), glare (from posterior subcapsular cataracts; common)

Investigations
- fundoscopy: areas of “bone-spicule” pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
electrophysiological tests: electroretinography (ERG) and electrooculography (EOG) assist in diagnosis

Treatment
- no treatments available to reverse the condition; cataract extraction improves visual function; vitamin A and vitamin E supplementation can reduce progression of disease in some patients

Age-Related Macular Degeneration
- leading cause of irreversible blindness in the Western world, associated with increasing age, usually bilateral but asymmetric

Classification
- Non-Exudative/“Dry” (Non-Neovascular) AMD
  - most common type of AMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow-white deposits between the RPE and Bruch’s membrane (area separating inner choroidal vessels from RPE)
  - geographic RPE atrophy: coalescence of depigmented RPE, clumps of focal hyperpigmentation or hypopigmentation
  - may progress to neovascular AMD

- Exudative/“Wet” (Neovascular) AMD
  - 10% of AMD, but 80% of AMD that results in severe vision loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch’s membrane, causing subsequent growth and proliferation of new, fine choroidal vessels
  - may lead to: serous detachment of overlying RPE and retina, hemorrhage and lipid precipitates into the subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of hemorrhagic RD, causing disciform scarring and severe central vision loss

Risk Factors
- female
- increasing age
- family history
- smoking
- Caucasian race
- blue irides

Clinical Features
- variable degree of progressive central vision loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

Investigations
- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography: assess type and location of choroidal neovascularization – pathologic new vessels leak dye
- OCT retinal imaging

Treatment
- non-neovascular “dry” AMD
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visor
- see Age-related Eye Disease Study 2 (AREDS2) in sidebar

- neovascular “wet” AMD
  - see Common Medications, OP42
  - intravitreal injection of anti-VEGF
    - pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea®)
    - see VEGF Inhibitors, OP43
  - laser photocoagulation for neovascularization
  - no definitive treatment for disciform scarring
  - photodynamic therapy with verteporfin (Visudyne®)
    - IV injection of verteporfin, followed by low intensity laser to area of choroidal neovascularization
  - see Age-related Eye Disease Study 2 (AREDS2)
    - The original AREDS formulation contains vitamin C, E and beta-carotene, zinc and copper; reduced risk of progression to advanced AMD by 2%. Addition of lutein + zeaxanthin, DHA+EP, or both to the AREDS formulation in primary analyses didn’t reduce risk of progression to advanced AMD. However, because of the potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.
**Glaucoma**

**Definition**
- progressive, pressure-sensitive, optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

**Background**
- aqueous is produced by the ciliary body and drains into the episcleral veins via the trabecular meshwork and the Canal of Schlemm
- an isolated increase in IOP is termed ocular hypertension (OHT) - should be followed for increased risk of developing glaucoma
- pressures > 21 mmHg increase the risk of developing glaucoma
- loss of peripheral vision most commonly precedes central vision loss
- structural changes commonly precede functional changes

**Investigations**
- VA testing
- slit-lamp exam to assess anterior chamber depth; gonioscopy lens to assess angle patency
- ophthalmoscopy to assess the disc features
- tonometry to measure IOP
- visual field testing
- pachymetry to measure corneal thickness
- follow-up includes optic disc examination, IOP measurement, and visual field testing to monitor course of disease

---

**Figure 18. Glaucomatous damage**

- Pallor and cupping of optic disc (C:D ratio 0.2-0.3)
- Concentric enlargement (C:D ratio 0.5)
- Superior expansion
- Advanced/total cupping

**Figure 19. Aqueous flow and sites of potential resistance**

- Average IOP = 15 ± 3 mmHg
- Normal C:D ≤ 0.4
- Suspect glaucoma if C:D ratio > 0.6, C:D ratio differs between eyes by > 0.2, or cup approaches disc margin
**Primary Open-Angle Glaucoma**

- most common form, >95% of all glaucoma cases
- within the trabecular meshwork and the Canal of Schlemm
- insidious and asymptomatic, screening is critical for early detection

**Major Risk Factors**
- ocular hypertension (IOP >21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic
- thin central cornea (OHTS trial)

**Minor Risk Factors**
- myopia
- HTN
- DM
- hyperthyroidism (Graves’ disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 wk of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

**Clinical Features**
- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased C:D ratio (vertical C:D >0.6)
  - significant C:D asymmetry between eyes (>0.2 difference)
  - thinning, notching of the neuroretinal rim
  - flame shaped disc hemorrhage
  - 360° of peripapillary atrophy
  - nerve fibre layer defect
  - large vessels become nasally displaced
- visual field loss
- slow, progressive, irreversible loss of peripheral vision
- paracentral defects, arcuate scotoma, and nasal step are characteristics (Figure 19)
- late loss of central vision if untreated

**Treatment**
- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see Glaucoma Medications, Table 14, OP42)
  - increase aqueous outflow
    - topical cholinergics
    - topical prostaglandin analogues
    - topical α-adrenergics
  - decrease aqueous production
    - topical β-blockers
    - topical and oral carbonic anhydrase inhibitor
    - topical α-adrenergics
  - laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
  - trabeculectomy: creation of a new outflow tract from anterior chamber to under conjunctiva forming a bleb
  - minimally invasive glaucoma surgery (MIGS): implantation of IOP lowering drainage devices (e.g. iStent) through an ab interno microincisional approach
  - serial optic nerve head examinations, IOP measurements, and visual field testing to monitor disease course

**Normal Tension Glaucoma**

- POAG with IOP in normal range
- often found in women >60 yr, but may occur earlier
- associated with migraines, peripheral vasospasm, systemic nocturnal hypotension, sleep apnea
- damage to optic nerve may be due to vascular insufficiency

**Treatment**
- treat reversible causes
Secondary Open Angle Glaucoma

- increased IOP secondary to ocular/systemic disorders that obstruct the trabecular meshwork
  - steroid-induced glaucoma
  - traumatic glaucoma
  - pigmentary dispersion syndrome
  - pseudoexfoliation syndrome

Primary Angle-Closure Glaucoma

- 5% of all glaucoma cases
- peripheral iris bows forward obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block and results in impaired drainage, leading to a sudden rise in IOP

Risk Factors
- hyperopia: small eye, big lens – large lens crowds the angle
- age >70 yr
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

Clinical Features
- red, painful eye = RED FLAG
- unilateral, but other eye at increased risk
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

Complications
- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae, resulting in permanent angle closure

Treatment
- OCULAR EMERGENCY: refer to ophthalmologist for acute angle closure glaucoma
  - aqueous suppressants and hyperosmotic agents
  - medical treatment (see Glaucoma Medications, Table 14, OP42)
    - miotic drops (pilocarpine) to reverse pupillary block
    - multiple topical IOP-lowering agents
    - hyperosmotic agents such as oral glycerine, or IV mannitol
  - laser iridotomy is definitive

Secondary Angle-Closure Glaucoma

Uveitis
- inflamed iris adheses to lens (posterior synechiae)

Neovascular Glaucoma
- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with PDR or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris and angle vessels
Pupils

• pupil size is determined by the balance between the sphincter muscle and the dilator muscle
• sphincter muscle is innervated by the parasympathetic nervous system carried by CN III
• dilator muscle is innervated by the sympathetic nervous system (SNS)
  ■ first order neuron = hypothalamus → brainstem → spinal cord
  ■ second order/preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
  ■ third order/postganglionic fibres originate in the superior cervical ganglion, neurotransmitter is norepinephrine
    ◆ as a diagnostic test, 4-10% cocaine prevents the re-uptake of norepinephrine, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner's Syndrome)
• see Neurology, Figure 8 N8

Pupillary Light Reflex

• light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → bilateral midbrain
• impulses enter bilaterally in midbrain via prepectal area and Edinger-Westphal nuclei
• nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes

α1 – Pupillary dilator muscle contraction (Mydriasis)
β2 – Ciliary muscle relaxation (Non-accommodation); increased aqueous humour production
M3 – Pupillary sphincter contraction (Miosis); increased ciliary muscle contraction (Accommodation)

Denervation Hypersensitivity

• when post-ganglionic fibres are damaged, the understimulated end-organs attempts to compensate by developing an excess of neuroreceptors and becomes hypersensitive
• postganglionic parasympathetic lesions (i.e. Adie’s pupil)
  ■ pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
• postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner’s syndrome)
  ■ pupil will dilate with 0.125% epinephrine, normal pupil will not

Local Disorders of Iris

• posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
• ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o’clock positions resulting in a vertically oval pupil that reacts poorly to light
• trauma (e.g. post-intraocular surgery)

Anisocoria

• unequal pupil size
• idiopathic/physiologic anisocoria
  ■ 20% of population
  ■ round, regular, <1 mm difference
  ■ pupils reactive to light and accommodation
  ■ responds normally to mydriatics/miotics
• post eye surgery
• see Table 9 for other causes of anisocoria
Patient with Anisocoria

Relevant history and examination with specific attention to:
- History of ocular trauma
- Check old photographs (ptosis, ocular deviation, long standing anisocoria)
- Use of topical medications
- Exposure to toxins and drugs
- Associated ocular and neurologic symptoms/signs

Which pupil is abnormal?
Examine pupils in light and dark

Anisocoria accentuated by darkness (small pupil abnormal)
- Dilation lag
- Pupil:
  - Small pupil does not dilate
  - Horner's syndrome

Anisocoria equal in light and dark
- Brisk reaction to light
  - Both pupils dilate symmetrically
  - Adie's tonic pupil
  - Physiologic anisocoria

Anisocoria accentuated by light (large pupil is abnormal)
- Sluggish to light
- Light near dissociation
  - Large pupil:
    - Constricts
    - Minimal/no constriction
  - Large pupil does not constrict
  - Use of 0.1% pilocarpine
  - Adie's tonic pupil
  - Pharmacologic anisocoria

Isolated
- Ptosis/Ophthalmoplegia
- Pupil:
  - Large pupil does not constrict
  - Use of 0.1% pilocarpine

Physiologic anisocoria
- Patient:
  - Use of 0.1% pilocarpine
  - Minimal/no constriction

Patient Must Fixate on Distant Target

Table 9. Summary of Conditions Causing Anisocoria

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features</th>
<th>Site of Lesion</th>
<th>Light and Accommodation</th>
<th>Anisocoria</th>
<th>Mydriatics/Miotics</th>
<th>Effect of Pilocarpine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABNORMAL MIOTIC PUPIL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argyll-Robertson Pupil</td>
<td>Irregular, usually bilateral</td>
<td>Midbrain</td>
<td>Poor in light; better to accommodation</td>
<td>Dilates/Constricts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horner's Syndrome</td>
<td>Round, unilateral, ptosis, anhidrosis, pseudoenophthalmos</td>
<td>Sympathetic system</td>
<td>Both brisk</td>
<td>Greater in dark</td>
<td>Dilates/Constricts</td>
<td></td>
</tr>
<tr>
<td><strong>ABNORMAL MYDRIATIC PUPIL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adie's Tonic Pupil</td>
<td>Irregular, larger in bright light</td>
<td>Ciliary ganglion</td>
<td>Poor in light, better to accommodation</td>
<td>Greater in light</td>
<td>Dilates/Constricts</td>
<td>Constricts (hypersensitivity to dilute pilocarpine)</td>
</tr>
<tr>
<td>CN III Palsy</td>
<td>Round</td>
<td>Superficial CN III</td>
<td>± fixed (acutely) at 7-9 mm</td>
<td>Greater in light</td>
<td>Dilates/Constricts</td>
<td>Constricts</td>
</tr>
<tr>
<td>Mydriatic Pupil</td>
<td>Round, uni- or bilateral</td>
<td>Iris sphincter</td>
<td>Fixed at 7-8 mm</td>
<td>Greater in light</td>
<td>No effect</td>
<td>Will not constrict</td>
</tr>
</tbody>
</table>
**Dilated Pupil (Mydriasis)**

**Sympathetic Stimulation**
- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

**Parasympathetic Understimulation**
- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, DM (may spare pupil), trauma
  - both mydriatics and CN III palsy cause pupil dilation; however, pupils in CN III palsy will constrict briskly to pilocarpine, while pupils dilated from mydriatics will not

**Acute Angle-Closure Glaucoma**
- fixed, mid-dilated pupil

**Adie’s Tonic Pupil**
- 80% unilateral, F>M
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
- dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- long-standing Adie's pupils are smaller than unaffected eye

**Trauma**
- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit-lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphinter ruptures

**Constricted Pupil (Miosis)**

**Senile Miosis**
- decreased sympathetic stimulation with age

**Parasympathetic Stimulation**
- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - cholinesterase inhibitor: phospholine iodide
  - opiates, barbiturates

**Horner’s Syndrome**
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis, anhydrosis of ipsilateral face/neck
- application of cocaine 4-10% (blocks reuptake of norepinephrine) to eye does not result in pupil dilation (vs. physiologic anisocoria), therefore confirms diagnosis
- hydroxyamphetamine 1% (stimulates norepinephrine release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- postganglionic lesions result in denervation hypersensitivity which will cause pupil to dilate with 0.125% epinephrine, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumour, Pancoast tumour, goitre, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabs dorsalis, cervical vertebral fractures

**Iritis**
- miotic pupil initially
- later, may be irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light

**Argyll-Robertson Pupil**
- both pupils irregular and <3 mm in diameter, ± ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of neurosyphilis or other conditions (DM, encephalitis MS, chronic alcoholism, CNS degenerative diseases)

**Other Causes**
- optic neuritis, retinal lesions
Relative Afferent Pupillary Defect

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light, caused by a lesion in visual afferent (sensory) pathway anterior to optic chiasm
- differential diagnosis: large RD, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, optic neuritis (most common)
- does not occur with media opacity (e.g. corneal edema, cataracts)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffected eye to the affected eye, “paradoxical” dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides
- if the defect is bilateral there is no RAPD, as dilation is measured relative to the other eye

Malignancies

- uncommon site for 1° malignancies
- see Retinoblastoma, OP38

Lid Carcinoma

Etiology
- basal cell carcinoma (rodent ulcer) (90%)
  - spread via local invasion, rarely metastasizes
  - ulcerated centre, indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
  - spread via local invasion, may also spread to nodes and metastasize
  - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
  - often masquerades as chronic blepharitis or recurrent chalazion
  - highly invasive, metastasizes
- Kaposi's sarcoma, malignant melanoma, Merkel cell tumour, metastatic tumour
Treatment
• incisional or excisional biopsies
• may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
• surgical reconstruction

Uveal Melanoma
• most common 1° intraocular malignancy in adults
• more prevalent in Caucasians
• arise from uveal tract, 90% choroidal melanoma
• hepatic metastases predominate

Clinical Features
• classic appearance of a pigmented dome-shaped mass extending from the ciliary body or the choroid
• diagnosis necessitates expertise of an ophthalmologist/ocular oncologist

Treatment
• imaging to investigate spread
• depending on the size of the tumour, either radiotherapy, enucleation, limited surgery

Metastases
• most common intraocular malignancy in adults
• most commonly from breast and lung in adults, neuroblastoma in children
• usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
• may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

Treatment
• local radiation, chemotherapy
• enucleation if blind, painful eye

Ocular Manifestations of Systemic Disease

HIV/AIDS
• up to 75% of patients with AIDS have ocular manifestations

External Ocular Signs
• Kaposi’s sarcoma
  • secondary to human herpes virus 8 (HHV-8), affects conjunctiva of lid or the globe
  • differential diagnosis: subconjunctival hemorrhage (non-clearing), hemangioma
  • multiple molluscum contagiosum
  • herpes simplex/zoster keratitis

Retina
• HIV retinopathy (most common)
  • cotton wool spots in >50% of HIV patients
  • intraretinal hemorrhage
  • CMV retinitis
  • ocular opportunistic infection developed when severely immunocompromised (CD4 count ≤50)
  • a necrotizing retinitis, with retinal hemorrhage and vasculitis, “brushfire” or “pizza pie” appearance
  • presents with scotomas (macular involvement and RD), blurred vision, and floaters
  • untreated infection will progress to other eye in 4-6 wk
  • treatment: virostatic agents (e.g. gancyclovir or foscarnet) via IV or intravitreal injection
• necrotizing retinitis
  • from herpes simplex virus, herpes zoster, toxoplasmosis
  • disseminated choroiditis
  • Pneumocystis carinii, Mycobacterium avium intracellulare, Candida

Other Systemic Infections
• herpes zoster
  • see Herpes Zoster, OP18
• candidal endophthalmitis
  • fluffy, white-yellow, superficial retinal infiltrate that may eventually result in vitritis
  • may present with inflammation of the anterior chamber
  • treatment: systemic amphotericin B, oral fluconazole
• toxoplasmosis
  - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous infiltration (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by Toxoplasma gondii protozoa transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folic acid, or clindamycin. Considering adding steroids if severe inflammation (iritis, macular or optic nerve involvement)

### Diabetes Mellitus

- most common cause of blindness in young people in North America
- loss of vision due to:
  - progressive microangiopathy leading to macular edema
  - progressive DR → neovascularization → traction → RD and vitreous hemorrhage
  - ruberosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

### Diabetic Retinopathy

#### Background
- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening of basement membrane)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

#### Classification
- non-proliferative: increased vascular permeability and retinal ischemia
  - microaneurysms
  - dot and blot hemorrhages
  - hard exudates (lipid deposits), non-specific for DR
  - macular edema
- advanced non-proliferative (or pre-proliferative)
  - non-proliferative findings plus:
    - venous beading (in ≥2 of 4 retinal quadrants)
    - intraretinal microvascular anomalies (IRMA) in 1 or 2 retinal quadrants
      - IRMA: dilated, leaky vessels within the retina
    - cotton wool spots (nerve fibre layer infarcts)
- proliferative
  - 5% of patients with DM will reach this stage
  - neovascularization of iris, disc, retina
  - neovascularization of iris (ruberosis iridis) can lead to neovascular glaucoma
  - vitreous hemorrhage, bleeding from fragile new vessels, fibrous tissue can contract causing tractional RD
  - may remain asymptomatic well beyond stage of optimal treatment
  - high risk of severe vision loss secondary to vitreous hemorrhage, RD

#### Screening Guidelines for Diabetic Retinopathy
- type 1 DM
  - screen for retinopathy beginning annually 5 yr after disease onset
  - annual screening indicated for all patients over 12 yr and/or entering puberty
- type 2 DM
  - initial examination at time of diagnosis, then annually
- pregnancy
  - ocular exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
  - gestational diabetics are not at risk for DR

#### Treatment
- Diabetic Control and Complications Trial (DCCT)
  - tight control of blood sugar decreases frequency and severity of microvascular complications
  - blood pressure control
  - focal laser for clinically significant macular edema
  - intravitreal injection of corticosteroid or anti-VEGF for fovea-involved diabetic macular edema
  - pan-retinal laser photocoagulation for PDR: reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
  - vitrectomy for non-clearing vitreous hemorrhage and tractional RD in PDR
  - vitrectomy before vitreous hemorrhage does not improve the visual prognosis

#### Lens Changes
- earlier onset of senile nuclear sclerotic and cortical cataracts
- may get hyperglycemic cataract due to sorbitol accumulation (rare)
- changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3-4 diopters
Extraocular Muscle Palsy
- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- may involve CN IV and VI
- usually recover within few months

Optic Neuropathy
visual acuity loss due to infarction of optic disc/nerve

Optic Neuropathy
visual acuity loss due to infarction of optic disc/nerve

Hypertension
retinopathy is the most common ocular manifestation
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema
- chronic HTN retinopathy: arteriovenous (AV) nicking, flame/blot retinal hemorrhages, microaneurysms, cotton wool spots
- increases risk of a number of other ocular diseases (DR, BRVO, CRAO/BRAO)

Table 10. Keith-Wagener-Barker Classification for Hypertensive Retinopathy

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Mild arterial narrowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Obvious arterial narrowing with focal irregularities</td>
</tr>
<tr>
<td>Group 3</td>
<td>Group 2 characteristics plus: Cotton wool spots, Hemorrhage and/or exudate</td>
</tr>
<tr>
<td>Group 4</td>
<td>Group 3 plus papilledema</td>
</tr>
</tbody>
</table>

Multiple Sclerosis
- see Neurology N52

Clinical Features
- blurred vision and decreased colour vision: secondary to optic neuritis
- central scotoma: due to damage to papillomacular bundle of retinal nerve fibres
- diplopia: secondary to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

Treatment
- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation, as this increases likelihood of eventual development of MS

Corticosteroids for Treating Optic Neuritis
Cochrane Database Syst Rev 2015;8:CD001430
Summary: no conclusive evidence of benefit in terms of recovery to normal visual acuity, visual field, or contrast sensitivity six months after infusion of IV or oral corticosteroids.
Results: after review of 6 RCTs evaluating systemic corticosteroids for treatment of acute optic neuritis, all meta-analyses show similar outcomes for placebo vs. corticosteroid group for visual acuity, contrast sensitivity, and visual field.
TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

Graves’ Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur secondary to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

Clinical

- initial inflammatory phase is followed by a quiescent cicatricial phase

Treatment

- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, proptosis, and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides

Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjögren’s syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)

Giant Cell Arteritis/Temporal Arteritis

- see Rheumatology, RH20

Clinical Features

- more common in women >60 yr
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and past medical history of polymyalgia rheumatica
- ischemic optic atrophy
- 50% lose vision in other eye if untreated

Diagnosis

- temporal artery biopsy + increased ESR (ESR can be normal, but likely 80-100 in first hour), increased CRP
- if biopsy of one side is negative, biopsy the other side

Treatment

- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation (DO NOT WAIT TO TREAT)

Sarcoidosis

- granulomatous uveitis with large “mutton fat” keratitic precipitates and posterior synechiae
- complications include glaucoma, cataracts, retinal hemorrhages, peripheral retina neovascularization and dry eye
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

Treatment

- topical/systemic steroids and mydriatics
Pediatric Ophthalmology

Strabismus

- Ocular misalignment in one or both eyes, can be found in up to 3% of children
- Classification
  - Manifest (constant) vs. latent (hidden) alignment
  - Comitant (deviation equal in all positions of gaze, also known as nonparalytic or concomitant) vs. incomitant (deviation worse in certain positions, also known as paralytic or restrictive)
  - Described in direction of deviation relative to the fixating eye
- Distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism)
- Complications: amblyopia, cosmesis

Heterotropia

- Manifest deviation
  - Deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

Types

- Exo (lateral deviation), eso- (medial deviation)
- Hyper- (upward deviation), hypo- (downward deviation)
- Esotropia = "crossed-eyes"; exotropia = "wall-eyed"

Tests

- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - Light reflex lateral to central cornea indicates esodeviation; light reflex medial to central cornea indicates exodeviation
  - False positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle κ)
- Cover test
  - The deviation can be quantified using prisms

Heterophoria

- Latent deviation
  - Deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- Hirschberg test will be normal (light reflexes symmetrical)
  - Very common – majority are asymptomatic
  - May be exacerbated or become manifest with asthenopia (eye strain, fatigue)

Tests

- Cover-uncover test
- Alternate cover test
  - Alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - Maintain cover over one eye for 2-3 s before rapidly shifting to other eye

Cover tests

Esotropia

Exotropia

Cover - Uncover tests

Esophoria

Exophoria

Figure 25: Cover and cover-uncover tests for detection of tropias and phorias
### Table 11. Paralytic vs. Non-Paralytic Strabismus

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Paralytic Strabismus</th>
<th>Nonparalytic Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Incomitant strabismus</td>
<td>Concomitant strabismus</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Often sudden but may be gradual or congenital</td>
<td>Usually gradual or shortly after birth; rarely sudden</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Any age; most often acquired</td>
<td>Usually during infancy</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Reduction or restriction in range of eye movements due to: Neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumour, trauma Muscular: myasthenia gravis (neuromuscular junction pathology), Graves’ disease Structural: restriction or entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall</td>
<td>Develops early in childhood No restriction in range of eye movements Monocular, alternating, or intermittent</td>
</tr>
<tr>
<td><strong>Diplopia</strong></td>
<td>Common</td>
<td>Uncommon; image from the misaligned eye is suppressed</td>
</tr>
<tr>
<td><strong>Visual Acuity in Other Eye</strong></td>
<td>Usually unaffected in the other eye, unless CN II is involved</td>
<td>Deviated eye may become amblyopic if not treated when the child is young Amblyopia treatment rarely successful after age 8-10 yr Amblyopia usually does not develop if child has alternating strabismus or intermittent which allows neural pathways for both eyes to develop</td>
</tr>
<tr>
<td><strong>Possibility of Amblyopia</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Neurologic Findings or Systemic Disease</strong></td>
<td>May be present</td>
<td>Usually absent</td>
</tr>
</tbody>
</table>

### Accommodative Esotropia
- normal response to approaching object is the triad of the near reflex: convergence, accommodation, and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over activation of the near reflex
- average age of onset is 2.5 yr
- usually reversible with correction of refractive error

### Non Accommodative Esotropia
- accounts for 50% of childhood strabismus most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

### Amblyopia

**Definition**
- a neurodevelopmental visual disorder with unilateral (or less commonly, bilateral) reduction of best corrected visual acuity that cannot be attributed only and directly to the effect of a structural abnormality of the eye
- it is caused by abnormal visual experience early in life and cannot be remedied immediately by spectacle glasses alone
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia). Other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors) and concomitant structural ocular problems

**Detection**
- “Holler Test”: young child upset if good eye is covered
- quantitative visual acuity by age 3-4 yr using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
- prognosis: 90% will have good vision restored and maintained if treated <4 yr old
Etiology and Management

- **strabismus**
  - correct with glasses for accommodative esotropia
  - occlusion therapy (see below)
  - surgery; recession (weakening) – moving muscle insertion further back on the globe; or resection (strengthening) – shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until ~8 yr of age
  - there is no proven value for vision training in the treatment of strabismus or amblyopia

- **anisometropia**
  - amblyopia usually in the more hyperopic eye
  - the more emmetropic (normal refraction) eye receives a clear image, while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if visual acuity difference persists after 4-8 wk of using glasses

- **deprivation amblyopia**
  - occlusion due to ptosis, cataract, retinoblastoma, corneal opacity
  - occlusion amblyopia: prolonged patching of good eye may cause it to become amblyopic

Occlusion Therapy

- patching the good eye to force the brain to use the non-dominant eye and redevelop its vision
- atropine cycloplegic drops to impair accommodation and blur vision of the better seeing eye

Risks

- permanent loss of vision in the affected eye
- possibility of injury to “remaining” good eye
- safety glasses or polycarbonate lenses recommended if visual acuity in worse eye is <20/50
- loss of stereopsis

Leukocoria

- white reflex (red reflex is absent)
- the presence of leukocoria warrants urgent referral to an ophthalmologist

Differential Diagnosis

- cataract
- retinoblastoma
- retinal coloboma
- ROP
- persistent hyperplastic primary vitreous or persistent fetal vasculature
- Coats disease (exudative retinal telangiectasis)
- toxocariasis
- RD

Retinoblastoma

- most common primary intraocular malignancy in children
- incidence: 1/15,000; sporadic or genetic transmission; screening of siblings/offspring essential
- unilateral (2/3) or bilateral (1/3)
- malignant – direct or hematogenous spread
- diagnosis
  - often presents with leukocoria or strabismus
  - U/S or CT scan may demonstrate calcified mass (present in most cases)

Treatment

- radiotherapy, chemotherapy combined with laser, cryopexy, and/or enucleation

Retinopathy of Prematurity

- vasoproliferative retinopathy that is a major cause of blindness in the developed world

Risk Factors

- non-black race (black infants have lower risk of developing ROP)
- low gestational age, birth weight <1500 g
- high oxygen exposure after birth (iatrogenic)
Classification (ROP Staging)
- stage 1: faint demarcation line at the junction between the vascularized and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial RD (4A: macula “on”, 4B: macula “off”)
- stage 5: total RD
- plus (+) disease: dilation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with circumferential extent of disease of 5 continuous or 8 cumulative clock hours (1-12) of ROP involvement

Treatment
- threshold disease is treated with cryotherapy or laser (laser is now the standard treatment, with better refractive outcome); more recently, off-label anti-VEGF intravitreal injections
- ROP beyond threshold level is either watched carefully (usually stage 4A) or treated with vitrectomy/scleral buckle

Prognosis
- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

Nasolacrimal System Defects
- congenital obstruction of the nasolacrimal duct (failure of canalization), usually occurs at 1-2 mo of age
- epiphora, crusting, discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac

Treatment
- massage over lacrimal sac at medial corner of eyelid
- vast majority spontaneously resolve in 9-12 mo, otherwise consider referral for duct probing

Ophthalmia Neonatorum
- newborn conjunctivitis in first month of life
- causes
  - chemical/toxic: silver nitrate, erythromycin (secondary to prophylaxis, self-limiting)
  - infectious: bacterial (e.g. N. gonorrhoeae – most common, C. trachomatis), herpes simplex virus
- diagnose using stains and cultures

Treatment
- systemic antibiotics with possible hospitalization if infectious etiology
- topical prophylaxis, most commonly with erythromycin (or silver nitrate), is required by law at birth

Congenital Glaucoma
- due to inadequate development of the filtering mechanism of the anterior chamber angle

Clinical Features
- cloudy cornea, increased IOP
- photophobia, epiphora
- buphthalmos (large cornea, “ox eye”, secondary to increased IOP), blepharospasm

Treatment
- filtration surgery is required soon after birth to prevent blindness

Ocular Trauma

Blunt Trauma
- caused by blunt object such as fist
- history: injury, ocular history, drug allergy, tetanus status
- exam: VA first, pupil size and reaction, EOM (diplopia), external and slit-lamp exam, ophthalmoscopy
- if VA normal or slightly reduced, globe less likely to be perforated
- if VA reduced may be perforated globe, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
• conjunctiva: subconjunctival hemorrhage
• cornea: abrasion – detect with fluorescein staining and cobalt blue filter using slit-lamp or ophthalmoscope
• anterior chamber: assess depth, hyphema, hypopyon
• iris: prolapse, iritis
• lens: cataract, dislocation
• retinal tear/detachment

**Penetrating Trauma**

- include ruptured globe ± prolapsed iris, intraocular foreign body
- rule out intraocular foreign body, especially if history of “metal striking metal”, CT orbit

**OCULAR EMERGENCY:** initial management - REFER IMMEDIATELY
- ABCs
  - don’t press on eye globe!
  - don’t check IOP if possibility of globe rupture
- check vision, diplopia
- apply rigid eye shield to minimize further trauma
- keep head elevated 30°-45° to keep IOP down
- keep NPO
- tetanus status
- give IV antibiotics
  - selecting appropriate agents depends on the mechanism of injury; Gram-positive bacteria are more commonly involved than Gram-negative; retained intraocular foreign objects increase the risk of infections with Bacillus species, whereas exposure to vegetable matter increase the risk of a fungal etiology

**Hyphema**

- blood in anterior chamber, often due to damage to root of the iris
- may occur with blunt trauma

**Treatment**
- refer to ophthalmology
- shield and bedrest x 5 d or as determined by ophthalmologist
- sleep with head upright
- may need surgical drainage if hyphema persists or if re-bleed

**Complications**
- risk of re-bleed highest on d 2-5, resulting in secondary glaucoma, corneal staining, and iris necrosis
- never prescribe Aspirin®, as it increases the risk of a re-bleed

**Blow-Out Fracture**

- see Plastic Surgery, PL33
- blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
- orbital rim remains intact
- inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
- infraorbital nerve courses along the floor of the orbit and may be damaged

**Clinical Features**
- pain and nausea at time of injury
- diplopia, restriction of EOM
- infraorbital and upper lip paresthesia (CN V2)
- enophthalmos (sunken eye), periorbital ecchymoses

**Investigations**
- plain films: Waters’ view and lateral
- CT: anteroposterior and coronal view of orbits

**Treatment**
- refrain from coughing, blowing nose
- systemic antibiotics may be indicated
- surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
- may delay surgery if the diplopia improves
Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks (thus, very guarded prognosis)

Treatment
- immediately irrigate at site of accident with water or buffered solution
  - irrigate with eyelids retracted in emergency department with IV drip until pH physiologic
  - swab upper and lower fornices to remove possible particulate matter
- do not attempt to neutralize an acid with a base, or vice versa
- cycloplegic drops to decrease iris spasm (pain) and prevent secondary glaucoma (due to posterior synechiae formation)
- topical antibiotics and patching
- topical steroids (by ophthalmologist) to decrease inflammation, use for <2 wk (in the case of a persistent epithelial defect)

Ocular Drug Toxicity

Table 12. Drugs with Ocular Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Corneal microdeposits and superficial keratopathy (vortex keratopathy) Rare: ischemic optic neuropathy</td>
</tr>
<tr>
<td>Atropine, benztropine</td>
<td>Papillary dilation (risk of angle closure glaucoma)</td>
</tr>
<tr>
<td>Bisphosphonates (Fosamax®, Actonel®)</td>
<td>Inflammatory eye disease (iritis, scleritis, episcleritis)</td>
</tr>
<tr>
<td>Chloroquine, hydroxychloroquine</td>
<td>Bull’s eye maculopathy Vortex keratopathy</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Anterior subcapsular cataract</td>
</tr>
<tr>
<td>Contraceptive pills</td>
<td>Decreased tolerance to contact lenses Migraine Optic neuritis Central vein occlusion benign increase intracranial pressure</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Yellow vision Blurred vision</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>Oculogyric crises Blurred vision</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Superficial keratopathy</td>
</tr>
<tr>
<td>Interferon</td>
<td>Retinal hemorrhages and cotton wool spots</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Steroids</td>
<td>Posterior subcapsular cataracts Glaucoma Papilledema (systemic steroids) Increased severity of HSV infections (geographic ulcers) Predisposition to fungal infections</td>
</tr>
<tr>
<td>Sulphonamides, NSAIDs</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Tamsulosin (Flomax®)</td>
<td>Intraoperative Floppy Iris Syndrome, which can complicate cataract surgery</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Papilledema (associated with pseudotumour cerebri)</td>
</tr>
<tr>
<td>Thebendazole</td>
<td>Pigmentary degeneration of retina</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Retinal deposition with macular sparing, peripheral visual field loss</td>
</tr>
<tr>
<td>Vitamin A toxicity</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Vitamin D toxicity</td>
<td>Band keratopathy</td>
</tr>
</tbody>
</table>
TOPICAL OCULAR DIAGNOSTIC DRUGS

**Fluorescein Dye**
- water soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope or slit-lamp)
- absorbed in areas of epithelial loss (ulcer or abrasion)
- also stains mucus and contact lenses

**Rose Bengal Stain**
- stains devitalized epithelial cells and mucus

**Anesthetics**
- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore NEVER prescribe

**Mydriatics**
- dilate pupils
  - cholinergic blocking (e.g. tropicamide – Mydriacyl®)
    - dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    - indications: refraction, ophthalmoscopy, therapy for iritis
  - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    - stimulate pupillary dilator muscles, no effect on accommodation
    - usually used with tropicamide for additive effects
  - side effects: HTN, tachycardia, arrhythmias

<table>
<thead>
<tr>
<th>Table 13. Mydriatic Cycloplegic Drugs and Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Tropicamide (Mydriacyl®) 0.5%, 1%</td>
</tr>
<tr>
<td>Cyclopentolate HCL 0.5%, 1%</td>
</tr>
<tr>
<td>Homatropine HBr 1%, 2%</td>
</tr>
<tr>
<td>Atropine sulfate 0.5%, 1%</td>
</tr>
<tr>
<td>Scopolamine HBr 0.25%, 5%</td>
</tr>
</tbody>
</table>

**GLAUCOMA MEDICATIONS**

<table>
<thead>
<tr>
<th>Table 14. Glaucoma Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Category</strong></td>
</tr>
<tr>
<td>α-Agonist Non-selective</td>
</tr>
<tr>
<td>epinephrine HCl 1% (Epinefrin®)</td>
</tr>
<tr>
<td>dipivalyl epinephrine 0.1% (Propine®)</td>
</tr>
<tr>
<td>oxazoline 0.2% (Alphagan®)</td>
</tr>
<tr>
<td>apraclonid ne 0.5% (Iopidine®)</td>
</tr>
<tr>
<td>β-Blocker Non-selective</td>
</tr>
<tr>
<td>timolol (Timoptic®)</td>
</tr>
<tr>
<td>levobunolol (Betagan®)</td>
</tr>
<tr>
<td>β1-selective betaxolol (Betoptic®)</td>
</tr>
<tr>
<td>Carbonic Anhydrase Inhibitor</td>
</tr>
<tr>
<td>dorzolamide (Trusopt®)</td>
</tr>
<tr>
<td>brinzolamide (Azopt®)</td>
</tr>
<tr>
<td>oral: acetazolamide (Diamox®), methazolamide (Neptazane®)</td>
</tr>
<tr>
<td>Parasympathomimetic (cholinergic stimulating)</td>
</tr>
<tr>
<td>pilocarpine (Pilopine®)</td>
</tr>
<tr>
<td>carbachol (Isopto Carbachol®)</td>
</tr>
<tr>
<td>Prostaglandin Analogues</td>
</tr>
<tr>
<td>latanoprost (Xalatan®)</td>
</tr>
<tr>
<td>travoprost (Travatan®)</td>
</tr>
<tr>
<td>bimatoprost (Lumigan®)</td>
</tr>
<tr>
<td>Cosopt® = timolol + dorzolamide; Xalacom® = timolol + latanoprost; Combigan® = timolol + brimonidine; DuoTrav® = timolol + travoprost; gtt = drop, gtt = drops</td>
</tr>
</tbody>
</table>

Green: Cholinergics
Red: Anti-Cholinergics
White: Anesthetics, Antibiotics, Artificial tears, Steroids
Yellow: Beta-Blockers
Blue: Beta-Blocker combinations
Purple: Alpha-Agonists
Teal: Prostaglandins
Orange: Carbonic Anhydrase Inhibitors
Tan: Fluoroquinolones
Grey: NSAIDs
Pink: Anti-inflammatories, Steroids
WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

VEGF Inhibitors
- block VEGF which prevents ocular angiogenesis and further development of choroidal neovascularization
- administered via intravitreal injections
- pegaptanib (Macugen®) is a selective anti-VEGF targeting VEGF isoform 165 (no longer widely used)
- ranibizumab (Lucentis®) is a non-selective anti-VEGF agent
- aflibercept (Eylea®) is another non-selective anti-VEGF agent, but is only FDA approved for metastatic breast cancer, colorectal cancer, and non-small cell lung cancer; therefore, its widespread ophthalmologic use is off-label

TOPICAL OCULAR THERAPEUTIC DRUGS

NSAIDs
- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

Anti-Histamines
- used to relieve red and itchy eye, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes

Decongestants
- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine (Isopto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle closure glaucoma

Antibiotics
- indications: bacterial conjunctivitis, keratitis, or blepharitis
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin polymyxin B, fluoroquinolones (ciprofloxacin [Ciloxan®], ofloxacin [Ocuflow®], moxifloxacin [Vigamox®], gatifloxacin [Zymar®])

Corticosteroids
- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®), loteprednol etabonate 0.5% (Lotamax®), difluprednate (Durezol®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  - potentiates HSV keratitis and fungal keratitis as well as masking symptoms
  - increased IOP, more rapidly in steroid responders (within weeks)
  - posterior subcapsular cataract (within months)
References

ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes NEJM 2010;363:233-244


# Orthopedics

**Acronyms** ........................................... 2

**Basic Anatomy Review** ............................... 2

**Fractures – General Principles** ...................... 4
Fracture Description
Approach to Fractures
Fracture Healing
General Fracture Complications

**Articular Cartilage** ................................. 6

**Orthopedic X-Ray Imaging** .......................... 7

**Orthopedic Emergencies** ............................ 8
Trauma Patient Workup
Open Fractures
Cauda Equina Syndrome
Compartment Syndrome
Osteomyelitis
Septic Joint

**Shoulder** ............................................. 10
Shoulder Dislocation
Rotator Cuff Disease
Acromioclavicular Joint Pathology
Clavicle Fracture
Frozen Shoulder (Adhesive Capsulitis)

**Humerus** ............................................. 15
Proximal Humeral Fracture
Humeral Shaft Fracture
Distal Humeral Fracture

**Elbow** .................................................. 17
Supracondylar Fracture
Radial Head Fracture
Olecranon Fracture
Elbow Dislocation
Epicondylitis

**Forearm** ............................................... 19
Radius and Ulna Shaft Fractures
Monteggia Fracture
Nightstick Fracture
Galeazzi Fracture

**Wrist** ................................................. 20
Colles’ Fracture
Smith’s Fracture
Complications of Wrist Fractures
Scaphoid Fracture

**Hand** .................................................. PL23

**Spine** .................................................. 22
Fractures of the Spine
Cervical Spine
Thoracolumbar Spine

**Pelvis** .................................................. 26
Pelvic Fracture

**Hip** .................................................... 27
Hip Dislocation
Hip Fracture
Arthritis of the Hip
Hip Dislocation Post-Total Hip Arthroplasty

**Femur** .................................................. 30
Femoral Diaphysis Fracture
Distal Femoral Fracture

**Knee** .................................................... 31
Evaluation of Knee
Cruciate Ligament Tears
Collateral Ligament Tears
Meniscal Tears
Quadriceps/Patellar Tendon Rupture
Dislocated Knee

**Patella** .................................................. 34
Patellar Fracture
Patellar Dislocation
Patellofemoral Syndrome (Chondromalacia Patellae)

**Tibia** .................................................... 36
Tibial Plateau Fracture
Tibial Shaft Fracture

**Ankle** .................................................... 37
Evaluation of Ankle and Foot Complaints
Ankle Fracture
Ankle Ligamentous Injuries

**Foot** ...................................................... 38
Talar Fracture
Calcaneal Fracture
Achilles Tendonitis
Achilles Tendon Rupture
Plantar Fasciitis (Heel Spur Syndrome)
Bunions (Hallux Valgus)
Metatarsal Fracture

**Pediatric Orthopedics** ................................. 41
Fractures in Children
Stress Fractures
Epiphyseal Injury
Slipped Capital Femoral Epiphysis
Developmental Dysplasia of the Hip
Legg-Calvé Perthes Disease (Coxa Plana)
Osgood-Schlatter Disease
Congenital Talipes Equinovarus (Club Foot)
Scoliosis

**Bone Tumours** ......................................... 45
Benign Active Bone Tumours
Benign Aggressive Bone Tumours
Malignant Bone Tumours

**Common Medications** ................................. 48

**References** ............................................. 49
Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles
Figure 2. (Left) Blood supply to the upper limb, (Right) Axillary and radial nerves: innervation of the upper limb

Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Motor</th>
<th>Sensory</th>
<th>Nerve Roots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary</td>
<td>Deltoid/Teres Minor/Triceps</td>
<td>Lateral upper arm (Sergeant’s Patch)</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>Biceps/Brachialis</td>
<td>Lateral forearm</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Radial</td>
<td>Triceps (medial and lateral heads)</td>
<td>Lateral dorsum of the hand</td>
<td>C5, C6, C7, C8</td>
</tr>
<tr>
<td>Median</td>
<td>Wrist flexors and abductors</td>
<td>Palmar thumb to radial half of 4th digit, and the dorsal tips of digits 1 to radial half of digit 4</td>
<td>C6, C7</td>
</tr>
<tr>
<td>Ulnar</td>
<td>Wrist flexors and adductors</td>
<td>Medial palm and dorsum of hand 5th digit and medial half of 4th digit</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Tibial</td>
<td>Ankle plantar flexion</td>
<td>Sole of foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Superficial Peroneal</td>
<td>Ankle eversion</td>
<td>Dorsum of foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Deep Peroneal</td>
<td>Ankle dorsiflexion and inversion</td>
<td>1st web space</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Sural</td>
<td></td>
<td>Lateral foot</td>
<td>S1, S2</td>
</tr>
<tr>
<td>Saphenous</td>
<td></td>
<td>Anteromedial ankle</td>
<td>L3, L4</td>
</tr>
</tbody>
</table>
Fractures – General Principles

Fracture Description

1. Name of Injured Bone

2. Integrity of Skin/Soft Tissue
   • closed: skin/soft tissue over and near fracture is intact
   • open: skin/soft tissue over and near fracture is lacerated or abraded, fracture exposed to outside environment, or contaminated (i.e. bowel)
   • signs: continuous bleeding from puncture site or fat droplets in blood are suggestive of an open fracture

3. Location (Figure 5)
   • epiphyseal: end of bone, forming part of the adjacent joint
   • metaphysal: the flared portion of the bone at the ends of the shaft
   • diaphyseal: the shaft of a long bone (proximal, middle, distal)
   • physis: growth plate
4. Orientation/Fracture Pattern (Figure 4)
- transverse: fracture line perpendicular (<30° of angulation) to long axis of bone; result of direct high energy force
- oblique: angular fracture line (30° - 60° of angulation); result of angulation and compressive force, high energy
- butterfly: fracture site fragment which looks like a butterfly
- segmental: a separate segment of bone bordered by fracture lines; result of high energy force
- spiral: complex, multi-planar fracture line; result of rotational force, low energy
- comminuted/multi-fragmentary: >2 fracture fragments
- intra-articular: fracture line crosses articular cartilage and enters joint
- avulsion: tendon or ligament tears/pulls off bone fragment; often in children, high energy
- compression/impacted: impaction of bone; typical sites are vertebrae or proximal tibia
- torus: a buckle fracture of one cortex, often in children (Figure 49)
- greenstick: an incomplete fracture of one cortex, often in children (Figure 49)
- pathologic: fracture through bone weakened by disease/tumour

5. Alignment of Fracture Fragments
- non-displaced: fracture fragments are in anatomic alignment
- displaced: fracture fragments are not in anatomic alignment
- distracted: fracture fragments are separated by a gap (opposite of impacted)
- impacted: fracture fragments are compressed, resulting in shortened bone
- angulated: direction of fracture fragments is separated by a gap (opposite of impacted)
- angulated: direction of fracture apex (e.g. varus/valgus)
- translated/shifted: percentage of overlapping bone at fracture site
- rotated: fracture fragment rotated about long axis of bone

---

**Approach to Fractures**

1. Clinical Assessment
- ABCs, primary survey, and secondary survey (ATLS protocol)
  - rule out other fractures/injuries
  - rule out open fracture
- AMPLE history (minimum): Allergies, Medications, Past medical history, Last meal, Events surrounding injury
  - mechanism of injury
  - previous significant injury or surgery to affected area
  - consider pathologic fracture with history of only minor trauma
- Physical exam: look (deformity, soft tissue integrity); feel (maximal tenderness, NVS-document best possible neurovascular exam, avoid ROM/moving injured area to prevent exacerbation)

2. Analgesia
3. Imaging (see Orthopedic X-Ray Imaging, OR7)
4. Splint Extremity
5. Management: Closed vs. Open Reduction
   1. obtain the reduction (see appropriate IV sedation, see Table 27, OR48)
     - closed reduction
       - apply traction in the long axis of the limb
       - reverse the mechanism that produced the fracture
       - reduce with IV sedation and muscle relaxation (fluoroscopy can be used if available)
     - indications for open reduction
       - “NO CAST”
       - other indications include
         - failed closed reduction
         - not able to cast or apply traction due to site (e.g. hip fracture)
         - pathologic fractures
       - potential for improved function with ORIF
     - ALWAYS re-check and document NVS after reduction and obtain post-reduction x-ray

---

**Displacement**
- Refers to position of the distal fragment relative to the proximal fragment

**Varus/Valgus Angulation**
- Varus = Apex away from midline
- Valgus = Apex toward midline

**Approach to Fractures**

**Figure 5. Schematic diagram of the long bone**

**Quick Motor Nerve Exam**
- Thumbs Up*: PIN (Median Nerve)
- "OK Sign": AIN (Median Nerve)
- "Spread Fingers": Ulnar Nerve

**X-Ray Rule of 2s**
- 2 sides = bilateral
- 2 views = AP + lateral
- 2 joints = joint above + below
- 2 times = before + after reduction

**Reasons for Splinting**
- Pain control
- Reduces further damage to vessels, nerves, and skin and may improve vascular status
- Decreases risk of inadvertently converting closed to open fracture
- Facilitates patient transport

**Indications for Open Reduction**
- NO CAST
- Non-union
- Open fracture
- Neurovascular Compromise
- Displaced intra-Articular fracture
- Salter-Harris 3,4,5
- PolyTrauma

**Buck's Traction**
- A system of weights, pulleys, and ropes that are attached to the end of a patient’s bed exerting a longitudinal force on the distal end of a fracture, improving its length, alignment, and rotation
2. maintain the reduction
   • external stabilization: splints, casts, traction, external fixator
   • internal stabilization: percutaneous pinning, extramedullary fixation (screws, plates, wires), IM fixa tion (rods)
   • follow-up: evaluate bone healing
3. rehabilitate to regain function and avoid joint stiffness

Fracture Healing

Normal Healing

<table>
<thead>
<tr>
<th>Period</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 0-3</td>
<td>Hematoma, macrophages surround fracture site</td>
</tr>
<tr>
<td>Weeks 3-6</td>
<td>Osteoclasts remove sharp edges, callus forms within hematoma</td>
</tr>
<tr>
<td>Weeks 6-12</td>
<td>Bone forms within the callus, bridging fragments</td>
</tr>
<tr>
<td>Months 6-12</td>
<td>Cortical gap is bridged by bone</td>
</tr>
<tr>
<td>Years 1-2</td>
<td>Normal architecture is achieved through remodelling</td>
</tr>
</tbody>
</table>

Figure 6 Stages of bone healing

Evaluation of Healing: Tests of Union

• clinical: no longer tender to palpation or stressing on physical exam
• x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

General Fracture Complications

Table 2. General Fracture Complications

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Compartment syndrome</td>
<td>Mal-/non-union</td>
</tr>
<tr>
<td></td>
<td>Neurological injury</td>
<td>AVN</td>
</tr>
<tr>
<td></td>
<td>Vascular injury</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>Heterotopic ossification</td>
</tr>
<tr>
<td></td>
<td>Implant failure</td>
<td>Post traumatic OA</td>
</tr>
<tr>
<td></td>
<td>Fracture blisters</td>
<td>Joint stiffness/adhesive capsulitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Sepsis</td>
<td>CRPS type I/RSD</td>
</tr>
<tr>
<td></td>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARDS secondary to fat embolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic shock</td>
<td></td>
</tr>
</tbody>
</table>

Articular Cartilage

Properties

• 2-4 mm layer covering ends of articulating bones, provides nearly frictionless surface
• avascular (nutrition from synovial fluid), aneural, alymphatic

ARTICULAR CARTILAGE DEFECTS

Etiology

• overt trauma, repetitive minor trauma (such as repetitive ankle sprains or patellar maltracking); common sports injury
• degenerative conditions such as early stage OA or osteochondritis dissecans

Clinical Features

• similar to symptoms of OA (joint line pain with possible effusion, etc.)
• often have predisposing factors, such as ligament injury, malalignment of the joint (varus/valgus), obesity, bone deficiency (AVN, osteochondritis dissecans, ganglion bone cysts), inflammatory arthropathy, and familial osteoarthropathy
• may have symptoms of locking or catching related to the torn/displaced cartilage

Investigations

• x-ray (to rule out bony defects and check alignment)
• MRI
• diagnostic arthroscopy (treatment is often guided by what is seen during arthroscopy)
Table 3. Outerbridge Classification of Chondral Defects

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chondral Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Softening and swelling of cartilage</td>
</tr>
<tr>
<td>II</td>
<td>Fragmentation and fissuring &lt;1/2&quot; in diameter</td>
</tr>
<tr>
<td>III</td>
<td>Fragmentation and fissuring &gt;1/2&quot; in diameter</td>
</tr>
<tr>
<td>IV</td>
<td>Erosion of cartilage down to bone</td>
</tr>
</tbody>
</table>

Treatment
- individualized
  - patient factors (age, skeletal maturity, activity level, etc.)
  - defect factors (Outerbridge Classification, subchondral bone involvement, etc.)
- non-operative
  - rest, NSAIDs, bracing
- operative
  - microfracture, osteochondral grafting (autograft or allograft) autologous chondrocyte implantation

Orthopedic X-Ray Imaging

General Principles
- x-ray 1 joint above and 1 below
  - obtain at least 2 orthogonal views ± specialized views

Table 4. Orthopedic X-Ray Imaging

<table>
<thead>
<tr>
<th>Site</th>
<th>Injury</th>
<th>X-Ray Views</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>Anterior dislocation</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Posterior dislocation</td>
<td>Axillary ± stress view with 10 lb in hand</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td>Trans-scapular</td>
</tr>
<tr>
<td></td>
<td>Frozen shoulder</td>
<td>Zanca view (10-15 cephalic tilt)</td>
</tr>
<tr>
<td>Arm</td>
<td>Humerus #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trans-scapular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axillary</td>
</tr>
<tr>
<td>Elbow/Forearm</td>
<td>Supracondylar #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Radial head #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Monteggia #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Night stick #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galeazzi #</td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>Colles’ #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Smith #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Scaphoid #</td>
<td>Scaphoid (wrist extension and ulnar deviation x 2 wk)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Pelvic #</td>
<td>AP pelvis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inlet and outlet views</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Judet views (oburator and iliac oblique for acetabular #)</td>
</tr>
<tr>
<td>Hip</td>
<td>Femoral head/neck #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Inte trochanteric #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Frog-leg lateral</td>
</tr>
<tr>
<td></td>
<td>SCFE</td>
<td>Dunn</td>
</tr>
<tr>
<td></td>
<td>FAI</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>Knee dislocation</td>
<td>AP standing, lateral</td>
</tr>
<tr>
<td></td>
<td>Femur/tibia #</td>
<td>Skyline – tangential view with knees flexed at 45° to see patellofemoral joint</td>
</tr>
<tr>
<td></td>
<td>Patella #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patella dislocation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patella femoral syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tibia shaft #</td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>Ankle #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortise view: ankle at 15° of internal rotation</td>
</tr>
<tr>
<td>Foot</td>
<td>Talar #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Calcaneal #</td>
<td>Lateral Harris Axial</td>
</tr>
<tr>
<td>Spine</td>
<td>Compression #</td>
<td>AP spine</td>
</tr>
<tr>
<td></td>
<td>Burst #</td>
<td>AP odontoid</td>
</tr>
<tr>
<td></td>
<td>Cervical spine #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oblique</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swimmer’s view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral flexion/extension view: evaluate subluxation of cervical vertebrae</td>
</tr>
</tbody>
</table>
Trauma Patient Workup

Etiology
- high energy trauma e.g. MVC, fall from height
- may be associated with spinal injuries or life-threatening visceral injuries

Clinical Features
- local swelling, tenderness, deformity of the limbs, and instability of the pelvis or spine
- decreased level of consciousness, hypotension/hypovolemia
- consider involvement of EoOH or other substances

Investigations
- trauma survey (see Emergency Medicine, ER7, ER15)
- x-rays: lateral cervical spine, AP chest, AP pelvis, AP and lateral all of bones suspected to be injured
- CT is also utilized to inspect for musculoskeletal injuries in the trauma setting
- other views of pelvis: AP, inlet, and outlet; Judet views for acetabular fracture (for Classification of Pelvic Fractures see Table 18, OR27)

Treatment
- ABCDEs and initiate resuscitation for life-threatening injuries
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- DVT prophylaxis

Complications
- hemorrhage – life-threatening (may produce signs and symptoms of hypovolemic shock)
- fat embolism syndrome (SOB, hypoxemia, petechial rash, thrombocytopenia, and neurological symptoms)
- venous thrombosis – DVT and PE
- bladder/urethral/bowel injury
- neurological damage
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic OA of joints with intra-articular fractures
- sepsis if missed open fracture

Open Fractures
- fractured bone and hematoma in communication with the external or contaminated environment

Emergency Measures
- ABCs, primary survey, and resuscitation as needed
- removal of obvious foreign material
- irrigate with normal saline if grossly contaminated
- cover wound with sterile dressings
- immediate IV antibiotics
- tetanus toxoid or immunoglobulin as needed
- reduce and splint fracture
- NPO and prepare for OR (blood work, consent, ECG, CXR)
  - operative irrigation and debridement within 6-8 h to decrease risk of infection
  - traumatic wound often left open to drain but vacuum-assisted closure dressing may be used
  - re-examine with repeat irrigation and debridement in 48 h

Table 5. Gustilo Classification of Open Fractures

<table>
<thead>
<tr>
<th>Gustilo Grade</th>
<th>Length of Open Wound</th>
<th>Description</th>
<th>Prophylactic Antibiotic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt; 1 cm</td>
<td>Minimal contamination and soft tissue injury</td>
<td>First generation cephalosporin (cefazolin) for 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simple or minimally comminuted fracture</td>
<td>If allergy use fluoroquinolone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If MRSA positive use vancomycin</td>
</tr>
<tr>
<td>II</td>
<td>1-10 cm</td>
<td>Moderate contamination</td>
<td>As per Grade I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate soft tissue injury</td>
<td></td>
</tr>
<tr>
<td>III*</td>
<td>&gt; 10 cm</td>
<td>IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound</td>
<td>First generation cephalosporin (cefazolin) for 3 d plus Gram-negative coverage (gentamicin) for at least 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound</td>
<td>For soil contamination, penicillin is added for clostridial coverage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIIC: Vascular injury/compromise</td>
<td></td>
</tr>
</tbody>
</table>

*Any high energy, comminuted fracture, shotgun, farmyard/soil/water contamination exposure to oral flora, or fracture >8 h old is immediately classified as Grade II

Antibiotics for Preventing Infection in Open Limb Fractures
Cochrane Qs Syst Rev 2004;1:CD0003764
Purpose: To review the evidence regarding the effectiveness of antibiotics in the initial treatment of open fractures of the limbs.
Methods: Randomized or quasi randomized controlled trials comparing antibiotic treatment with placebo or no treatment in preventing acute wound infection were identified and reviewed. Data were extracted and pooled for analysis.
Results: Eight studies (n=1,106) were reviewed. The use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo (RRI=0.43, 95% CI 0.29, 0.65; ARR=0.07, 95% CI 0.03-0.15).
Conclusions: Antibiotics reduce the incidence of early infections in open fractures of the limbs.
Cauda Equina Syndrome

- see Neurosurgery, NS27

Compartment Syndrome

- increased interstitial pressure in an anatomical compartment (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment), with little room for expansion
- interstitial pressure exceeds capillary perfusion pressure, leading to muscle necrosis (in 4-6 h) and eventually nerve necrosis

Etiology

- intracompartmental
  - fracture (particularly tibial shaft or paediatric supracondylar and forearm fractures)
  - reperfusion injury, crush injury, or ischemia
- extracompartmental: constrictive dressing (circumferential cast), poor position during surgery, circumferential burn

Clinical Features

- pain out of proportion to injury (typically first symptom)
- pain with active contraction of compartment
- pain with passive stretch (most sensitive)
- swollen, tense compartment
- suspicious history

- 5 Ps: late sign – do not wait for these to develop to make the diagnosis!

Investigations

- usually not necessary, as compartment syndrome is a clinical diagnosis
- in children or unconscious patients where clinical exam is unreliable, compartment pressure monitoring with catheter AFTER clinical diagnosis is made (normal = 0 mmHg; elevated ≥30 mmHg or [measured pressure – dBP] ≤30 mmHg)

Treatment

- non-operative
  - remove constrictive dressings (casts, splints), elevate limb at the level of the heart
- operative
  - urgent fasciotomy
  - 48-72 h post-operative: wound closure ± necrotic tissue debridement

Complications

- Volkmann’s ischemic contracture: ischemic necrosis of muscle, followed by secondary fibrosis, and finally calcification; especially following supracondylar fracture of humerus
- rhabdomyolysis, renal failure secondary to myoglobinuria

Osteomyelitis

- bone infection with progressive inflammatory destruction

Etiology

- most commonly caused by *S. aureus*
- mechanism of spread: hematogenous (most common) vs. direct inoculation vs. contiguous focus
- risk factors: recent trauma/surgery, immunocompromised patients, DM, IV drug use, poor vascular supply, peripheral neuropathy

- Plain Film Findings of Osteomyelitis
  - Soft tissue swelling
  - Lytic bone destruction*
  - Periostial reaction (formation of new bone, especially in response to #)*
*Generally not seen on plain films until 10-12 d after onset of infection
Clinical Features
- symptoms: pain and fever
- on exam: erythema, tenderness, edema common ± abscess/draining sinus tract; impaired function/WB

Diagnosis
- see Medical Imaging, MI23
- workup includes: WBC and differential, ESR, CRP, blood culture, aspirate culture/bone biopsy

Table 6. Treatment of Osteomyelitis

<table>
<thead>
<tr>
<th>Acute Osteomyelitis</th>
<th>Chronic Osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV antibiotics 4-6 wk; started empirically and adjusted after obtaining blood and aspirate cultures</td>
<td>Surgical debridement</td>
</tr>
<tr>
<td>± surgery (IGD) for abscess or significant involvement</td>
<td>Antibiotics: both local (e.g. antibiotic beads) and systemic (IV)</td>
</tr>
<tr>
<td>± hardware removal (if present)</td>
<td></td>
</tr>
</tbody>
</table>

Septic Joint
- joint infection with progressive destructive if left untreated

Etiology
- most commonly caused by S. aureus in adults
- consider coagulase-negative Staphylococcus in patients with prior joint replacement
- consider Neisseria gonorrhoeae in sexually active adults and newborns
- most common route of infection is hematogenous
- risk factors: young/elderly (age >80 yr), RA, prosthetic joint, recent joint surgery, skin infection/ulcer, IV drug use, previous intra-articular corticosteroid injection, immune compromise (cancer, DM, alcoholism)

Clinical Features
- inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling, pain on active and passive ROM, ± fever

Investigations
- x-ray (to rule out fracture, tumour, metabolic bone disease), ESR, CRP, WBC, blood cultures
- joint aspirate: cloudy yellow fluid, WBC >50,000 with >90% neutrophils, protein level >4.4 mg/dL, joint glucose level <60% blood glucose level, no crystals, positive Gram stain results
- listen for heart murmur (to reduce suspicion of infective endocarditis, use Duke Criteria)

Treatment
- IV antibiotics, empiric therapy (based on age and risk factors), adjust following joint aspirate C&S results
- non-operative
  - therapeutic joint aspiration, serially if necessary (if early diagnosis and joint superficial)
  - operative
    - arthroscopic/open irrigation and irrigation and drainage ± decompression

Shoulder Dislocation

complete separation of the glenohumeral joint; may be anterior or posterior

Investigations
- anterior dislocation X-rays: AP, trans-scapular, axillary views
- posterior dislocation X-rays: AP, trans-scapular, axillary; or CT scan

Rapid progression of signs and symptoms (over hours) necessitates need for serial examinations

Acute osteomyelitis is a medical emergency which requires an early diagnosis and appropriate antimicrobial and surgical treatment

Most commonly affected joints in descending order
knee → elbow → ankle → sternoclavicular joint

Plain Film Findings in a Septic Joint
- Early (0-3 d): usually normal; may show soft-tissue swelling or joint space widening from localized edema
- Late (4-6 d): joint space narrowing and destruction of cartilage

Serial C-reactive protein (CRP) can be used to monitor response to therapy

Does This Adult Patient Have Septic Arthritis?
JAMA 2007;297(13):1478-1488

Purpose: To review the accuracy and precision of the clinical evaluation for the diagnosis of nongonococcal bacterial arthritis.

Methods: Review of 14 studies including 6242 patients of which 653 had positive synovial culture (gold standard diagnostic tool for septic arthritis).

Results/Conclusions: Age, diabetes mellitus, rheumatoid arthritis, joint surgery, hip or knee prosthesis, skin infection, and human immunodeficiency virus type 1 infection significantly increase the probability of septic arthritis. Joint pain, history of joint swelling, and fever are useful clinical findings in identifying patients with a monoarticular arthritis who may have septic arthritis. Laboratory findings from an arthrocentesis are also required and helpful prior to Gram stain and culture. The presence of increased WBC increases the likelihood ratio (for counts <25,000/µL: LR, 0.32; 95% CI, 0.23-0.43; for counts ≥25,000/µL: LR, 2.9; 95% CI, 2.5-3.4; for counts ≥100,000/µL: LR, 12.5-48.4). A polymorphonuclear cell count of ≥90% increases the LR of septic arthritis by 3.4, while a PMN cell count of <90% reduces the LR by 0.34.

Posterior Shoulder Dislocation

Up to 60-80% are missed on initial presentation due to poor physical exam and radiographs

There are 4 Joints in the Shoulder
- glenohumeral, AC, sternoclavicular (SC), scapulothoracic
Table 7. Anterior and Posterior Shoulder Dislocation

<table>
<thead>
<tr>
<th>Anterior Shoulder Dislocation (&gt;90%)</th>
<th>Posterior Shoulder Dislocation (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td></td>
</tr>
<tr>
<td>Abducted arm is externally rotated/hyperextended, or blow to posterior shoulder</td>
<td>Adducted, internally rotated, flexed arm</td>
</tr>
<tr>
<td>Involuntary, usually traumatic; voluntary, atraumatic</td>
<td>FOOSH</td>
</tr>
<tr>
<td></td>
<td>3 Es (epileptic seizure, EtOH, electrocution)</td>
</tr>
<tr>
<td></td>
<td>Blow to anterior shoulder</td>
</tr>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Pain, arm slightly abducted and externally rotated with inability to internally rotate</td>
<td>Pain, arm is held in adduction and internal rotation; external rotation is blocked</td>
</tr>
<tr>
<td><strong>Shoulder Exam</strong></td>
<td></td>
</tr>
<tr>
<td>“Squared off” shoulder</td>
<td></td>
</tr>
<tr>
<td>Positive apprehension test: patient looks apprehensive with gentle shoulder abduction and external rotation to 90° as humeral head is pushed anteriorly and recreates feeling of anterior dislocation (see Figure 11)</td>
<td>Positive posterior apprehension (“jerk”) test: with patient supine flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will “jerk” back with the sensation of subluxation (see Figure 11)</td>
</tr>
<tr>
<td>Positive relocation test: a posteriorly directed force applied during the apprehension test relieves apprehension since anterior subluxation is prevented</td>
<td>Note: the posterior apprehension test is used to test for recurrent posterior instability, NOT for acute injury</td>
</tr>
<tr>
<td>Positive sulcus sign: presence of subacromial indentation with distal traction on humerus indicates inferior shoulder instability (see Figure 11)</td>
<td></td>
</tr>
<tr>
<td><strong>Neurovascular Exam Including</strong></td>
<td></td>
</tr>
<tr>
<td>Axillary nerve: sensory patch over deltoid and deltoid contraction</td>
<td>Full neurovascular exam as per anterior shoulder dislocation</td>
</tr>
<tr>
<td>Musculocutaneous nerve: sensory patch on lateral forearm and biceps contraction</td>
<td></td>
</tr>
<tr>
<td><strong>RADIOGRAPHIC FINDINGS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Axillary View</strong></td>
<td></td>
</tr>
<tr>
<td>Humeral head is anterior</td>
<td>Humeral head is posterior</td>
</tr>
<tr>
<td><strong>Trans-scapular Y View</strong></td>
<td></td>
</tr>
<tr>
<td>Humeral head is anterior to the centre of the “Mercedes-Benz” sign</td>
<td>Humeral head is posterior to centre of “Mercedes-Benz” sign</td>
</tr>
<tr>
<td><strong>AP View</strong></td>
<td></td>
</tr>
<tr>
<td>Sub coracoid lie of the humeral head is most common</td>
<td>Partial vacancy of glenoid fossa (vacant glenoid sign) and &gt;6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign)</td>
</tr>
<tr>
<td><strong>Hill-Sachs and Bony Bankart Lesions</strong></td>
<td></td>
</tr>
<tr>
<td>± Hill-Sachs lesion: compression fracture of posterior humeral head due to forceful impaction of an anteriorly dislocated humeral head against the glenoid rim (see Figure 10)</td>
<td>± reverse Hill-Sachs lesion (75% of cases): divot in anterior humeral head</td>
</tr>
<tr>
<td>± bony Bankart lesion: avulsion of the anterior glenoid labrum (with attached bone fragments) from the glenoid rim (see Figure 10)</td>
<td>± reverse bony Bankart lesion: avulsion of the posterior glenoid labrum from the bony glenoid rim</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td></td>
</tr>
<tr>
<td>Closed reduction with IV sedation and muscle relaxation</td>
<td>Closed reduction with sedation and muscle relaxation</td>
</tr>
<tr>
<td>Traction-countertraction: assistant stabilizes torso with a folded sheet wrapped across the chest while the surgeon applies gentle steady traction</td>
<td>Inferior traction on a flexed elbow with pressure on the back of the humeral head</td>
</tr>
<tr>
<td>Stimson: while patient lies prone with arm hanging over table edge, hang a 5 lb weight on wrist for 15-20 min</td>
<td>Obtain post-reduction x-rays</td>
</tr>
<tr>
<td>Hippocratic method: place heel into patient’s axilla and apply traction to arm</td>
<td>Check post reduction NVS</td>
</tr>
<tr>
<td>Cunningham’s method: low risk, low pain; if not successful try above methods</td>
<td>Sling in abduction and external rotation x 3 wk, followed by shoulder rehabilitation (dynamic stabilizer strengthening)</td>
</tr>
<tr>
<td>Obtain post-reduction x-rays</td>
<td></td>
</tr>
<tr>
<td>Check post-reduction NVS</td>
<td></td>
</tr>
<tr>
<td>Sling x 3 wk (avoid abduction and external rotation), followed by shoulder rehabilitation (dynamic stabilizer strengthening)</td>
<td></td>
</tr>
</tbody>
</table>

**Prognosis**
- recurrence rate depends on age of first dislocation
- <20 yr = 65-95%; 20-40 yr = 60-70%; >40 yr = 2-4% 

**Specific Complications**
- rotator cuff or capsular or labral tear (Bankart/SLAP lesion), shoulder stiffness
- injury to axillary nerve/artery, brachial plexus
- recurrent/unreduced dislocation (most common complication)
Rotator Cuff Disease

- rotator cuff consists of 4 muscles that act to stabilize the humeral head within the glenoid fossa

**Table 8. Rotator Cuff Muscles (SITS)**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Proximal</th>
<th>Muscle Attachments</th>
<th>Nerve Supply</th>
<th>Muscle Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraspinatus</td>
<td>Scapula</td>
<td>Greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
<td>Abduction</td>
</tr>
<tr>
<td>Infraspinatus</td>
<td>Scapula</td>
<td>Greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
<td>External rotation</td>
</tr>
<tr>
<td>Teres Minor</td>
<td>Scapula</td>
<td>Greater tuberosity of humerus</td>
<td>Axillary nerve</td>
<td>External rotation</td>
</tr>
<tr>
<td>Subscapularis</td>
<td>Scapula</td>
<td>Lesser tuberosity of humerus</td>
<td>Subscapular nerve</td>
<td>Internal rotation and adduction</td>
</tr>
</tbody>
</table>

SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

**Etiology**
- anything that leads to a narrow subacromial space
- most commonly, a relative imbalance of rotator cuff and larger shoulder muscles, allowing for superior translation and subsequent wear of the rotator cuff muscle tendons
  - glenohumeral muscle weakness leading to abnormal motion of humeral head
  - scapular muscle weakness leading to abnormal motion of acromion
- acromial abnormalities, such as congenital narrow space or osteophyte formation or Type III acromion morphology
  1. outlet/subacromial impingement: “painful arc syndrome”, compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the undersurface of the acromion, AC joint, and CA ligament
  2. bursitis and tendonitis
  3. rotator cuff thinning and tear if left untreated

**Clinical Features**
- insidious onset, but may present as an acute exacerbation of chronic disease, night pain, and difficulty sleeping on affected side
- pain worse with active motion (especially overhead); passive movement generally permitted
- weakness and loss of ROM, especially between 90°-130° (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity
- rule out bicep tendinosis: Speed test; SLAP lesion: O’Brien’s test

**Investigations**
- X-ray: AP view may show high riding humerus relative to glenoid, indicating large tear, evidence of chronic tendinitis
- MRI: coronal/sagittal, oblique and axial orientations are useful for assessing full/partial tears and tendinopathy ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
- arthrogram: can assess full thickness tears, difficult to assess partial tears

**Bigliani Classification of Acromion Morphology**
- Type I – flat
- Type II – curved
- Type III – hooked

**Screening Out Rotator Cuff Tears**
- No night pain (SN 87.7%)
- No painful arc (SN 91.5%)
- No impingement signs (SN 97.2%)
- No weakness
*Returning to the bedside: Using the history and physical examination to identify rotator cuff tears
JAM Geri Soc 2000;48:1633-1637
Treatment

- **non-operative**
  - for mild (“wear”) or moderate (“tear”) cases
  - physiotherapy, NSAIDs ± steroid injection
- **operative**
  - indication: severe (“repair”)
  - impingement that is refractory to 2-3 mo physiotherapy and 1-2 corticosteroid injections
  - arthroscopic or open surgical repair (i.e. acromioplasty, rotator cuff repair)

### Table 9. Rotator Cuff Special Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Examination</th>
<th>Positive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jobe’s Test</td>
<td>Supraspinatus: place the shoulder in 90° of abduction and 30° of forward flexion and internally rotate the arm so that the thumb is pointing toward the floor</td>
<td>Weakness with active resistance suggests a supraspinatus tear</td>
</tr>
<tr>
<td>Lift-off Test</td>
<td>Subscapularis: internally rotate arm so dorsal surface of hand rests on lower back; patient instructed to actively lift hand away from back against examiner resistance (use Belly Press Test if too painful)</td>
<td>Inability to actively lift hand away from back suggests a subscapularis tear</td>
</tr>
<tr>
<td>Posterior-Cuff Test</td>
<td>Infraspinatus and teres minor: arm positioned at patient’s side in 90° of flexion; patient instructed to externally rotate arm against the resistance of the examiner</td>
<td>Weakness with active resistance suggests posterior cuff tear</td>
</tr>
<tr>
<td>Neer’s Test</td>
<td>Rotator cuff impingement: passive shoulder flexion</td>
<td>Pain elicited between 130-170° suggests impingement</td>
</tr>
<tr>
<td>Hawkins-Kennedy Test</td>
<td>Rotator cuff impingement: shoulder flexion to 90° and passive internal rotation</td>
<td>Pain with internal rotation suggests impingement</td>
</tr>
<tr>
<td>Painful Arc Test</td>
<td>Rotator cuff tendinopathy: patient instructed to actively abduct the shoulder</td>
<td>Pain with abduction &gt;90° suggests tendinopathy</td>
</tr>
<tr>
<td>Speed’s Test</td>
<td>Apply resistance to the forearm when the arm is in forward flexion with the elbows fully extended.</td>
<td>Pain in the bicipital groove</td>
</tr>
<tr>
<td>O’Brien’s Test</td>
<td>SLAP lesion: forward flexion of the arm to 90 degrees while keeping the arm extended. Arm is adducted 10-15 degrees. Internally rotate the arm so thumb is facing down and apply a downward force. Repeat the test with arm externally rotated</td>
<td>Pain or clicking in the glenohumeral joint in internal rotation but not external rotation</td>
</tr>
</tbody>
</table>

Figure 13. Rotator cuff tests
**Acromioclavicular Joint Pathology**

- subluxation or dislocation of AC joint
- 2 main ligaments attach clavicle to scapula: AC and CC ligaments

**Mechanism**
- fall onto shoulder with adducted arm or direct trauma to point of shoulder

**Clinical Features**
- pain with adduction of shoulder and/or palpation over AC joint
- palpate step deformity between distal clavicle and acromion (with dislocation)
- limited ROM

**Investigations**
- X-rays: bilateral AP, Zanca view (10-15° cephalic tilt), axillary

**Treatment**
- non-operative
  - sling 1-3 wk, ice, analgesia, early ROM and rehabilitation
- operative
  - indication: Rockwood Class IV-VI (III if labourer or high level athlete)
  - number of different approaches involving AC/CC ligament reconstruction or screw/hook plate insertion

**Table 10. Rockwood Classification of Acromioclavicular Joint Separation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Joint sprain, absence of complete tear of either ligament</td>
<td>Non-operative</td>
</tr>
<tr>
<td>II</td>
<td>Complete tear of AC ligament, incomplete tear of CC ligament, without marked elevation of lateral clavicular head</td>
<td>Non-operative</td>
</tr>
<tr>
<td>III</td>
<td>Complete tear of AC and CC ligaments, ≥5 mm elevation at AC joint, superior aspect of acromion is below the inferior aspect of the clavicle</td>
<td>Most non-operative, operative if labourer or high level athlete Will heal with step deformity, although most fully functional in 4-6 mo</td>
</tr>
<tr>
<td>IV-VI</td>
<td>Based on the anatomical structure the displaced clavicle is in proximity to</td>
<td>Operative in most cases</td>
</tr>
</tbody>
</table>

**Clavicle Fracture**

- incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
- common in children (unites rapidly without complications)

**Mechanism**
- fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

**Clinical Features**
- pain and tenting of skin
- arm is clasped to chest to splint shoulder and prevent movement

**Investigations**
- evaluate NVS of entire upper limb
- X-ray: AP, 45° cephalic tilt (superior/inferior displacement), 45° caudal tilt (AP displacement) CT: useful for medial phyleal fractures and sternoclavicular injury

**Treatment**
- medial and middle-third clavicle fractures
  - simple sling x 1-2 wk
  - early ROM and strengthening once pain subsides
  - if fracture is shortened >2 cm, consider ORIF
- distal-third clavicle fractures
  - undisplaced (with ligaments intact): sling x 1-2 wk
  - displaced (CC ligament injury): ORIF

**Specific Complications** *(see General Fracture Complications, OR6)*
- cosmetic bump usually only complication
- shoulder stiffness, weakness with repetitive activity
- pneumothorax, brachial plexus injuries, and subclavian vessel (all very rare)
Frozen Shoulder (Adhesive Capsulitis)

- disorder characterized by progressive pain and stiffness of the shoulder, usually resolving spontaneously after 18 mo

**Mechanism**
- primary adhesive capsulitis
  - idiopathic, usually associated with DM
  - usually resolves spontaneously in 9-18 mo
- secondary adhesive capsulitis
  - due to prolonged immobilization
  - shoulder-hand syndrome: CRPS/RSD characterized by arm and shoulder pain, decreased motion, and diffuse swelling
  - following MI, stroke, shoulder trauma
  - poorer outcomes

**Clinical Features**
- gradual onset (weeks to months) of diffuse shoulder pain with:
  - decreased active AND passive ROM
  - pain worse at night and often prevents sleeping on affected side
  - increased stiffness as pain subsides: continues for 6-12 mo after pain has disappeared

**Investigations**
- X-ray: AP (neutral, internal/external rotation), scapular Y, axillary
  - may be normal, or may show demineralization from disease

**Treatment**
- freezing phase
  - active and passive ROM (physiotherapy)
  - NSAIDs and steroid injections if limited by pain
- thawing phase
  - manipulation under anesthesia and early physiotherapy
  - arthroscopy for debridement/decompression

Humerus

Proximal Humeral Fracture

**Mechanism**
- young: high energy trauma (MVC)
- elderly: FOOSH from standing height in osteoporotic individuals

**Clinical Features**
- proximal humeral tenderness, deformity with severe fracture, swelling, painful ROM, bruising extends down arm and chest

**Investigations**
- test axillary nerve function (deltoid contraction and skin over deltoid)
- X-rays: AP, trans-scapular, axillary are essential
- CT scan: to evaluate for articular involvement and fracture displacement

**Classification**
- Neer classification is based on 4 fracture locations or ‘parts’
- displaced: displacement >1 cm and/or angulation >45°
- the Neer system regards the number of displaced fractures, not the fracture line, in determining classification
- ± dislocated/subluxed: humeral head dislocated/subluxed from glenoid

**Treatment**
- treat osteoporosis if needed
- non-operative
  - nondisplaced: broad arm sling immobilization, begin ROM within 14 d to prevent stiffness
  - minimally displaced (85% of patients) - closed reduction with sling immobilization x 2 wk, gentle ROM
- operative
  - ORIF (anatomic neck fractures, displaced, associated dislocated glenohumeral joint)
  - hemiarthroplasty or reverse TSA may be necessary, especially in elderly

Specific Complications (see General Fracture Complications, OR6)
- AVN, nerve palsy (45%; typically axillary nerve), malunion, post-traumatic arthritis

Conditions Associated with an Increased Incidence of Adhesive Capsulitis
- Prolonged immobilization (most significant)
- Female gender
- Age >49 yr
- DM (5x)
- Cervical disc disease
- Hyperthyroidism
- Stroke
- MI
- Trauma and surgery
- Autoimmune disease

Stages of Adhesive Capsulitis
1. Freezing phase: gradual onset, diffuse pain (lasts 6-9 mo)
2. Frozen phase: decreased ROM impacting functioning (lasts 4-9 mo)
3. Thawing phase: gradual return of motion (lasts 5-26 mo)

Neer Classification
- Based on 4 parts of humerus
  - Greater Tuberosity
  - Lesser Tuberosity
  - Humeral Head
  - Shaft
- One-part fracture: any of the 4 parts with none displaced
- Two-part fracture: any of the 4 parts with 1 displaced
- Three-part fracture: displaced fracture of surgical neck + displaced greater tuberosity or lesser tuberosity
- Four-part fracture: displaced fracture of surgical neck + both tuberosities

Anatomic neck fractures disrupt blood supply to the humeral head and AVN of the humeral head may ensue
Humerus

**Humeral Shaft Fracture**

**Mechanism**
- high energy: direct blows/MVC (especially young); low energy: FOOSH, twisting injuries, metastases (in elderly)

**Clinical Features**
- pain, swelling, weakness ± shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment: look for drop wrist, sensory impairment, dorsum of hand

**Investigations**
- X-ray: AP and lateral radiographs of the humerus, including the shoulder and elbow joints

**Treatment**
- in general, humeral shaft fractures are treated non-operatively
- non-operative
  - ± reduction; can accept deformity due to compensatory ROM of shoulder
  - hanging cast (weight of arm in cast provides traction across fracture site) with collar and cuff sling immobilization until swelling subsides, then Sarmiento functional brace, followed by ROM
- operative
  - indications: see “NO CAST” (OR5), pathological fracture, “floating elbow” (simultaneous unstable humeral and forearm fractures)
  - ORIF: plating (most common), IM rod insertion, external fixation

**Specific Complications** (see General Fracture Complications, OR6)
- radial nerve palsy: expect spontaneous recovery in 3-4 mo, otherwise send for EMG
- non-union: most frequently seen in middle 1/3
- decreased ROM
- compartment syndrome

**Distal Humeral Fracture**

**Mechanism**
- young: high energy trauma (MVC)
- elderly: FOOSH

**Clinical Features**
- elbow pain and swelling
- assess brachial artery

**Investigations**
- X-ray: AP and lateral of humerus and elbow
- CT scan: helpful when suspecting shear fracture of capitulum or trochlea

**Classification**
- supracondylar, distal single column, distal bicondylar, and coronal shear fractures

**Treatment**
- goal is to restore ROM 30-130° flexion (unsatisfactory outcomes in 25%)
- non-operative
  - cast immobilization (in supination for lateral condyle fracture; pronation for medial condyle fractures)
- operative
  - indications: displaced, supracondylar, bicondylar
  - closed reduction and percutaneous pinning; ORIF; total elbow arthroplasty (bicondylar in elderly)

The anterior humeral line refers to an imaginary line drawn along the anterior surface of the humeral cortex that passes through the middle third of the capitellum when extended inferiorly. In subtle supracondylar fractures, the anterior humeral line is disrupted, typically passing through the anterior third of the capitellum.
Elbow

Supracondylar Fracture

- subclass of distal humerus fracture: extra-articular, fracture proximal to capitulum and trochlea, usually transverse
- most common in pediatric population (peak age ~7 yr old), rarely seen in adults
- AIN (median nerve) injury commonly associated with extension type

Mechanism
- >96% are extension injuries via FOOSH (e.g. fall off monkey bars); <4% are flexion injuries

Clinical Features
- pain, swelling, point tenderness
- neurovascular injury: assess median and radial nerves, radial artery (check radial pulse)

Investigations
- X-ray: AP lateral of elbow
  - disruption of anterior humeral line suggests supracondylar fracture
  - fat pad sign: a sign of effusion and can be indicative of occult fracture

Treatment
- reduction indications: evidence of arterial obstruction, unacceptable angulation, displaced (>50%) non-operative
  - nondisplaced: long arm plaster slab in 90° flexion x 3 wk
  - operative
    - indications: displaced, vascular injury, open fracture
    - requires percutaneous pinning followed by limb cast with elbow flexed <90°
    - in adults, ORIF is necessary

Specific Complications (see General Fracture Complications, OR6)
- stiffness is most common
- brachial artery injury (kinking can occur if displaced fracture), median or ulnar nerve injury, compartment syndrome (leads to Volkmann’s ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)

Radial Head Fracture

- a common fracture of the upper limb in young adults

Mechanism
- FOOSH with elbow extended and forearm pronated

Clinical Features
- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, ± mechanical block to forearm pronation and supination
- pain on pronation/supination

Investigations
- X-ray: enlarged anterior fat pad (“sail sign”) or the presence of a posterior fat pad indicates effusion which could occur with occult radial head fractures

Table 11. Classification and Treatment of Radial Head Fractures

<table>
<thead>
<tr>
<th>Mason Class</th>
<th>Radiographic Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nondisplaced fracture</td>
<td>Elbow slab or sling x 3-5 d with early ROM</td>
</tr>
<tr>
<td>2</td>
<td>Displaced fracture</td>
<td>ORIF: angulation &gt;30°, involves ≥1/3 of the radial head, or ≥3 mm of joint incongruity exists</td>
</tr>
<tr>
<td>3</td>
<td>Comminuted fracture</td>
<td>Radial head excision ± prosthesis (if ORIF not feasible)</td>
</tr>
<tr>
<td>4</td>
<td>Comminuted fracture with posterior elbow dislocation</td>
<td>Radial head excision ± prosthesis</td>
</tr>
</tbody>
</table>

Specific Complications (see General Fracture Complications, OR6)
- myositis ossificans – calcification of muscle
- recurrent instability (if MCL injured and radial head excised)
**Olecranon Fracture**

**Mechanism**
- direct trauma to posterior aspect of elbow (fall onto the point of the elbow) or FOOSH

**Clinical Features**
- localized pain, palpable defect
- ± loss of active extension due to avulsion of triceps tendon

**Investigations**
- X-ray: AP and lateral (require true lateral to determine fracture pattern)

**Treatment**
- non-operative
  - non-displaced (<2 mm, stable): cast x 3 wk (elbow in 90° flexion), then gentle ROM
  - displaced: ORIF (plate and screws or tension band wiring) and early ROM if stable

**Elbow Dislocation**
- third most common joint dislocation after shoulder and patella
  - anterior capsule and collateral ligaments disrupted

**Mechanism**
- elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion
  - usually the radius and ulna are dislocated together, or the radial head dislocates and the ulna remains ("Monteggia")
  - 80% are posterior/posterolateral, anterior are rare and usually devastating

**Clinical Features**
- elbow pain, swelling, deformity
- flexion contracture
- ± absent radial or ulnar pulses

**Investigations**
- x-ray: AP and lateral views

**Treatment**
- assess NVS before reduction: brachial artery, median and ulnar nerves (can become entrapped during manipulation)
- non-operative
  - closed reduction under conscious sedation (post-reduction x-rays required)
  - Parvin's method: patient lies prone with arm hanging down; apply gentle traction downwards on wrist; as olecranon slips distally, gently lift up the arm at elbow to reduce joint
  - long-arm splint with forearm in neutral rotation and elbow in 90° flexion
  - early ROM (<2 wk)
- operative
  - indications: complex dislocation or persistent instability after closed reduction
  - ORIF

**Specific Complications** (see General Fracture Complications, OR6)
- stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture
- recurrent instability uncommon

**Epicondylitis**
- lateral epicondylitis = "tennis elbow", inflammation of the common extensor tendon as it inserts into the lateral epicondyle
- medial epicondylitis = "golfer's elbow", inflammation of the common flexor tendon as it inserts into the medial epicondyle

**Mechanism**
- repeated or sustained contraction of the forearm muscles/chronic overuse

**Clinical Features**
- point tenderness over humeral epicondyle and/or distal to it
- pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
- generally a self-limited condition, but may take 6-18 mo to resolve
Treatment
- non-operative (very good outcomes)
  - rest, ice, NSAIDs
  - use brace/strap
  - physiotherapy, stretching, and strengthening
  - corticosteroid injection
- operative
  - indication: failed 6-12 mo conservative therapy
  - percutaneous or open release of common tendon from epicondyle

Forearm

Radius and Ulna Shaft Fractures

Mechanism
- high-energy direct or indirect (MVA, fall from height, sports) trauma
- fractures usually accompanied by displacement due to high force

Clinical Features
- deformity, pain, swelling
- loss of function in hand and forearm

Investigations
- X-ray: AP and lateral of forearm ± oblique of elbow and wrist
- CT if fracture is close to joint

Treatment
- goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
- ORIF with plates and screws; closed reduction with immobilization usually yields poor results for displaced forearm fractures (except in children)

Specific Complications (see General Fracture Complications, OR6)
- soft tissue contracture resulting in limited forearm rotation – surgical release of tissue may be warranted

Monteggia Fracture

- fracture of the proximal ulna with radial head dislocation and proximal radioulnar joint injury
- more common and better prognosis in the pediatric age group when compared to adults

Mechanism
- direct blow on the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

Clinical Features
- pain, swelling, decreased rotation of forearm ± palpable lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

Investigations
- X-ray: AP, lateral elbow, wrist and forearm

Treatment
- adults: ORIF of ulna with indirect radius reduction in 90% of patients (ORIF of radius if unsuccessful)
- splint and early post-operative ROM if elbow completely stable, otherwise immobilization in plaster with elbow flexed for 6 wk
- pediatrics: attempt closed reduction and immobilization in plaster with elbow flexed for Bado Type I-III, surgery for Type IV

Specific Complications (see General Fracture Complications, OR6)
- PIN: most common nerve injury; observe for 3 mo as most resolve spontaneously
- radial head instability/redislocation
- radioulnar synostosis
**Nightstick Fracture**
- isolated fracture of ulna without dislocation of radial head

**Mechanism**
- direct blow to forearm (e.g., holding arm up to protect face)

**Treatment**
- non-operative
  - non-displaced
  - below elbow cast (x 10 d), followed by forearm brace (~8 wk)
- operative
  - displaced
  - ORIF if >50% shaft displacement or >10° angulation

**Galeazzi Fracture**
- fracture of the distal radial shaft with disruption of the DRUJ
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis

**Mechanism**
- hand FOOSH with axial loading of pronated forearm or direct wrist trauma

**Clinical Features**
- pain, swelling, deformity, and point tenderness at fracture site

**Investigations**
- X-ray: AP, lateral elbow, wrist, and forearm
  - shortening of distal radius >5 mm relative to the distal ulna
  - widening of the DRUJ space on AP
  - dislocation of radius with respect to ulna on true lateral

**Treatment**
- all cases are operative
  - ORIF of radius; afterwards, assess DRUJ stability by balloting distal ulna relative to distal radius
  - if DRUJ is stable and reducible, splint for 10-14 d with early ROM encouraged
  - if DRUJ is unstable, ORIF or percutaneous pinning with long arm cast in supination x 6 wk

**Wrist**

**Colles’ Fracture**
- extra-articular transverse distal radius fracture (~2 cm proximal to the radiocarpal joint) with dorsal displacement ± styloid fracture
- most common fracture in those >40 yr, especially in women and those with osteoporotic bone

**Mechanism**
- FOOSH

**Clinical Features**
- “dinner fork” deformity
- swelling, ecchymosis, tenderness

**Investigations**
- X-ray: AP and lateral wrist

**Treatment**
- goal is to restore radial height (13 mm), radial inclination (22°), volar tilt (11°), as well as DRUJ stability and useful forearm rotation
  - non-operative
    - closed reduction (think opposite of the deformity)
      - hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
      - closed reduction: 1) traction with extension (exaggerate injury), 2) traction with ulnar deviation, pronation, flexion (of distal fragment – not at wrist)
      - dorsal slab/below elbow cast for 5-6 wk
      - x-ray at 1 wk, 3 wk, and at cessation of immobilization to ensure reduction is maintained
    - obtain post-reduction films immediately; repeat reduction if necessary
  - ORIF Colles’ Fracture if Post-Reduction Demonstrates
    - Radial shortening >3 mm or,
    - Dorsal tilt >10° or,
    - Intra-articular displacement/step-off >2 mm

**Indications for surgical management of Colles’ Fracture**
- Displaced intra-articular fracture
- Comminuted
- Severe osteoporosis
- Dorsal angulation >5° or volar tilt >20°
- >5 mm radial shortening
Smith’s Fracture

Mechanism
• volar displacement of the distal radius (i.e. reverse Colles’ fracture)

Investigations
• X-ray: AP and lateral wrist

Treatment
• usually unstable and needs ORIF
• if patient is poor operative candidate, may attempt non-operative treatment
  • closed reduction with hematoma block (reduction opposite of Colles’)
  • long-arm cast in supination x 6 wk

Complications of Wrist Fractures

Table 12. Early and Late Complications of Wrist Fractures

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult reduction ± loss of reduction</td>
<td>Malunion, radial shortening</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Painful wrist secondary to ulnar prominence</td>
</tr>
<tr>
<td>Extensor pollicis longus tendon rupture</td>
<td>Frozen shoulder “shoulder-hand syndrome”)</td>
</tr>
<tr>
<td>Acute carpal tunnel syndrome</td>
<td>Post-traumatic arthritis</td>
</tr>
<tr>
<td>Finger swelling with venous block</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Complications of a tight cast/spint</td>
<td>CRPS/RSD</td>
</tr>
</tbody>
</table>

Scaphoid Fracture

Epidemiology
• common in young men; not common in children or in patients beyond middle age
• most common carpal bone injured
• may be associated with other carpal or wrist injuries (e.g. Colles’ fracture)

Mechanism
• FOOSH: impaction of scaphoid on distal radius, most commonly resulting in a transverse fracture through the waist (65%), dorsal (10%), or proximal (25%) scaphoid

Clinical Features
• pain with resisted pronation
• tenderness in the anatomical “snuff box”, over scaphoid tubercle, and pain with long axis compression into scaphoid
• usually nondisplaced

Investigations
• X-ray: AP, lateral, scaphoid views with wrist extension and ulnar deviation
• ± CT or MRI
• bone scan rarely used
  • note: a fracture may not be radiologically evident up to 2 wk after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 wk later to rule out a fracture; if x-ray still negative, order CT or MRI

Treatment
• early treatment critical for improving outcomes
• non-operative
  • non-displaced (<1 mm displacement/<15° angulation): long arm thumb spica cast x 4 wk, then short arm cast until radiographic evidence of healing is seen (2-3 mo)
• operative
  • displaced: ORIF with headless/countersink compression screw is the mainstay treatment

Scaphoid Fracture Special Tests
• Tender snuff box: 100% sensitivity, but 29% specific, as it is also positive with many other injuries of radial aspect of wrist with FOOSH

Figure 21. Colles’ fracture and associated bony deformity

Figure 22. Normal wrist angles + wrist angles in Colles’ fracture
Note the relative shortening of the radius relative to the ulna on AP view in Colles’ fracture
Specific Complications (see General Fracture Complications, OR6)

- most common: nonunion/malunion (use bone graft from iliac crest or distal radius with fixation to heal)
- AVN of the proximal fragment
- delayed union (recommend surgical fixation)
- scaphoid nonunion advanced collapse (SNAC) – chronic nonunion leading to advanced collapse and arthritis of wrist

Prognosis

- proximal fifth fracture: AVN rate 100%; proximal third fracture: AVN rate 33%
- waist fractures have healing rates of 80-90%
- distal third fractures have healing rates close to 100%

Hand

- see Plastic Surgery, PL23

Spine

Fractures of the Spine

- see Neurosurgery, NS33

Cervical Spine

General Principles

- C1 (atlas): no vertebral body, no spinous process
- C2 (axis): odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
  - nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra), C8 nerve root exits below C7 vertebra
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord

Special Testing

- compression test: pressure on head worsens radicular pain
- distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain
Table 13. Cervical Radiculopathy/Neuropathy

<table>
<thead>
<tr>
<th>Root</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Deltoid</td>
<td>Biceps Biceps</td>
<td>Triceps Triceps</td>
<td>Interossei Interossei</td>
</tr>
<tr>
<td></td>
<td>Biceps</td>
<td>Brachioradialis</td>
<td>Wrist flexion Finger extension</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>Axillary nerve</td>
<td>Thumb</td>
<td>Index and middle finger Ring and little finger</td>
<td></td>
</tr>
<tr>
<td>Reflex</td>
<td>Biceps</td>
<td>Biceps Brachioradialis Triceps</td>
<td>Triceps Finger jerk</td>
<td></td>
</tr>
</tbody>
</table>

X-Rays for C-Spine
- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- lateral
  - vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
  - angulation: between adjacent vertebral bodies (>11° is abnormal)
  - disc or facet joint widening
  - anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
- oblique: evaluate pedicles and intervertebral foramen
- ± swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
- ± lateral flexion/extension view: evaluate subluxation of cervical vertebrae

Differential Diagnosis of C-Spine Pain
- neck muscle strain, cervical spondylosis, cervical stenosis, RA (spondylitis), traumatic injury, whiplash, myofascial pain syndrome

C-SPINE INJURY
- see Neurosurgery, NS35

Thoracolumbar Spine

General Principles
- spinal cord terminates at conus medullaris (L1/2)
- individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)

Special Tests
- straight leg raise: passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down posterior/lateral leg to knee ± into foot
- Lasegue maneuver: dorsiflexion of foot during straight leg raise makes symptoms worse or if leg is less elevated, dorsiflexion will bring on symptoms
- femoral stretch test: with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular symptoms of unilateral pain in anterior thigh

Table 14. Lumbar Radiculopathy/Neuropathy

<table>
<thead>
<tr>
<th>Root</th>
<th>L4</th>
<th>L5</th>
<th>S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Quadriceps (knee extension + hip adduction)</td>
<td>Extensor hallucis longus Gluteus medius (hip abduction)</td>
<td>Peroneus longus + brevis (ankle eversion) Gastrocnemius + soleus (plantar flexion)</td>
</tr>
<tr>
<td>Sensory</td>
<td>Medial malleolus</td>
<td>1st dorsal webspace and lateral leg</td>
<td>Lateral foot</td>
</tr>
<tr>
<td>Screening Test</td>
<td>Squat and Rise</td>
<td>Heel Walking</td>
<td>Walking on Toes</td>
</tr>
<tr>
<td>Reflex</td>
<td>Knee (patellar)</td>
<td>Medial hamstring*</td>
<td>Ankle (Achilles)</td>
</tr>
<tr>
<td>Test</td>
<td>Femoral stretch</td>
<td>Straight leg raise</td>
<td>Straight leg raise</td>
</tr>
</tbody>
</table>

*D: Unreliable

Differential Diagnosis of Back Pain
1. mechanical or nerve compression (>90%)
   - degenerative (disc, facet, ligament)
   - peripheral nerve compression (disc herniation)
   - spinal stenosis (congenital, osteophyte, central disc)
   - cauda equina syndrome
2. others (<10%)
   - neoplastic (primary, metastatic, multiple myeloma)
   - infectious (osteomyelitis, TB)
   - metabolic (osteoporosis)
   - traumatic fracture (compression, distraction, translation, rotation)
   - spondyloarthropathies (ankylosing spondylitis)
   - referred (aorta, renal, ureter, pancreas)
DEGENERATIVE DISC DISEASE
- loss of vertebral disc height with age resulting in
  - bulging and tears of annulus fibrosus
  - change in alignment of facet joints
  - osteophyte formation

Mechanism
compression over time with age

Clinical Features
- axial back pain without radicular symptoms
- pain worse with axial loading and flexion
- negative straight leg raise

Investigations
- X-ray, MRI, provocative discography

Treatment
- non-operative
  - staying active with modified activity
  - back strengthening
  - NSAIDs
  - do not treat with opioids; no proven efficacy of spinal traction or manipulation
- operative – rarely indicated
  - decompression ± fusion
  - no difference in outcome between non-operative and surgical management at 2 yr

SPINAL STENOSIS
- narrowing of spinal canal <10 mm
- congenital (idiopathic, osteopetrosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylosis, Paget's disease, trauma)

Clinical Features
- ± bilateral back and leg pain
- neurogenic claudication
- ± motor weakness
- normal back flexion; difficulty with back extension (Kemp sign)
- positive straight leg raise, pain not worse with Valsalva

Investigations
- CT/MRI reveals narrowing of spinal canal but gold standard = CT myelogram

Treatment
- non-operative
  - vigorous physiotherapy (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
- operative
  - indication: non-operative failure >6 mo
  - decompressive surgery

Table 15. Differentiating Claudication

<table>
<thead>
<tr>
<th></th>
<th>Neurogenic</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravation</td>
<td>With standing or exercise</td>
<td>Walking set distance</td>
</tr>
<tr>
<td></td>
<td>Walking distance variable</td>
<td></td>
</tr>
<tr>
<td>Alleviation</td>
<td>Change in position (usually flexion, sitting, lying down)</td>
<td>Stop walking</td>
</tr>
<tr>
<td>Time</td>
<td>Relief in ~10 min</td>
<td>Relief in ~2 min</td>
</tr>
<tr>
<td>Character</td>
<td>Neurogenic ± neurological deficit</td>
<td>Muscular cramping</td>
</tr>
</tbody>
</table>

MECHANICAL BACK PAIN
- back pain NOT due to prolapsed disc or any other clearly defined pathology

Clinical Features
- dull backache aggravated by activity and prolonged standing
- morning stiffness
- no neurological signs

Treatment
- symptomatic (analgesics, physiotherapy)
- prognosis: symptoms may resolve in 4-6 wk, others become chronic

Cauda equina syndrome and ruptured aortic aneurysms are causes of low back pain that are considered surgical emergencies
LUMBAR DISC HERNIATION
- tear in annulus fibrosus allows protrusion of nucleus pulposus causing either a central, posterolateral, or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
- 3:1 male:female
- only 5% become symptomatic
- usually a history of flexion-type injury

Clinical Features
- back dominant pain (central herniation) or leg dominant pain (lateral herniation)
- tenderness between spinous processes at affected level
- muscle spasm ± loss of normal lumbar lordosis
- neurological disturbance is segmental and varies with level of central herniation
  - motor weakness (L4, L5, S1)
  - diminished reflexes (L4, S1)
  - diminished sensation (L4, L5, S1)
- positive straight leg raise
- positive contralateral SLR
- positive Lasegue and Bowstring sign
- cauda equina syndrome (present in 1-10%): surgical emergency

Investigations
- X-ray MRI, consider a post-void residual volume to check for urinary retention; post-void >100 mL should heighten suspicion for cauda equina syndrome

Treatment
- non-operative
  - symptomatic
    - extension protocol
    - NSAIDS
- operative
  - indication: progressive neurological deficit, failure of symptoms to resolve within 3 mo, or cauda equina syndrome due to central disc herniation
  - surgical discectomy
- prognosis
  - 90% of patients improve in 3 mo with non-operative treatment

Table 16. Types of Low Back Pain

<table>
<thead>
<tr>
<th>Disc Origin</th>
<th>Mechanical Back Pain</th>
<th>Direct Nerve Root Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Dominance</td>
<td>Back</td>
<td>Leg</td>
</tr>
<tr>
<td>Aggravation</td>
<td>Flexion</td>
<td>Extension, standing, walking</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>More sudden</td>
</tr>
<tr>
<td>Duration</td>
<td>Long (weeks, months)</td>
<td>Shorter (days, weeks)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Relief of strain, exercise</td>
<td>Relief of strain, exercise</td>
</tr>
</tbody>
</table>

Figure 27. Disc herniation causing nerve root compression

SPONDYLOLYSIS

Definition
- defect in the pars interarticularis with no movement of the vertebral bodies

Mechanism
- trauma: gymnasts, weightlifters, backpackers, loggers, labourers
Clinical Features
- activity-related back pain, pain with unilateral extension (Michelis' test)

Investigations
- oblique X-ray: “collar” break in the “Scottie dog’s” neck
- bone scan
- CT scan

Treatment
- non-operative
  - activity restriction, brace, stretching exercise

ADULT ISTHMIC SPONDYLOLISTHESIS

Definition
- defect in pars interarticularis causing a forward translation or slippage of one vertebra on another, usually at L5-S1, less commonly at L4-5

Mechanism
- congenital (children), degenerative (adults), traumatic pathological, teratogenic

Clinical Features
- lower back pain radiating to buttocks relieved with sitting
- neurogenic claudication
- L5 radiculopathy
- Meyerding Classification (percentage of slip)

Investigations
- X-ray (AP, lateral, oblique flexion-extension views), MRI

Treatment
- non-operative
  - activity restriction, bracing, NSAIDS
- operative

Table 17. Classification and Treatment of Spondylolisthesis

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage of Slip</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-25%</td>
<td>Symptomatic operative fusion only for intractable pain</td>
</tr>
<tr>
<td>2</td>
<td>25-50</td>
<td>Same as above</td>
</tr>
<tr>
<td>3</td>
<td>50-75</td>
<td>Decompression for spondylolisthesis and spinal fusion</td>
</tr>
<tr>
<td>4</td>
<td>75-100</td>
<td>Same as above</td>
</tr>
<tr>
<td>5</td>
<td>&gt;100</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Specific Complications
- may present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

Pelvis

Pelvic Fracture

Mechanism
- young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- elderly: fall from standing height, low energy trauma
- lateral compression, vertical shear, or anteroposterior compression fractures

Clinical Features
- pain, inability to bear weight
- local swelling, tenderness
- deformity of lower extremity
- pelvic instability
Investigations
- X-ray: AP pelvis, inlet and outlet views, Judet views (obturator and iliac oblique for acetabular fracture)
  - 6 cardinal radiographic lines of the acetabulum: ilioischial line, iliopectineal line, teardrop, roof, poste ior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture
- assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)
  - if involved, the fracture is considered an open fracture

Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Stability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Rotationally stable</td>
<td>A1: fracture not involving pelvic ring (i.e. avulsion or iliac wing fracture)</td>
</tr>
<tr>
<td></td>
<td>Vertically stable</td>
<td>A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3: transverse sacral fracture</td>
</tr>
<tr>
<td>B</td>
<td>Rotationally unstable</td>
<td>B1: open book (external rotation)</td>
</tr>
<tr>
<td></td>
<td>Vertically stable</td>
<td>B2: lateral compression – ipsilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B2-1: with anterior ring rotation/displacement through ipsilateral rami</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B2-2: with anterior ring rotation/displacement through non-ipsilateral rami (bucket-handle)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B3: bilateral</td>
</tr>
<tr>
<td>C</td>
<td>Rotationally unstable</td>
<td>C1: unilateral</td>
</tr>
<tr>
<td></td>
<td>Vertically unstable</td>
<td>C1-1: iliac fracture, C1-2: sacroiliac fracture-dislocation C1-3: sacral fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C2: bilateral with 1 side type B and 1 side type C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C3: bilateral both sides type C</td>
</tr>
</tbody>
</table>

Treatment
- ABCDEs
- non-operative treatment: protected weight bearing
  - indication: stable fracture
- emergency management
  - IV fluids/blood
  - pelvic binder/sheeting
  - external fixation vs. emergent angiography/embolization
  - ± laparotomy (if FAST/DPL positive)
- operative treatment: ORIF
  - indications
    - unstable pelvic ring injury
    - disruption of anterior and posterior SI ligament
    - symphysis diastasis >2.5 cm
    - vertical instability of the posterior pelvis
    - open fracture

Specific Complications (see General Fracture Complications, OR6)
- hemorrhage (life-threatening)
- injury to rectum or urogenital structures
- obstetrical difficulties, sexual and voiding dysfunction
- persistent SI joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high risk of DVT/PE

Hip

Hip Dislocation

full trauma survey (see Emergency Medicine: Patient Assessment/Management, ER2)
- examine for neurovascular injury PRIOR to open or closed reduction
- reduce hip dislocations within 6 h to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 wk post-reduction
- see Hip Dislocation Post-Total Hip Arthroplasty, OR29

ANTERIOR HIP DISLOCATION
- mechanism: posteriorly directed blow to knee with hip widely abducted
- clinical features: shortened, abducted, externally rotated limb
- treatment
  - closed reduction under conscious sedation/GA
  - post-reduction CT to assess joint congruity

Possible Radiological Findings
- Pubic rami fractures: superior/inferior
- Pubic symphysis diastasis: common in AP compression (N=5 mm)
- Sacral fractures: common in lateral compression
- SI joint diastasis: common in AP compression (N=1-4 mm)
- Disrupted anterior column (iliopectineal line) or posterior column (ilioischial line)
- “Teardrop” displacement: acetabular fracture
- iliac, ischial avulsion fractures
- Displacement of the major fragment: superior (VS), open book (APC), bucket handle (LC)
**POSTERIOR HIP DISLOCATION**

- most frequent type of hip dislocation
- mechanism: severe force to knee with hip flexed and adducted
  - e.g. knee into dashboard in MVC
- clinical features: shortened, adducted, internally rotated limb
- treatment
  - closed reduction under conscious sedation/GA only if no associated femoral neck fracture or ipsilateral displacement
  - ORIF if unstable, intra-articular fragments, or posterior wall fracture
  - post-reduction CT to assess joint congruity and fractures
  - if reduction is unstable, put in traction x 4-6 wk

**COMPLICATIONS FOR ALL HIP DISLOCATIONS**

- post-traumatic OA
- AVN of femoral head
- fracture of femoral head, neck, or shaft
- sciatic nerve palsy in 25% (10% permanent)
- HO
- thromboembolism - DVT/PE

**Hip Fracture**

**General Features**

- acute onset of hip pain
- unable to weight-bear
- shortened and externally-rotated leg
- painful ROM

**Table 19. Overview of Hip Fractures**

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Definition</th>
<th>Mechanism</th>
<th>Special Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Neck</td>
<td>Intracapsular (See Garden Classification, Table 20)</td>
<td>Young: MVC, fall from height</td>
<td>Same as general</td>
<td>X-Ray: AP hip, AP pelvis, cross table lateral hip</td>
<td>See Table 20</td>
<td>DVT, non-union, AVN, dislocation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elderly: fall from standing, rotational force</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intertrochanteric</td>
<td>Extracapsular fracture including the greater and lesser trochanters and transitional bone between the neck and shaft</td>
<td>Same as femoral neck fracture</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-Ray: AP pelvis, AP/lateral hip</td>
<td>Closed reduction under fluoroscopy then dynamic hip screw or IM nail</td>
<td>DVT, varus displacement of proxim i fragment, mal otation, non-union, failure of fixation device</td>
</tr>
<tr>
<td>Stable: intact posteromedial cortex</td>
<td></td>
<td>Direct or indirect force transmitted to the intertrochanteric area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unstable: non-intact posteromedial cortex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtrochanteric</td>
<td>Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft</td>
<td>Young: high energy trauma</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-Ray: AP pelvis, AP/lateral hip and femur</td>
<td>Closed open under fluoroscopy, then plate fixation or IM nail</td>
<td>Malalignment, non-union, wound infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elderly: osteopenic bone + fall, pathological fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 34. Subcapital, intertrochanteric, and subtrochanteric hip fractures**

**Rochester Method to Reduce Posterior Dislocations**

- Patient lying supine with hip and knee flexed on injured side
- Surgeon stands on patient’s injured side
- Surgeon passes one arm under patient’s flexed knee, reaching to place that hand on patient’s other knee (thus supporting patient’s injured leg)
- With other hand, surgeon grasps patient’s ankle on injured side, applying traction, while assistant stabilizes pelvis
- Reduction via traction, internal rotation, then external rotation once femoral head clears acetabular rim

**X-Ray Features of Subcapital Hip Fractures**

- Disruption of Shenton’s line (a radiographic line drawn along the upper margin of the obturator foramen, extending along the inferomedial side of the femoral neck)
- Altered neck-shaft angle (normal is 120-130°)

**DVT Prophylaxis in Hip Fractures**

LMWH (i.e. enoxaparin 40 mg SC bid), fondaparinux, low dose heparin on admission, do not give <12 h before surgery

**AVN of Femoral Head**

- Distal to proximal blood supply along femoral neck to head (medial and lateral femoral circumflex arteries)
- Susceptible to AVN if blood supply disrupted

**Comparative Effectiveness of Pain Management Interventions for Hip Fracture: A Systematic Review**

**Study:** Randomized controlled trials (RCTs); nonrandomized controlled trials (non-RCTs); and cohort studies of pain management techniques in older adults after acute hip fracture.

**Conclusions:** Nerve blockade seems to be effective in reducing acute pain after hip fracture. Low-level evidence suggests that preoperative traction does not reduce acute pain. Evidence was insufficient on the benefits and harms of many other interventions.
Table 20. Garden Classification of Femoral Neck Fractures

<table>
<thead>
<tr>
<th>Type</th>
<th>Displacement</th>
<th>Extent</th>
<th>Alignment</th>
<th>Trabeculae</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>“Incomplete”</td>
<td>Valgus or neutral</td>
<td>Malaligne</td>
<td>Internal fixation to prevent displacement (valgus impacted fracture)</td>
</tr>
<tr>
<td>II</td>
<td>None</td>
<td>Complete</td>
<td>Neutral</td>
<td>Aligned</td>
<td>Internal fixation to prevent displacement</td>
</tr>
<tr>
<td>III</td>
<td>Some</td>
<td>Complete</td>
<td>Varus</td>
<td>Malaligned</td>
<td>Young: ORIF Elderly: hemi-/total hip arthroplasty</td>
</tr>
<tr>
<td>IV</td>
<td>Complete</td>
<td>Complete</td>
<td>Varus</td>
<td>Aligned</td>
<td>Young: ORIF Elderly: hemi-/total hip arthroplasty</td>
</tr>
</tbody>
</table>

Figure 35. Garden classification of femoral neck fractures

Arthritis of the Hip

Etiology
- OA, inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders, or septic arthritis

Clinical Features
- pain (groin, medial thigh) and stiffness aggravated by activity better with rest in OA
- RA: morning stiffness >1 h, multiple joint swelling, hand nodules
- decreased ROM (internal rotation is lost first)
- crepitus
- effusion
- ± fixed flexion contracture leading to apparent limb shortening (Thomas test)
- ± Trendelenburg sign

Investigations
- X-ray: weight-bearing views of affected joint
  - OA: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes
  - RA: osteopenia, erosion, joint space narrowing, subchondral cysts
- blood work: ANA, RF

Treatment
- non-operative
  - weight reduction, activity modification, physiotherapy, analgesics, walking aids
- operative
  - indication advanced disease
  - realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
  - complications with arthroplasty: component loosening dislocation, HO, thromboembolism, infection, neurovascular injury, limb length discrepancy
  - arthroplasty is standard of care in most patients with hip arthritis

Hip Dislocation Post-Total Hip Arthroplasty

- occurs in 1-4% of primary THA and 10-16% of revision THAs
- risk factors: neurological impairment, post-traumatic arthritis, revision surgery, substance abuse

Mechanism
- THA that is unstable when hip is flexed, adducted, and internally rotated, or extended and externally rotated (avoid flexing hip >90° or crossing legs for ~6 wk after surgery)

Investigations
- X-ray: AP pelvis, AP and lateral hip
Treatment
- non-operative
  - closed reduction: external abduction splint to prevent hip adduction (most often)
- operative
  - indication: 2 or more dislocations with evidence of polyethylene wear, malalignment, hardware failure
  - revision THA
  - conversion to hemiarthroplasty with a larger femoral head
  - resection arthroplasty is a last resort

Complications
- sciatic nerve palsy in 25% (10% permanent)
- HO
- infection

Femur

Femoral Diaphysis Fracture

Mechanism
- high energy trauma (MVC, fall from height, gunshot wound)
  - pathologic as a result of malignancy, osteoporosis, bisphosphonate use
  - in children, can result from low energy trauma (spiral fracture)

Clinical Features
- shortened, externally rotated leg (if fracture displaced)
- inability to weight-bear
- often open injury, always a Gustilo III (Table 5)
- Winquist and Hansen classification

Investigations
- X-ray: AP pelvis, AP/lateral hip, femur, knee

Treatment
- non-operative (uncommon)
  - indication: non-displaced femoral shaft fractures in co-morbid patients
  - long leg cast
- operative
  - ORIF with anterograde IM nail (most common) or retrograde IM nail; external fixator for unstable patients, open fractures, or highly vascular areas; or plate and screws for open growth plates within 24 h
  - early mobilization and strengthening

Complications
- blood loss
- fat embolism leading to ARDS
- extensive soft tissue damage
- ipsilateral hip dislocation/fracture (2-6%)
- nerve injury

Distal Femoral Fracture

- fractures from articular surface to 5 cm above metaphyseal flare

Mechanism
- direct high energy force or axial loading
- three types: extra articular, partial articular, complete articular

Clinical Features
- extreme pain
- knee effusion (hemarthrosis)
- neurovascular deficits can occur with displaced fracture

Investigations
- X-ray: AP, lateral
- CT, angiography if diminished pulses
Treatment
- non-operative (uncommon)
  - indication: non-displaced extra-articular fracture
  - hinged knee brace
- operative
  - indication: displaced fracture, intra-articular fracture, non-union
  - ORIF or retrograde IM nail if supracondylar and non-commminuted
  - early mobilization and strengthening

Specific Complications (see General Fracture Complications, OR6)
- femoral artery tear
- popliteal artery injury
- nerve injury
- extensive soft tissue injury
- angulation deformities

Knee

Evaluation of Knee

Common Complaints
- locking, instability, and swelling
  - torn meniscus/loose body in joint
- pseudo-locking: limited ROM without mechanical block
  - effusion, muscle spasm after injury, arthritis
- painful clicking (audible)
  - torn meniscus
- giving way: instability
  - cruciate ligament or meniscal tear, patellar dislocation

Special Tests of the Knee

- anterior and posterior drawer tests (Figure 39)
  - demonstrate ACL and PCL, respectively
    - knee flexed at 90°, foot immobilized, hamstrings released
    - if able to sublux tibia anteriorly (anterior drawer test), then ACL may be torn
    - if able to sublux tibia posteriorly (posterior drawer test), then PCL may be torn
    - anterior drawer test for ACL: 3.8 positive likelihood ratio, 0.30 negative likelihood ratio

- Lachman test
  - demonstrates torn ACL
  - hold knee in 10-20° flexion, stabilizing the femur
  - try to sublux tibia anteriorly on femur
  - similar to anterior drawer test, more reliable due to less muscular stabilization
  - for ACL: 25.0 positive likelihood ratio, 0.1 negative likelihood ratio

- pivot shift sign
  - demonstrates torn ACL
  - start with the knee in extension
  - internally rotate foot, slowly flex knee while palpating and applying a valgus force
  - if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the “pivot”)
  - reverse pivot shift (start in flexion, externally rotate, apply valgus and extend knee) suggests torn PCL
  - composite assessment for ACL: 25.0 positive likelihood ratio, 0.04 negative likelihood ratio
  - composite assessment for PCL: 21.0 positive likelihood ratio, 0.05 negative likelihood ratio

- posterior sag sign
  - demonstrates torn PCL
  - may give a false positive anterior drawer sign
  - flex knees and hips to 90°, hold ankles and knees
  - view from the lateral aspect
  - if one tibia sags posteriorly compared to the other, its PCL is torn

- collateral ligament stress test
  - palpate ligament for “opening” of joint space while testing
  - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
  - repeat tests with knee in 20° flexion to relax joint capsule
  - opening in 20° flexion due to MCL damage only
  - opening in 20° of flexion and full extension is due to MCL, cruciate, and joint capsule damage

- Thessaly test
  - demonstrates meniscal tear
  - patient stands flat footed on one leg while the examiner provides his or her hands for balance. The patient then flexes the knee to 20° and rotates the femur on the tibia medially and laterally three times while maintaining the 20° flexion
Knee

- positive for a meniscal tear if the patient experiences medial or lateral joint line discomfort
- for medial meniscus: 29.67 positive likelihood ratio, 0.11 negative likelihood ratio
- for lateral meniscus: 23.0 positive likelihood ratio, 0.083 negative likelihood ratio

- tests for meniscal tear
  - joint line tenderness
    - joint line pain when palpated
    - palpate one side at a time and watch patient’s eyes
  - for meniscal tear: 0.9 positive likelihood ratio, 1.1 negative likelihood ratio
  - crouch compression test
  - joint line pain when squatting (anterior pain suggests patellofemoral pathology)
  - McMurray’s test (Figure 40)
    - with knee in flexion, palpate joint line for painful “pop/click”
    - lateral meniscus tear exam: internally rotate foot, varus stress, and extend knee
    - medial meniscus tear exam: externally rotate foot, valgus stress, and extend knee
  - for meniscal tear: 1.3 positive likelihood ratio, 0.8 negative likelihood ratio
  - composite assessment for meniscal tears: 2.7 positive likelihood ratio, 0.4 negative likelihood ratio

X-Rays
- AP standing, lateral
- skyline: tangential view with knees flexed at 45° to see patellofemoral joint
- 3-foot standing view: useful in evaluating leg length and varus/valgus alignment
- Ottawa Knee Rules (see Emergency Medicine, ER16)

Cruciate Ligament Tears

- ACL tear much more common than PCL tear

<table>
<thead>
<tr>
<th>Table 21. Comparison of ACL and PCL Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior Cruciate Ligament</strong></td>
</tr>
<tr>
<td>Anatomy</td>
</tr>
<tr>
<td>Mechanism</td>
</tr>
<tr>
<td>History</td>
</tr>
<tr>
<td>Physical</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
</tbody>
</table>

Collateral Ligament Tears

**Mechanism**
- valgus force to knee = MCL tear
- varus force to knee = LCL tear

**Clinical Features**
- swelling/effusion
- tenderness above and below joint line medially (MCL) or laterally (LCL)
- joint laxity with varus or valgus force to knee
  - laxity with endpoint suggests partial tear
  - laxity with no endpoint suggests a complete tear
- test for other injuries (e.g. O’Donoghue’s unhappy triad), common peroneal nerve injury

**Investigations**
- x-ray: AP and lateral; MRI
Knee

Treatment
• non-operative
  ■ partial tear: immobilization x 2-4 wk with early ROM and strengthening
  ■ complete tear: immobilization at 30° flexion
• operative
  ■ indication: multiple ligamentous injuries
  ■ surgical repair of ligaments

Meniscal Tears
• medial tear much more common than lateral tear

Mechanism
• twisting force on knee when it is partially flexed (e.g. stepping down and turning)
  • requires moderate trauma in young person, but only mild trauma in elderly due to degeneration

Clinical Features
• immediate pain, difficulty weight-bearing, instability, and clicking
• increased pain with squatting and/or twisting
• effusion (hemarthrosis) with insidious onset (24-48 h after injury)
• joint line tenderness medially or laterally
• locking of knee (if portion of meniscus mechanically obstructing extension)

Investigations
• MRI, arthroscopy

Treatment
• non-operative
  ■ indication: not locked
  ■ ROM and strengthening (NSAIDs)
• operative
  ■ indication: locked or failed non-operative treatment
  ■ arthroscopic repair/partial meniscectomy

Quadriceps/Patellar Tendon Rupture

Mechanism
• sudden forceful contraction of quadriceps during an attempt to stop
  • more common in obese patients and those with pre-existing degenerative changes in tendon
    ■ DM, SLE, RA, steroid use, renal failure on dialysis

Clinical Features
• inability to extend knee or weight-bear
• possible audible “pop”
• patella in lower or higher position with palpable gap above or below patella, respectively
• may have an effusion

Investigations
• ask patient to straight leg raise (unable with complete rupture)
• knee X-ray to rule out patellar fracture, MRI to distinguish between complete and partial tears
• lateral view: patella alta with patellar tendon rupture, patella baja (infera) with quadriceps tendon rupture

Treatment
• non-operative
  ■ indication: incomplete tears with preserved extension of knee
  ■ immobilization in brace
• operative
  ■ indication: complete ruptures with loss of extensor mechanism
  ■ early surgical repair: better outcomes compared with delayed repair (>6 wk post-injury)
  ■ delayed repair complicated by quadriceps contracture, patella migration, and adhesions
Dislocated Knee

Mechanism
- high energy trauma
- by definition, caused by tears of multiple ligaments

Clinical Features
- classified by relation of tibia with respect to femur
  - anterior, posterior, lateral, medial, rotary
- knee instability
- effusion
- pain
- ischemic limb
- Schenck classification

Investigations
- X-ray: AP, lateral, skyline
- associated radiographic findings include tibial plateau fracture dislocations, proximal fibular fractures, and avulsion of fibular head
- ABI (abnormal if <0.9)
- arteriogram or CT angiogram if abnormal vascular exam (such as abnormal pedal pulses)

Treatment
- urgent closed reduction
  - complicated by interposed soft tissue
  - assessment of peroneal nerve, tibial artery, and ligamentous injuries
  - emergent operative repair if vascular injury, open fracture or dislocation, non-reducible dislocation, compartment syndrome
  - knee immobilization x 6-8 wk

Specific Complications
- high incidence of associated injuries
- popliteal artery tear
- peroneal nerve injury
- capsular tear
- chronic instability, stiffness, post-traumatic arthritis

Patella

Patellar Fracture

Mechanism
- direct blow to the patella: fall, MVC (dashboard)
- indirect trauma by sudden flexion of knee against contracted quadriceps

Clinical Features
- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- ± effusion/hemarthrosis

Investigations
- X-rays: AP, lateral, skyline
  - do not confuse with bipartite patella: congenitally unfused ossification centres with smooth margins on X-ray at superolateral corner

Treatment
- non-operative
  - indication: non-displaced (step-off <2-3 mm and fracture gap <1-4 mm)
    - straight leg immobilization 1-4 wk with hinged knee brace, weight bearing as tolerated
    - progress in flexion after 2-3 wk
    - physiotherapy: quadriceps strengthening when pain has subsided
  - operative
    - indication: displaced (>2 mm), comminuted, disrupted extensor mechanism
    - ORIF, if comminuted may require partial/complete patellectomy
    - goal: restore extensor mechanism with maximal articular congruency

Complications
- Symptomatic wiring
- Loss of reduction
- Osteonecrosis (proximal fragment)
- Hardware failure
- Knee stiffness
- Nonunion
- Infection
Patellar Dislocation

Mechanism
- usually a non-contact twisting injury
- lateral displacement of patella after contraction of quadriceps at the start of knee flexion in an almost straight knee joint
- direct blow, e.g. knee/helmet to knee collision

Risk Factors
- young, female
- obesity
- high-riding patella (patella alta)
- genu valgus
- Q-angle (quadriceps angle) ≥20°
- shallow intercondylar groove
- weak vastus medialis
- tight lateral retinaculum
- ligamentous laxity (Ehlers-Danlos)

Clinical Features
- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced
- positive patellar apprehension test
- often recurrent, self-reducing
- concomitant MCL injury
- increased Q-angle
- J-sign

Investigations
- X-rays: AP, lateral, skyline view of patella
- check for fracture of medial patella (most common) and lateral femoral condyle

Treatment
- non-operative first
  - NSAIDs, activity modification, and physical therapy
  - short-term immobilization for comfort, then 6 wk controlled motion
  - progressive weight bearing and isometric quadriceps strengthening
- operative
  - indication: if recurrent or if loose bodies present
  - surgical tightening of medial capsule and release of lateral retinaculum, possible tibial tuberosity transfer, or proximal tibial osteotomy

Patellofemoral Syndrome (Chondromalacia Patellae)

- syndrome of anterior knee pain associated with idiopathic articular changes of patella

Risk Factors
- malalignment causing patellar maltracking (Q angle ≥20°, genu valgus)
- post-trauma
- deformity of patella or femoral groove
- recurrent patellar dislocation, ligamentous laxity
- excessive knee strain (athletes)

Mechanism
- softening, erosion, and fragmentation of articular cartilage, predominantly medial aspect of patella
- commonly seen in active young females

Clinical Features
- deep, aching anterior knee pain
  - exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting, or kneeling
- insidious onset and vague in nature
- sensation of instability, pseudolocking
- pain with extension against resistance through terminal 30–40°
- pain with compression of patella with knee ROM or resisted knee extension
- swelling rare, minimal if present
- palpable crepitus

Investigations
- X-ray: AP, lateral, skyline – may find chondrosis, lateral patellar tilt, patella alta/baja, or shallow sulcus
- CT-scan
- MRI – best to assess articular cartilage
Treatment
- non-operative
  - continue non-impact activities; rest and rehabilitation
  - NSAIDs
  - physiotherapy: vastus medialis and core strengthening
- operative
  - indication: failed non-operative treatment
  - tibial tubercle elevation
  - arthroscopic shaving/debridement
  - lateral release of retinaculum

Tibia Plateau Fracture

Mechanism
- varus/valgus load ± axial loading (e.g. fall from height)
- femoral condyles driven into proximal tibia
- can result from minor trauma in those with osteoporosis

Clinical Features
- frequency: lateral > bicondylar > medial
- medial fractures require higher energy – often have concomitant vascular injuries
- knee effusion
- inability to bear weight
- swelling
- associated with compartment syndrome, ACL injury, and meniscal tears
- Schatzker classification

Investigations
- X-ray: AP, lateral, oblique
- CT: pre-operative planning, identify articular depression and comminution
- ABI if any differences in pulses between extremities

Treatment

<table>
<thead>
<tr>
<th>Approach #1 (based on amount of depression seen on x-ray)</th>
<th>Non-operative indication (if depression on x-ray is &lt;3 mm): straight leg immobilization x 4-6 wk with progressive ROM weight bearing</th>
<th>Operative indication (if depression is &gt;3 mm): ORIF often requiring bone grafting to elevate depressed fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach #2 (based on varus/valgus instability)</td>
<td>Non-operative indication (if minimal varus/valgus instability [&lt;15°]): straight leg immobilization x 4-6 wk with progressive ROM weight bearing</td>
<td>Operative indication (if significant varus/valgus instability [&gt;15°]): ORIF often requiring bone grafting to elevate depressed fragment</td>
</tr>
</tbody>
</table>

Specific Complications (see General Fracture Complications, OR6)
- ligamentous injuries
- meniscal lesions
- AVN
- infection
- OA

Tibial Shaft Fracture
- most common long bone fracture and open fracture

Mechanism
- low energy pattern: torsional injury
- high energy: including MVC, falls, sporting injuries

Clinical Features
- pain, inability to weight bear
- open vs. closed
- neurovascular compromise

Investigations
- X-ray: AP lateral
  - full length, plus knee and ankle

Schatzker Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of lateral plateau split fracture</td>
</tr>
<tr>
<td>II</td>
<td>Lateral split-depressed fracture</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lateral plateau: pure depression fracture</td>
</tr>
<tr>
<td>IV</td>
<td>Medial plateau fracture</td>
</tr>
<tr>
<td>V</td>
<td>Bicondylar plateau fracture</td>
</tr>
<tr>
<td>VI</td>
<td>Bicondylar with metaphyseal/diaphyseal involvement</td>
</tr>
</tbody>
</table>

Figure 44. Tibial shaft fracture treated with IM nail and screws
Treatment
• non-operative
  ■ indication: closed and minimally displaced or adequate closed reduction
  • long leg cast x 8-12 wk, functional brace after
• operative
  ■ indication: displaced or open
  • if displaced and closed: ORIF with IM nail, plate and screws, or external fixator
  • if open: antibiotics, I&D, external fixation or IM nail, and vascularized coverage of soft tissue defects

Specific Complications (see General Fracture Complications, OR6)
• high incidence of neurovascular injury and compartment syndrome
• poor soft tissue coverage (critical to outcome)

Ankle

Evaluation of Ankle and Foot Complaints

Special Tests
• anterior drawer: examiner attempts to displace the foot anteriorly against a fixed tibia
• talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated by X-ray

X-Ray
• AP, lateral
• mortise view: ankle at 15° of internal rotation
  • gives true view of ankle joint
  • joint space should be symmetric with no talar tilt
• Ottawa Ankle Rules should guide X-ray use (see Emergency Medicine, ER17); nearly 100% sensitivity
• ± CT to better characterize fractures

Ankle Fracture

Mechanism
• pattern of fracture depends on the position of the ankle when trauma occurs
• generally involves
  ■ ipsilateral ligamentous tears or transverse bony avulsion
  ■ contralateral shear fractures (oblique or spiral)
• classification systems
  ■ Danis-Weber
  ■ Lauge-Hansen: based on foot's position and motion relative to leg

Treatment
• non-operative
  ■ indication: non-displaced, no history of dislocation
  • below knee cast, NWB
• operative
  ■ indications
    • any fracture-dislocation: restore vascularity, minimize articular injury, reduce pain and skin pressure
    • most of type B, and all of type C
    • talar malleolar (medial, posterior, lateral) fractures
    • talar tilt >10°
    • medial clear space on X-ray greater than superior clear space
    • open fracture/open joint injury
  • ORIF

Complications
• high incidence of post-traumatic arthritis

Tibial shaft fractures have high incidence of compartment syndrome and are often associated with soft tissue injuries

Ottawa Ankle Rules (see Emergency Medicine, ER17)
X-rays are only required if:
  Pain in the malleolar zone AND bony tenderness over the distal 6 cm of the posterior aspect of the tibia or tip of the medial or lateral malleolus OR inability to weight bear both immediately after injury and in the ER

Figure 45 Ring principle of the ankle and Danis-Weber classification
Ankle Ligamentous Injuries

- see Figure 46 for ankle ligaments

Medial Ligament Complex (deltoid ligament)
- eversion injury
- usually avulses medial or posterior malleolus and strains syndesmosis

Lateral Ligament Complex (Anterior Talofibular, Calcaneofibular, Posterior Talofibular)
- inversion injury, >90% of all ankle sprains
- ATF most commonly and severely injured if ankle is plantarflexed
- swelling and tenderness anterior to lateral malleolus
- +++ ecchymosis
- positive ankle anterior drawer
- may have significant medial talar tilt on inversion stress X-ray

Treatment
- non-operative
  - microscopic tear (Grade I)
    - rest, ice, compression, elevation
  - macroscopic tear (Grade II)
    - strap ankle in dorsiflexion and eversion x 4-6 wk
    - physiotherapy: strengthening and proprioceptive retraining
  - complete tear (Grade III)
    - below knee walking cast x 4-6 wk
    - physiotherapy: strengthening and proprioceptive retraining
- surgical intervention may be required if chronic symptomatic instability develops

Foot

Talar Fracture

Mechanism
- axial loading or hyperdorsiflexion (MVC, fall from height)
- 60% of talus covered by articular cartilage
- talar neck is most common fracture of talus (50%)
- tenuous blood supply runs distal to proximal along talar neck
- high risk of AVN with displaced fractures

Investigations
- X-ray: AP, lateral, Canale view
- CT to better characterize fracture
- MRI can clearly define extent of AVN

Treatment
- non-operative
  - indication: non-displaced
    - NWB, below-knee cast x 6 wk
  - operative
    - indication: displaced
    - ORIF (high rate of nonunion, AVN)
    - neck fracture: ORIF

Calcaneal Fracture

- most common tarsal fracture

Mechanism
- high energy, axial loading: fall from height onto heels
- 10% of fractures associated with compression fractures of thoracic or lumbar spine (rule out spine injury)
- 75% are intra-articular and 10% are bilateral

Clinical Features
- marked swelling, bruising on heel/sole
- wider, shortened, flatter heel when viewed from behind
- varus heel

With a history of significant trauma from axial loading of lower limb, always consider spinal injuries, femoral neck, tibial plateau, and talar/ calcaneal fractures

Calcaneal Fracture

- most common tarsal fracture

Mechanism
- high energy, axial loading: fall from height onto heels
- 10% of fractures associated with compression fractures of thoracic or lumbar spine (rule out spine injury)
- 75% are intra-articular and 10% are bilateral

Clinical Features
- marked swelling, bruising on heel/sole
- wider, shortened, flatter heel when viewed from behind
- varus heel

Figure 46. Ankle ligament complexes
Investigations
• X-rays: AP, lateral, oblique foot (mandatory views); can also assess with Broden view, Harris view, or AP ankle.
• loss of Bohler’s angle
• CT: gold standard, assess intra-articular extension

Treatment
• closed vs. open reduction is controversial
• NWB cast x 3 mo with early ROM and strengthening

Achilles Tendonitis

Mechanism
• chronic inflammation from activity or poor-fitting footwear
• may also develop heel bumps (retrocalcaneobursitis or Haglund deformity)

Clinical Features
• pain, stiffness, and crepitus with ROM
• thickened tendon, palpable bump

Investigations
• X-ray: lateral, evaluate bone spur and calcification; U/S, MRI (to assess degenerative change)

Treatment
• non-operative
  • rest, NSAIDs, shoe wear modification (orthotics, open back shoes)
  • heel sleeves and pads are mainstay of non-operative treatment
  • gentle gastrocnemius-soleus stretching, eccentric training with physical therapy, deep tissue calf massage
  • shockwave therapy in chronic tendonitis
  • DO NOT inject steroids (risk of tendon rupture)

Achilles Tendon Rupture

Mechanism
• loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
• secondary to chronic tendonitis, steroid injection

Clinical Features
• audible pop, sudden pain with push-off movement
• pain or inability to plantarflex
• palpable gap
• apprehensive toe off when walking
• weak plantarflexion strength
• Thompson test: with patient prone, squeeze calf, normal response is plantar flexion
  • no passive plantarflexion = positive test = ruptured tendon

Investigations
• X-ray (to rule out other pathology), U/S or MRI (for partial vs. complete ruptures)

Treatment
• non-operative
  • indication: low athletic demand or elderly
  • cast foot in plantar flexion (to relax tendon) x 8-12 wk
• operative
  • indication: high athletic demand
  • surgical repair, then cast as above x 6-8 wk

Plantar Fasciitis (Heel Spur Syndrome)

Definition
• inflammation of plantar aponeurosis at calcaneal origin
• common in athletes (especially runners, dancers)
• also associated with obesity, DM, seronegative and seropositive arthritis

Mechanism
• repetitive strain injury causing microtears and inflammation of plantar fascia

Figure 47. X-ray of bony heel spur
Clinical Features

• insidious onset of heel pain, pain when getting out of bed, and stiffness
• intense pain when walking from rest that subsides as patient continues to walk, worse at end of day with prolonged standing
• swelling, tenderness over sole
• greatest at medial calcaneal tubercle and 1-2 cm distal along plantar fascia
  pain with toe dorsiflexion (stretches fascia)

Investigations

• plain radiographs to rule out fractures
• often see bony exostoses (heel spurs) at insertion of fascia into medial calcaneal tubercle
• spur is secondary to inflammation, not the cause of pain

Treatment

• non-operative
  ■ pain control and stretching programs are first-line
  ■ rest, ice, NSAIDs, steroid injection
  ■ physiotherapy: Achilles tendon and plantar fascia stretching, extracorporeal shockwave therapy
  ■ orthotics with heel cup – to counteract pronation and disperse heel strike forces
• operative
  ■ indication: failed non-operative treatment
  ■ endoscopic surgical release of fascia
  ■ spur removal is not required

Bunions (Hallux Valgus)

Definition

• bony deformity characterized by medial displacement of first metatarsal and lateral deviation of hallux

Mechanism

• valgus alignment on 1st MTP (hallux valgus) causes eccentric pull of extensor and intrinsic muscles
• many associated deformities in foot from altered mechanics
• reactive exostosis forms with thickening of the skin, creating a bunion
• most often associated with poor-fitting footwear (high heel and narrow toe box)
• can be hereditary (70% have family history)
• 10x more frequent in women

Clinical Features

• painful bursa over medial eminence of 1st MT head
• pronation (rotation inward) of great toe
• numbness over medial aspect of great toe

Investigations

• X-ray: standing AP/lateral/sesamoid view, NWB oblique

Treatment

• indications: painful corn or bunion, overriding 2nd toe
• non-operative (first-line)
  ■ properly fitted shoes (low heel) and toe spacer
• operative: goal is to restore normal anatomy, not cosmetic reasons alone
  ■ osteotomy with realignment of 1st MTP joint (Chevron Procedure)
  ■ arthrodesis

Metatarsal Fracture

• as with the hand, 1st, 4th, 5th MT are relatively mobile while the 2nd and 3rd are fixed
• use Ottawa Foot Rules to determine need for x-ray

Table 22. Types of Metatarsal Fractures

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Mechanism</th>
<th>Clinical Treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avulsion of Base of 5th MT</td>
<td>Sudden inversion followed by contraction of peroneus brevis</td>
<td>Tender base of 5th MT</td>
<td>Requires ORIF if displaced</td>
</tr>
<tr>
<td>Midshaft 5th MT (Jones Fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 5th MT</td>
<td>*NWB BK cast x 6 wk ORIF if athlete</td>
</tr>
<tr>
<td>Shaft 2nd, 3rd MT (March Fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 2nd or 3rd MT</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>1st MT</td>
<td>Trauma</td>
<td>Painful 1st MT</td>
<td>ORIF if displaced otherwise</td>
</tr>
<tr>
<td>Tarso-MT Fracture – Dislocation (Lisfranc Fracture)</td>
<td>Fall onto plantar flexed foot or direct crush injury</td>
<td>Shortened forefoot prominent base</td>
<td>*NWB BK cast x 3 wk then walking cast x 2 wk</td>
</tr>
</tbody>
</table>
Pediatric Orthopedics

Fractures in Children

- type of fracture
  - thicker, more active periosteum results in pediatric-specific fractures: greenstick (one cortex), torus (i.e. ‘buckle’, impacted cortex) and plastic (bowing)
  - distal radius fracture most common in children (phalanges second), the majority are treated with closed reduction and casting
  - adults fracture through both cortices
- epiphyseal growth plate
  - weaker part of bone, susceptible to fractures
  - plate often mistaken for fracture on x-ray and vice versa (X-ray opposite limb for comparison), especially in elbow
  - tensile strength of bone < ligaments in children, therefore clinician must be confident that fracture and/or growth plate injury have been ruled out before diagnosing a sprain
  - intra-articular fractures have worse consequences in children because they usually involve the growth plate
- anatomic reduction
  - gold standard with adults
  - may cause limb length discrepancy in children (overgrowth)
  - accept greater angular deformity in children (remodelling minimizes deformity)
- time to heal
  - shorter in children
  - always be aware of the possibility of child abuse
  - make sure stated mechanism compatible with injury
  - high index of suspicion with fractures in non-ambulating children (<1 yr); look for other signs, including X-ray evidence of healing fractures at different sites and different stages of healing
  - common suspicious fractures in children: metaphyseal corner fracture (hallmark of non-accidental trauma), femur fracture < 1 yo, humeral shaft < 3 yo, sternal fractures, posterior rib fractures, spinous process fractures

Stress Fractures

Mechanism
- insufficiency fracture
  - stress applied to a weak or structurally deficient bone
- fatigue fracture
  - repetitive, excessive force applied to normal bone
- most common in adolescent athletes
- tibia is most common site

Diagnosis
- localized pain and tenderness over the involved bone
- plain films may not show fracture for 2 wk
- bone scan positive in 12-15 d

Treatment
- rest from strenuous activities to allow remodelling (can take several months)

Epiphyseal Injury

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Straight through; Stable)</td>
<td>Transverse through growth plate</td>
<td>Closed reduction and cast immobilization (except SCFE – ORIF); heals well, 95% do not affect growth</td>
</tr>
<tr>
<td>II (Above)</td>
<td>Through metaphysis and along growth plate</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>III (Low)*</td>
<td>Through epiphysis to plate and along growth plate</td>
<td>Anatomic reduction by ORIF to prevent growth arrest, avoid fixation across growth plate</td>
</tr>
<tr>
<td>IV (Through and through)*</td>
<td>Through epiphysis and metaphysis</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>V (Ram)*</td>
<td>Crush injury of growth plate</td>
<td>High incidence of growth arrest; no specific treatment</td>
</tr>
</tbody>
</table>

* Types II – IV are more likely to cause growth arrest and progressive deformity
Slipped Capital Femoral Epiphysis

Definition
- type I Salter-Harris epiphyseal injury at proximal hip
- most common adolescent hip disorder, peak incidence at pubertal growth spurt
- risk factors: male, obese (#1 factor), hypothyroid (risk of bilateral involvement)

Etiology
- multifactorial
  - genetic: autosomal dominant, black children at highest risk
  - cartilaginous physis hypertrophies too rapidly under growth hormone effects
  - sex hormone secretion, which stabilizes physis, has not yet begun
  - overweight: mechanical stress
  - trauma: causes acute slip

Clinical Features
- acute: sudden, severe pain with limp
- chronic (typically): groin and anterior thigh pain, may present with knee pain
  - positive Trendelenburg sign on affected side, due to weakened gluteal muscles
  - tender over joint capsule
  - restricted internal rotation, abduction, flexion
  - Whitman’s sign: obligatory external rotation during passive flexion of hip
  - Loder classification: stable vs. unstable (provides prognostic information)
    - unstable means patient cannot ambulate even with crutches

Investigations
- X-ray: AP, frog-leg, lateral radiographs both hips
  - posterior and medial slip of epiphysis
  - disruption of Klein’s line
  - AP view may be normal or show widened/lucent growth plate compared with opposite side

Treatment
- operative
  - mild/moderate slip: stabilize physis with pins in current position
  - severe slip: ORIF or pin physis without reduction and osteotomy after epiphyseal fusion

Complications
- AVN (roughly half of unstable hips), chondrolysis (loss of articular cartilage, resulting in narrowing of joint space), pin penetration, premature OA, loss of ROM

Developmental Dysplasia of the Hip

Definition
- abnormal development of hip, resulting in dysplasia and subluxation/dislocation of hip
- most common orthopedic disorder in newborns

Etiology
- due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
- spectrum of conditions
  - dislocated femoral head completely out of acetabulum
  - dislocatable head in socket
  - head subluxates out of joint when provoked
  - dysplastic acetabulum, more shallow and more vertical than normal
- if painful, suspect septic dislocation (normally painless)

Physical Exam
- diagnosis is clinical
  - limited abduction of the flexed hip (<60°)
  - affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
  - Barlow’s test (checks if hips are dislocatable (Figure 51))
    - flex hips and knees to 90° and grasp thigh
    - fully adduct hips, push posteriorly to try to dislocate hips
  - Ortolani’s test (checks if hips are dislocated (Figure 51))
    - initial position as above but try to reduce hip with fingertips during abduction
    - positive test: palpable clunk is felt (not heard) if hip is reduced
  - Galeazzi’s sign
    - knees at unequal heights when hips and knees flexed
    - dislocated hip on side of lower knee
    - difficult test if child <1 yr
    - Trendelenburg test and gait useful if older (>2 yr)
Pediatric Orthopedics

Investigations
- U/S in first few months to view cartilage (bone is not calcified in newborns until 4-6 mo)
- follow-up radiograph after 3 mo
- X-ray signs (at 4-6 mo): false acetabulum, acetabular index >25°, broken Shenton's line, femoral neck above Hilgenreiner's line, ossification centre outside of inner lower quadrant (quadrants formed by intersection of Hilgenreiner's and Perkin's lines)

Treatment
- 0-6 mo: reduce hip using Pavlik harness to maintain abduction and flexion
- 6-18 mo: reduction under GA, hip spica cast x 2-3 mo (if Pavlik harness fails)
- >18 mo: open reduction; pelvic and/or femoral osteotomy

Complications
- redislocation, inadequate reduction, stiffness
- AVN of femoral head

Legg-Calvé-Perthes Disease (Coxa Plana)

Definition
- idiopathic AVN of femoral head, presents at 4-8 yr of age
- 12% bilateral, M>F = 5:1, 1/1,200
- associations
  - family history
  - low birth weight
  - abnormal pregnancy/delivery
  - ADHD in 33% of cases, delayed bone age in 89%
  - second-hand smoke exposure
  - Asian, Inuit, Central European
- key features
  - AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodelling of regenerated bone

Clinical Features
- child with antalgic or Trendelenburg gait ± pain
- intermittent knee, hip, groin, or thigh pain
- flexion contracture (stiff hip): decreased internal rotation and abduction of hip
- limb length discrepancy (late)

Investigations
- X-ray: AP pelvis, frog leg laterals
- may be negative early (if high index of suspicion, move to bone scan or MRI)
- eventually, characteristic collapse of femoral head (diagnostic)

Treatment
- goal is to preserve ROM and keep femoral head contained in acetabulum
- non-operative
  - physiotherapy: ROM exercises
  - brace in flexion and abduction x 2-3 yr (controversial)
- operative
  - femoral or pelvic osteotomy (>8 yr of age or severe)
    - prognosis better in males, <6 yr, <50% of femoral head involved, abduction >30°
  - 60% of involved hips do not require operative intervention
  - natural history is early onset OA and decreased ROM

Osgood-Schlatter Disease

Definition
- inflammation of patellar ligament at insertion point on tibial tuberosity
- M>F
- age of onset: boys 12-15 yr; girls 8-12 yr

Mechanism
- repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)

Clinical Features
- tender lump over tibial tuberosity
- pain on resisted leg extension
- anterior knee pain exacerbated by jumping or kneeling, relieved by rest

Investigations
- X-ray lateral knee: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

5 Fs that Predispose to Developmental Dysplasia of the Hip
- Family history
- Female
- Frank breech
- First born
- Left hip

Figure 52. Pelvic x-ray and reference lines and angles for assessment of DDH
- Triradiate Cartilage
  - y-shaped epiphyseal plate at junction of ilium, ischium and pubis
- Hilgenreiner’s Line
  - Line running between triradiate cartilages
- Perkin’s Line
  - Line through lateral margin of acetabulum, perpendicular to Hilgenreiner’s Line
- Shenton’s Line
  - Arced line along inferior border of femoral neck and superior margin of obturator foramen
- Acetabular Index
  - Angle between Hilgenreiner’s Line and line from triradiate cartilage to point on lateral margin of acetabulum

Most common in adolescent athletes, especially jumping/sprinting sports
Children diagnosed with coxa plana <6 yr of age have improved prognosis
Treatment
- benign, self limited condition, does not resolve until growth halts
- non-operative (majority)
  - may restrict activities such as basketball or cycling
  - NSAIDs, rest, flexibility, isometric strengthening exercises
  - casting if symptoms do not resolve with conservative management
- operative: ossicle excision in refractory cases (patient is skeletally mature with persistent symptoms)

Congenital Talipes Equinovarus (Club Foot)

Definition
- congenital foot deformity
- muscle contractures resulting in CAVE deformity
- bony deformity: talar neck medial and plantar deviated; varus calcaneus and rotated medially around talus; navicular and cuboid medially displaced
- 1-2/1,000 newborns, 50% bilateral, occurrence M>F, severity F>M

Etiology
- intrinsic causes (neurologic, muscular, or connective tissue diseases) vs. extrinsic (intrauterine growth restriction); may be idiopathic, neurogenic, or syndrome-associated
- fixed deformity

Physical Exam
- examine hips for associated DDH
- examine knees for deformity
- examine back for dysraphism (unfused vertebral bodies)

Treatment
- largely non-operative via Ponseti Technique (serial manipulation and casting)
  - correct deformities in CAVE order
    - change strapping/cast q1-2wk
    - surgical release in refractory case (rare)
      - delayed until 3-4 mo of age
  - 3 yr recurrence rate = 5-10%
  - mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf muscle atrophy

Scoliosis

Definition
- lateral curvature of spine with vertebral rotation
- age: 10-14 yr
- more frequent and more severe in females

Etiology
- idiopathic: most common (90%)
- congenital: vertebrae fail to form or segment
- neuromuscular: UMN or LMN lesion, myopathy
- postural: leg length discrepancy, muscle spasm
- other: osteochondrodystrophies, neoplastic, traumatic

Clinical Features
- ± back pain
- primary curve where several vertebrae affected
- secondary curves above and below fixed 1° curve to try and maintain normal position of head and pelvis
- asymmetric shoulder height when bent forward
- Adam’s test: rib hump when bent forward
- prominent scapulae, creased flank, asymmetric pelvis
- associated posterior midline skin lesions in neuromuscular scolioses
  - café-au-lait spots, dimples, neurofibromas
  - axillary freckling, hemangiomas, hair patches
- associated pes cavus or leg atrophy
- apparent leg length discrepancy

Investigations
- X-ray: 3-foot standing, AP, lateral
  - measure curvature: Cobb angle
  - may have associated kyphosis
**Bone Tumours**

- primary bone tumours are rare after 3rd decade
- metastases to bone are relatively common after 3rd decade

**Clinical Features**

- malignant (primary or metastasis): local pain and swelling (wk – mo), worse on exertion and at night, ± soft tissue mass
- benign: usually asymptomatic
- minor trauma often initiating event that calls attention to lesion

**Table 24. Distinguishing Benign from Malignant Bone Lesions on X-Ray**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No periosteal reaction</td>
<td>Acute periosteal reaction</td>
</tr>
<tr>
<td></td>
<td>• Codman’s triangle (Figure 55)</td>
</tr>
<tr>
<td></td>
<td>• &quot;Onion skin&quot;</td>
</tr>
<tr>
<td></td>
<td>• “Sunburst”</td>
</tr>
<tr>
<td>Thick endosteal reaction</td>
<td>Broad border between lesion and normal bone</td>
</tr>
<tr>
<td>Well developed bone formation</td>
<td>Varied bone formation</td>
</tr>
<tr>
<td>Intraosseous and even calcification</td>
<td>Extraosseous and irregular calcification</td>
</tr>
</tbody>
</table>

*Adapted from: Buckhoult RW, Heckman JD. Rockwood & Green’s Fractures in Adults. Volume 1. Philadelphia: Lippincott Williams & Wilkins, 2001. p558*

**Diagnosis**

- malignancy is suggested by rapid growth, warmth, tenderness, lack of sharp definition
- staging should include
  - blood work including liver enzymes
  - CT chest
  - bone scan
  - bone biopsy
    - should be referred to specialized centre prior to biopsy
    - classified into benign, benign aggressive, and malignant
  - MRI of affected bone

**Benign Active Bone Tumours**

**BONE-FORMING TUMOURS**

**Osteoid Osteoma**

- bone tumour arising from osteoblasts
- peak incidence in 2nd and 3rd decades, M:F = 2:1
- proximal femur and tibia diaphysis most common locations
- not known to metastasize
- radiographic findings: small, round radiolucent nidus (<1.5 cm) surrounded by dense sclerotic bone ("bull’s eye")
- symptoms: produces severe intermittent pain from prostaglandin secretion and COX1/2 expression, mostly at night (diurnal prostaglandin production), thus is characteristically relieved by NSAIDs
- treatment: NSAIDs for night pain; surgical resection of nidus

**FIBROUS LESIONS**

**Fibrous Cortical Defect**

- or non-ossifying fibroma; fibrous bone lesion
- most common benign bone tumour in children, typically asymptomatic and an incidental finding
- occur in as many as 35% of children, peak incidence between 2-25 yr old; higher prevalence in males
- femur and proximal tibia most common locations, 50% of patients have multiple defects that are usually bilateral, symmetrical
- radiographic findings: diagnostic, metaphyseal eccentric 'bubbly' lytic lesion near physis; thin, smooth/lobulated, well-defined sclerotic margin
- treatment: most lesions resolve spontaneously
Osteochondroma
- cartilage capped bony tumour
- 2nd and 3rd decades, M:F = 1.8:1
- most common of all benign bone tumours – 45%
- 2 types: sessile (broad based and increased risk of malignant degeneration) vs. pedunculated (narrow stalk)
- metaphysis of long bone near tendon attachment sites (usually distal femur, proximal tibia, or proximal humerus)
- radiographic findings: cartilage-capped bony spur on surface of bone (“mushroom” on x-ray)
- may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
- generally very slow growing and asymptomatic unless impinging on neurovascular structure (‘painless mass’)
  - growth usually ceases when skeletal maturity is reached
- malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)
- treatment: typically observation; surgical excision if symptomatic

Enchondroma
- hyaline cartilage tumour; majority asymptomatic, presenting as incidental finding or pathological fracture
- 2nd and 3rd decades
- 60% occur in the small tubular bones of the hand and foot; others in femur (20% - Figure 56), humerus, ribs
- benign cartilaginous growth, an abnormality of chondroblasts, develops in medullary cavity
  - single/multiple enlarged rarefied areas in tubular bones
  - lytic lesion with sharp margination and irregular central calcification (stippled/punctate/popcorn appearance)
  - malignant degeneration to chondrosarcoma occurs in 1-2% (pain in absence of pathologic fracture is an important clue)
  - not known to metastasize
  - treatment: observation with serial x-rays; surgical curettage if symptomatic or lesion grows

CYSTIC LESIONS

Unicameral/Solitary Bone Cyst
- most common cystic lesion; serous fluid-filled lesion
- children and young adults, peak incidence during first 2 decades, M:F = 2:1
- proximal humerus and femur most common
- symptoms: asymptomatic, or local pain; complete pathological fracture (50% of presentations) or incidental detection
- radiographic findings: lytic translucent area on metaphyseal side of growth plate, cortex thinned/expanded; well-defined lesion
- treatment: aspiration followed by steroid injection; curettage ± bone graft indicated if re-fracture likely

Benign Aggressive Bone Tumours

Giant Cell Tumours/Aneurysmal Bone Cyst/Osteoblastoma
- affects patients of skeletal maturity, peak 3rd decade
- osteoblastoma: found in the distal femur, proximal tibia, distal radius, sacrum, tarsal bones, spine
- giant cell tumour: pulmonary metastases in 3%
- aneurysmal bone cysts (Figure 57): either solid with fibrous/granular tissue, or blood-filled
- radiographic findings
  - giant cell tumour: eccentric lytic lesions in epiphyses adjacent to subchondral bone; may break through cortex; T2 MRI enhances fluid within lesion (hyper-intense signal)
  - aneurysmal bone cyst: expanded with honeycomb shape
  - osteoblastoma: often nonspecific; calcified central nidus (>2 cm) with radiolucent halo and sclerosis
- symptoms: local tenderness and swelling, pain may be progressive (giant cell tumours), ± symptoms of nerve root compression (osteoblastoma)
- 15% recur within 2 yr of surgery

Treatment
- intralesional curettage ± bone graft or cement
- wide local excision of expendable bones
Malignant Bone Tumours

Table 25. Most Common Malignant Tumour Types for Age

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No periosteal reaction</td>
<td>Acute periosteal reaction</td>
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<td>Intraosseous and even calcification</td>
<td>Extraosseous and irregular calcification</td>
</tr>
</tbody>
</table>


Osteosarcoma
- malignant bone tumour
- most frequently diagnosed in 2nd decade of life (60%), 2nd most common primary malignancy in adults
- history of Paget’s disease (elderly patients), previous radiation treatment
- predilection for sites of rapid growth: distal femur (45% - Figure 58), proximal tibia (20%), and proximal humerus (15%)
  - invasive, variable histology; frequent metastases without treatment (lung most common)
- painful symptoms: progressive pain, night pain, poorly defined swelling, decreased ROM
- radiographic findings
  - characteristic periosteal reaction: Codman’s triangle (Figure 55) or “sunburst” spicule formation (tumour extension into periosteum)
  - destructive lesion in metaphysis may cross epiphyseal plate
- management: complete resection (limb salvage, rarely amputation), neo-adjuvant chemo; bone scan – rule out skeletal metastases, CT chest – rule out pulmonary metastases
- prognosis: 70% survival (high-grade); 90% survival (low-grade)

Chondrosarcoma
- malignant chondrogenic tumour
- primary (2/3 cases)
  - previous normal bone, patient >40 yr; expands into cortex to cause pain, pathological fracture
- secondary (1/3 cases)
  - malignant degeneration of pre-existing cartilage tumour such as enchondroma or osteochondroma
  - age range 25-45 yr, better prognosis than primary chondrosarcoma
- symptoms: progressive pain, uncommonly palpable mass
- radiographic findings: in medullary cavity, irregular “popcorn” calcification (Figure 59)
- treatment: unresponsive to chemotherapy, treat with aggressive surgical resection + reconstruction; regular follow-up X-rays of resection site and chest
- prognosis: 10 yr survival 90% for low-grade, 20-40% for high-grade

Ewing’s Sarcoma
- malignant, small round cell sarcoma
- most occur between 5-25 yr old
- florid periosteal reaction in metaphyses of long bone with diaphyseal extension
- metastases frequent without treatment
- signs/symptoms: presents with pain, mild fever, erythema, and swelling; anemia, increased WBC, ESR, LDH (mimics an infection)
- radiographic findings: moth-eaten appearance with periosteal lamellated pattern (“onion-skinning”)
- treatment: resection, chemotherapy, radiation
- prognosis – 70% survival, worst prognostic factor is distant metastases

Multiple Myeloma
- proliferation of neoplastic plasma cells
- most common primary malignant tumour of bone in adults (~43%)
- 90% occur in people >40 yr old, M:F = 2:1; twice as common in African-Americans
- signs/symptoms: localized bone pain (cardinal early symptom), compression/pathological fractures, renal failure, nephritis, high incidence of infections (e.g. pyelonephritis/pneumonia), systemic (weakness, weight loss, anorexia)
- labs: anemia, thrombocytopenia, increased ESR, hypercalcemia, increased Cr
- radiographic findings: multiple, “punched-out” well-demarcated lesions, no surrounding sclerosis, marked bone expansion
- diagnosis
  - serum/urine immunoelectrophoresis (monoclonal gammopathy)
  - CT-guided biopsy of lytic lesions at multiple bony sites
Common Medications

- treatment: chemotherapy, bisphosphonates, radiation, surgery for symptomatic lesions or impending fractures – debulking, internal fixation
- prognosis: 5 yr survival 30%; 10 yr survival 11%
- see Hematology, H49

Bone Metastases
- most common cause of bone lesions in adults; typically age >40
- 2/3 from breast or prostate; also consider thyroid, lung, kidney
- usually osteolytic; prostate occasionally osteoblastic
- may present with mechanical pain and/or night pain, pathological fracture, hypercalcemia
- bone scan for MSK involvement, MRI for spinal involvement may be helpful
- treatment: pain control, bisphosphonates, stabilization of impending fractures if Mirel’s Criteria >8 (ORIF, IM rod, bone cement)

Table 26. Mirel’s Criteria for Impending Fracture Risk and Prophylactic Internal Fixation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Upper arm</td>
<td>Lower extremity</td>
</tr>
<tr>
<td>Peritrochanteric</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Lesion</td>
<td>Blastic</td>
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<tr>
<td>Mixed</td>
<td></td>
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<tr>
<td>Lytic</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>&lt;1/3 bone diameter</td>
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<tr>
<td>1/3-2/3 diameter</td>
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<tr>
<td>&gt;2/3 diameter</td>
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</tbody>
</table>

Common Medications

Table 27. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefazolin (Ancef*)</td>
<td>1-2 g IV q8h</td>
<td>Prophylactically before orthopedic surgery</td>
<td>First generation cephalosporin; do not use with penicillin allergy</td>
</tr>
<tr>
<td>heparin</td>
<td>5000 IU SC q12h</td>
<td>To prevent venous thrombosis and pulmonary emboli</td>
<td>Monitor platelets, follow PTT which should rise 1.5-2x</td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dalteparin (Fragmin®)</td>
<td>5000 IU SC OD</td>
<td>DVT prophylaxis especially in hip and knee surgery</td>
<td>Fixed dose, no monitoring, improved bioavailability, increased bleeding rates</td>
</tr>
<tr>
<td>enoxaparin (Lovenox®)</td>
<td>30-40 mg SC bid</td>
<td></td>
<td></td>
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<tr>
<td>fondaparinux (Arixtra®)</td>
<td>2.5 mg SC OD</td>
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<tr>
<td>oral anticoagulants</td>
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<tr>
<td>dabigatran (Pradaxa®)</td>
<td>110 mg PO x1 then 220 mg PO OD</td>
<td>DVT prophylaxis especially TKA and THA</td>
<td>Predictable, no monitoring, oral administration; no antidote</td>
</tr>
<tr>
<td>rivaroxaban (Xarelto®)</td>
<td>10 mg PO OD</td>
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<tr>
<td>apixaban</td>
<td>2.5 mg PO bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>midazolam (Versed®)</td>
<td>0.02-0.04 mg/kg IV</td>
<td>Conscious sedation for short procedures</td>
<td>Medication used during fracture reduction – monitor for respiratory depression</td>
</tr>
<tr>
<td>fentanyl (Sublimaze®)</td>
<td>0.5-3 µg/kg IV</td>
<td>Conscious sedation for short procedures</td>
<td>Short acting anesthetic used in conjunction with midazolam (Versed®)</td>
</tr>
<tr>
<td>triamcinolone (Aristocort®)</td>
<td>0.5-1 mL of 25 mg/mL</td>
<td>Suspension (injected into inflamed joint or bursa); amount varies by joint size</td>
<td>Potent anti-inflammatory effect; increased pain for 24 h, rarely causes fat necrosis and skin depigmentation</td>
</tr>
<tr>
<td>naproxen (Aleve®, Naprosyn®)</td>
<td>250-500 mg bid</td>
<td>Pain due to inflammation, arthritis, soft tissue injury</td>
<td>NSAID, may cause gastric erosion and bleeding</td>
</tr>
<tr>
<td>misoprostol (Cytotec®)</td>
<td>200 µg qid</td>
<td>Prophylaxis of HO after THA</td>
<td>Use with indomethacin</td>
</tr>
<tr>
<td>indomethacin (Indocid®)</td>
<td>25 mg PO tid</td>
<td>Prophylaxis of HO after THA</td>
<td>Use with misoprostol</td>
</tr>
<tr>
<td>ibuprofen (Advil®, Motrin®)</td>
<td>200-400 mg tid</td>
<td>Pain (including post-operative), inflammation (including arthritis)</td>
<td>NSAID, may cause gastric erosion and bleeding</td>
</tr>
<tr>
<td>propofol (Diprivan®)</td>
<td>1-2 mg/kg IV maintenance 0.5 mg/kg</td>
<td>Conscious sedation for short procedures</td>
<td>Short acting anesthetic often used in conjunction with fentanyl (Sublimaze®)</td>
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<tr>
<td>Chapter Title</td>
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<td>Acronyms</td>
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<td>Basic Anatomy Review</td>
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<td>Ear</td>
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<td>Head and Neck</td>
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<td>Anatomical Triangles of the Neck</td>
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<td>Differential Diagnoses of Common Presentations</td>
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<tr>
<td>Dizziness</td>
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<td>Nasal Obstruction</td>
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<td>Normal Hearing Physiology</td>
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<td>Types of Hearing Loss</td>
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<td>Pure Tone Audiometry</td>
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<td>Auditory Brainstem Response</td>
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<td>Tinnitus</td>
<td>15</td>
<td></td>
<td></td>
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<tr>
<td>Diseases of the External Ear</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerumen Impaction</td>
<td></td>
<td></td>
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<td>Exostoses</td>
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<td>Diseases of the Middle Ear</td>
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<td>Acute Otitis Media and Otitis Media with Effusion</td>
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<td>Otosclerosis</td>
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<tr>
<td>Diseases of the Inner Ear</td>
<td>19</td>
<td></td>
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<td>Congenital Sensorineural Hearing Loss</td>
<td></td>
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<td>Drug Ototoxicity</td>
<td></td>
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<td>Noise-Induced Sensorineural Hearing Loss</td>
<td></td>
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<td>Temporal Bone Fractures</td>
<td></td>
<td></td>
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<tr>
<td>Facial Nerve (CN VII) Paralysis</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>23</td>
<td></td>
<td></td>
</tr>
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<td>Allergic Rhinitis (i.e. Hay Fever)</td>
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<td>Vasomotor Rhinitis</td>
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<td>Rhinosinusitis</td>
<td>24</td>
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<tr>
<td>Acute Bacterial Rhinosinusitis</td>
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<td></td>
<td></td>
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<tr>
<td>Chronic Rhinosinusitis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Epistaxis</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoarseness</td>
<td>28</td>
<td></td>
<td></td>
</tr>
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<td>Acute Laryngitis</td>
<td></td>
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<td>Laryngeal Carcinoma</td>
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<td>Salivary Glands</td>
<td>30</td>
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<td>Parotid Gland Neoplasms</td>
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<td>Neck Masses</td>
<td>31</td>
<td></td>
<td></td>
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<tr>
<td>Approach to a Neck Mass</td>
<td></td>
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<td></td>
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<tr>
<td>Evaluation</td>
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<td>32</td>
<td></td>
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<td>Brachial Cleft Cysts/Sinuses/Fistulae</td>
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<td></td>
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<td>Lymphatic, Venous, or Mixed Venolymphatic Malformations</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms of the Head and Neck</td>
<td>34</td>
<td></td>
<td></td>
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<td>Thyroid Carcinoma</td>
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<td>Pediatric Otolaryngology</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Otitis Media</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Tonsillectomy</td>
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<td>Airway Problems in Children</td>
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<td>Signs of Airway Obstruction</td>
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<td>Acute Laryngotraceobronchitis (Croup)</td>
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<td>Laryngomalacia</td>
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<td>Deep Neck Space Infection</td>
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<td>Common Medications</td>
<td>46</td>
<td></td>
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</tr>
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<td>References</td>
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**Acronyms**

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<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ABR</td>
<td>auditory brainstem response</td>
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<tr>
<td>AC</td>
<td>air conduction</td>
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<td>ADOM</td>
<td>acute otitis media</td>
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<tr>
<td>Baha</td>
<td>bone anchored hearing aid</td>
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<tr>
<td>BC</td>
<td>bone conduction</td>
</tr>
<tr>
<td>CHL</td>
<td>conductive hearing loss</td>
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<tr>
<td>CPA</td>
<td>cerebellopontine angle</td>
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<tr>
<td>EAC</td>
<td>external auditory canal</td>
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<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>FAP</td>
<td>familial adenomatous polyposis</td>
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<tr>
<td>FESS</td>
<td>functional endoscopic sinus surgery</td>
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<tr>
<td>FNA</td>
<td>fine needle aspiration</td>
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<td>GERD</td>
<td>gastroesophageal reflux disease</td>
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<tr>
<td>GPA</td>
<td>granulomatosis with polyangiitis</td>
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<td>HbN</td>
<td>head and neck</td>
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<tr>
<td>HL</td>
<td>hearing loss</td>
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<tr>
<td>HPV</td>
<td>human papillomavirus</td>
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<td>INCS</td>
<td>intranasal corticosteroids</td>
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<td>middle ear effusion</td>
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<td>MBI</td>
<td>middle ear inflammation</td>
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<td>OME</td>
<td>otitis media with effusion</td>
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<td>OSA</td>
<td>obstructive sleep apnea</td>
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<td>RA</td>
<td>rheumatoid arthritis</td>
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<td>SCC</td>
<td>squamous cell carcinoma</td>
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<td>SCM</td>
<td>sternocleidomastoid</td>
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<td>SNHL</td>
<td>sensorineural hearing loss</td>
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<tr>
<td>SRT</td>
<td>speech reception threshold</td>
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<tr>
<td>TEF</td>
<td>tracheoesophageal fistula</td>
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<tr>
<td>TM</td>
<td>tympanic membrane</td>
</tr>
<tr>
<td>TNM</td>
<td>tumour, node, metastases</td>
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<tr>
<td>URTI</td>
<td>upper respiratory tract infection</td>
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</table>

**Basic Anatomy Review**

**Ear**

![Surface anatomy of the external ear; anatomy of ear](image)

Figure 1. Surface anatomy of the external ear; anatomy of ear

![Tympanic membrane viewed through speculum](image)

Figure 2. Normal appearance of right tympanic membrane on otoscopy
**Nose**

![Nasal Anatomy Diagram](image)

Figure 3. Nasal anatomy

![Nasal Septum Diagram](image)

Figure 4. Nasal septum and its arterial supply (see *Epistaxis*, OT26 for detailed blood supply)

![Paranasal Sinuses Diagram](image)

Figure 5. Anatomy of the four paranasal sinuses: maxillary, ethmoid, sphenoid and frontal

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**Throat**

![Larynx Diagram](image)

Figure 6. Anatomy of a normal larynx; superior view of larynx on indirect laryngoscopy
Head and Neck

Figure 7. Extratemporal segment of facial nerve
Branches of facial nerve (in order from superior to inferior)
By M. Romanova 2010

Figure 8. Blood supply to the face
Branches of the external carotid artery (in order from inferior to superior)
Some Angry Lady Figured Out PMS

Figure 9. Anatomy of the neck
By Inessa Stanishevskaya 2012 after © Katsynya Proshunier 2014
Anatomical Triangles of the Neck

Anterior triangle
• bounded by anterior border of SCM, midline of neck, and lower border of mandible
• divided into:
  - submental triangle: bounded by both anterior belly of digastric and hyoid bone
  - digastric triangle: bounded by anterior and posterior bellies of digastric and inferior border of mandible
  - carotid triangle: bounded by sternocleidomastoid, anterior border of omohyoid, and posterior belly of digastric
  - contains tail of parotid, submandibular gland, hypoglossal nerve, carotid bifurcation, and lymph nodes

Posterior triangle
• bounded by posterior border of sternocleidomastoid, anterior border of trapezius, and middle third of clavicle
• divided into:
  - occipital triangle: superior to posterior belly of omohyoid
  - subclavian triangle: inferior to posterior belly of omohyoid
  - contains: spinal accessory nerve and lymph nodes

---

Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of Neck

<table>
<thead>
<tr>
<th>Nodal Group/Level</th>
<th>Location</th>
<th>Drainage</th>
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<tbody>
<tr>
<td>1. Suboccipital (S)</td>
<td>Base of skull, posterior</td>
<td>Posterior scalp</td>
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<tr>
<td>2. Retroauricular (R)</td>
<td>Superficial to mastoid process</td>
<td>Scalp, temporal region, external auditory meatus, posterior pinna</td>
</tr>
<tr>
<td>3. Parotid-preauricular (P)</td>
<td>Anterior to ear</td>
<td>External auditory meatus, anterior pinna, soft tissue of frontal and temporal regions, root of nose, eyelids, palpebral conjunctiva</td>
</tr>
<tr>
<td>4. Submental (Level IA)</td>
<td>Anterior bellies (midline) of digastric muscles, tip of mandible, and hyoid bone</td>
<td>Floor of mouth, anterior tongue, anterior mandibular alveolar ridge, lower lip</td>
</tr>
<tr>
<td>5. Submandibular (Level IB)</td>
<td>Anterior belly of digastic muscle, stylohyoid muscle, body of mandible</td>
<td>Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland</td>
</tr>
<tr>
<td>6. Upper jugular (Levels IIA and IIB)</td>
<td>Skull base to inferior border of hyoid bone along SCM muscle</td>
<td>Oral cavity, nasal cavity, naso/oro/hypopharynx, larynx, parotid glands</td>
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<tr>
<td>7. Middle jugular (Level III)</td>
<td>Inferior border of hyoid bone to inferior border of cricoid cartilage along SCM muscle</td>
<td>Oral cavity, naso/oro/hypopharynx, larynx</td>
</tr>
<tr>
<td>8. Lower jugular* (Level IV)</td>
<td>Inferior border of cricoid cartilage to clavicle along SCM muscle</td>
<td>Hypopharynx, thyroid, cervical esophagus, larynx</td>
</tr>
<tr>
<td>9. Posterior triangle** (Levels VA and VB)</td>
<td>Posterior border of SCM, anterior border of trapezius, from skull base to clavicle</td>
<td>Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck</td>
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<tr>
<td>10. Anterior compartment*** (Level VI)</td>
<td>Hyoid bone (midline) to suprasternal notch between the common carotid arteries</td>
<td>Thyroid gland, glottic and subglottic larynx, apex of inferior cornus cervical esophagus</td>
</tr>
</tbody>
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*Virchow node: left lower jugular (level IV) supraclavicular node
**Includes some supravacuicular nodes
***Includes pretracheal, pre-cricoid, paratracheal, and prethyroidal nodes
Differential Diagnoses of Common Presentations

**Dizziness**

- **True Vertigo**
  - Peripheral (Vestibular)
    - Benign paroxysmal positional vertigo (BPPV)
    - Labyrinthitis
    - Ménière's disease
    - Vestibular neuritis
    - Autoimmune inner ear disease
    - Cholesteatoma
    - Ototoxic drug exposure
    - Perilymph fistula
    - Recurrent vestibulopathy
    - Superior semicircular canal dehiscence
    - Temporal bone fracture
  - Central
    - Cerebrovascular disorders
    - Vertebrobasilar insufficiency
    - Transient ischemic attacks
    - Wallenberg's syndrome
    - Cerebellar infarction
    - Migraineus vertigo
    - Multiple sclerosis
    - Inflammation
    - Meningitis
    - Cerebellar abscess
    - Trauma: cerebellar contusion
    - Toxic: alcohol, hypnотics, drugs
    - Tumours
    - CPA tumours
    - Posterior fossa tumours
    - Glomus tumour

- **Non-Vertiginous**
  - Organic Diseases
    - Cardiac
      - Arrhythmias
      - Aortic stenosis
      - Vasovagal
    - Orthostatic hypotension
    - Anemia
    - Peripheral neuropathy
    - Visual impairment
  - Functional
    - Depression
    - Anxiety
    - Panic disorder
    - Personality disorder
    - Phobic dizziness

True nystagmus and vertigo caused by a peripheral lesion will never last longer than a few weeks, due to compensation from the cerebellum (unless there is a history of cerebellar ischemia/stroke). Central lesions do not compensate, therefore nystagmus and vertigo will persist.

5 “D”s of Vertebrobasilar Insufficiency
- Drop attacks
- Diplopia
- Dysarthria
- Dizziness
- Dysphagia

**Otalgia**

- **External Ear**
  - Infection
    - Auricular cellulitis
    - External canal abscess
    - Herpes simplex/zoster
    - Otis externa
  - Trauma
    - Burns
    - Frostbite
    - Hematoma
    - Lacerations
    - Other
    - Cerumen impaction
    - Foreign body
    - Ne. plasm of external canal

- **Middle Inner Ear**
  - Infection
    - AOM
    - Mastoiditis
    - Myringitis
    - Otis media with effusion
    - Skull base infections
  - Trauma
    - Barotrauma
    - Traumatic perforation
    - Other
    - Cholesteatoma
    - Neoplasm
    - Wegener's granulomatosis

- **Referred Pain**
  - Infection
    - Ramsay Hunt syndrome
    - Tonsillitis
    - Tracheitis
  - Trauma
    - Cervical arthritus
    - Thyroditis
  - Other
    - Glossopharyngeal neuralgia
    - Neoplasm of oral cavity, larynx, pharynx
    - Teeth
    - TMJ syndrome
    - Trismus

Figure 11. Differential diagnosis of dizziness

Figure 12. Differential diagnosis of otalgia
**Hearing Loss**

**Conductive**
- External Ear
  - Impacted cerumen
  - Otitis externa
  - Foreign body
  - Keratosis obturans
  - Exostoses, osteomas
  - Tumour of canal
  - Congenital stenosis/microtia
- Middle Ear
  - AOM
  - Otitis media with effusion
  - Otosclerosis
  - Tympanosclerosis
  - Eustachian tube dysfunction
  - Cholesteatoma
  - Ossicular malformations
  - Ossicular discontinuity
  - Hernytaurix
  - Middle ear tumour

**Sensorineural**
- Genetic
  - Non-syndrome associated
  - Syndrome associated
  - Intrauterine infections (i.e. TORCH)
  - Teratogens
  - Perinatal hypoxia
  - Prematurity/low birth weight
  - Hyperbilirub nema
- Presbycusis
  - Noise-induced
  - Menière’s disease
  - Labyrinthitis
  - Sudden SNHL
  - Autoimmune inner ear disease
  - Ototoxic drug exposure
  - Temporal bone trauma
  - Infectious
    - Postmeningitis
    - Syphilis
    - Viral: mumps, CMV, HSV
  - Neoplastic
    - Acoustic neuroma
    - CPA tumours
    - Vascular occlusion
    - Auditory neuropathy

Common causes in bold

**Figure 13. Differential diagnosis of hearing loss**

**Tinnitus**

**Subjective**
- Only heard by patient (common)
  - Otologic
    - Presbycusis
    - Noise-induced hearing loss
    - Otitis media with effusion
    - Menière’s disease
    - Otosclerosis
    - Cerumen
    - Foreign body against TM
    - Drugs
      - ASA
      - NSAIDs
      - Aminoglycosides
      - Ant hypertensives
      - Heavy metals
      - Metabolic
        - Hyper/hypothyroidism
        - Hyperlipidemia
      - Vitamin A, B, Zinc deficiency
      - Neurologic
        - Head trauma
        - Multiple sclerosis
        - CPA tumours
        - Psychiatric
        - Anxiety
        - Depression

**Objective**
- Can be heard by others (rare)
  - Vascular
    - Benign intracranial hypertension
      - Arteriovenous malformation
      - Glomus tympanicum
      - Glomus jugulare
    - Arterial bruits:
      - High-riding carotid artery
      - Vascular loop
      - Persistent stapedial artery
      - Carotid stenosis
    - Venous hum:
      - High jugular bulb
      - Hypertension
      - Hyper/hypothyroidism
  - Mechanical
    - Patulous eustachian tube
    - Palatal myoclonus
    - Stapedius muscle spasm

Common causes in bold

**Figure 14. Differential diagnosis of tinnitus**
### Nasal Obstruction

**Table 2. Differential Diagnosis of Nasal Obstruction**

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<td>Choanal atresia</td>
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<td>Foreign bodies</td>
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<td>Enlarged turbinates</td>
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<td>Tumour</td>
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</tr>
<tr>
<td>Benign: polyps, inverting papilloma</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td></td>
</tr>
<tr>
<td>Esthesioneuroblastoma (olfactory neuroblastoma)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Nasal Septum</strong></td>
<td><strong>Nasal Septum</strong></td>
</tr>
<tr>
<td>Septal deviation</td>
<td>Septal deviation</td>
</tr>
<tr>
<td>Septal hematoma/abscess</td>
<td>Septal hematoma/abscess</td>
</tr>
<tr>
<td>Dislocated septum</td>
<td>Dislocated septum</td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td></td>
</tr>
<tr>
<td>Adenoid hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Tumour</td>
<td></td>
</tr>
<tr>
<td>Benign: juvenile nasopharyngeal angiofibroma (JNA), polyps</td>
<td></td>
</tr>
<tr>
<td>Malignant: nasopharyngeal carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
</tr>
<tr>
<td>Granulomatous diseases, diabetes vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

### Hoarseness

**Table 3. Differential Diagnosis of Hoarseness**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Acute/chronic laryngitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Laryngotracheobronchitis (croup)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>GERD</td>
</tr>
<tr>
<td></td>
<td>Vocal cord polyps/nodules</td>
</tr>
<tr>
<td></td>
<td>Lifestyle: smoking, chronic EtOH use</td>
</tr>
<tr>
<td>Trauma</td>
<td>External laryngeal trauma</td>
</tr>
<tr>
<td></td>
<td>Endoscopy and endotracheal tube (e.g. intubation granuloma)</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Benign tumour</td>
</tr>
<tr>
<td></td>
<td>Papillomas (HPV infection)</td>
</tr>
<tr>
<td></td>
<td>Minor salivary gland tumours</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Cysts</td>
<td>Retention cysts</td>
</tr>
<tr>
<td>Systemic</td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Virilization</td>
</tr>
<tr>
<td>Neurologic: vocal cord paralysis due to superior ± recurrent laryngeal nerve injury</td>
<td>Central lesions</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular accident (CVA)</td>
</tr>
<tr>
<td></td>
<td>Head injury</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis (MS)</td>
</tr>
<tr>
<td></td>
<td>Skull base tumours</td>
</tr>
<tr>
<td></td>
<td>Arnold-Chiari malformation</td>
</tr>
<tr>
<td></td>
<td>Peripheral lesions</td>
</tr>
<tr>
<td></td>
<td>Unilateral</td>
</tr>
<tr>
<td></td>
<td>Lung malignancy</td>
</tr>
<tr>
<td>Functional</td>
<td>Psychogenic aphonyia (hysterical aphonyia)</td>
</tr>
<tr>
<td>Congenital</td>
<td>Laryngomalacia</td>
</tr>
<tr>
<td></td>
<td>Laryngeal web</td>
</tr>
<tr>
<td></td>
<td>Laryngeal atresia</td>
</tr>
</tbody>
</table>

Lung malignancy is the most common cause of extralaryngeal vocal cord paralysis.
Neck Mass

Figure 15. Differential diagnosis of a neck mass

Hearing

Normal Hearing Physiology

- **conductive pathway** (EAC to cochlea): air conduction of sound down the EAC → vibration of TM → sequential vibration of middle ear ossicles (malleus, incus, stapes) → transmission of amplified vibrations from stapes footplate to the oval window of the cochlea → transmitted vibrations via cochlear fluid create movement along the basilar membrane within the cochlea

- **neural pathway** (nerve to brain): basilar membrane vibration stimulates overlying hair cells in the organ of Corti → stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII → cochlear nucleus → superior olivary nucleus → lateral lemniscus → inferior colliculus → Sylvian fissure of temporal lobe

Types of Hearing Loss

1. **Conductive Hearing Loss**
   - conduction of sound to the cochlea is impaired
   - can be caused by external and middle ear disease

2. **Sensorineural Hearing Loss**
   - defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
   - can be caused by disease of the inner ear (cochlea), acoustic nerve (CN VIII), brainstem, or cortex

3. **Mixed Hearing Loss**
   - combination of conductive and sensorineural hearing loss

Auditory Acuity

- whispered-voice test: mask one ear and whisper into the other tuning fork tests (see Table 4; audiogram is of greater utility)
  - Rinne test
    - 512 Hz tuning fork is struck and held firmly on mastoid process to test bone conduction (BC); the tuning fork is then placed beside the pinna to test air conduction (AC)
    - If AC > BC → positive Rinne (normal)
  - Weber test
    - 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative) or is lateralized to one side (Weber right, Weber left)
    - can place vibrating fork on patient’s chin while they clench their teeth, or directly on teeth to elicit more reliable response
    - will only lateralize if difference in hearing loss between ears is > 6 dB

Order of the Neural Pathway (with corresponding waves on ABR)

E COUL
  - Eighth cranial nerve (I – II)
  - Cochlear nucleus (III)
  - Superior olivary nucleus
  - Lateral lemniscus (IV – V)
  - Inferior colliculus

The Weber test is more sensitive in detecting conductive hearing loss than the Rinne test.
Table 4. The Interpretation of Tuning Fork Tests

<table>
<thead>
<tr>
<th>Examples</th>
<th>Weber</th>
<th>Rinne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or bilateral sensorineural hearing loss</td>
<td>Central</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided conductive hearing loss, normal left ear</td>
<td>Lateralizes to right</td>
<td>BC &gt; AC (−) right</td>
</tr>
<tr>
<td>Right-sided sensorineural hearing loss, normal left ear</td>
<td>Lateralizes to left</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided severe sensorineural hearing loss or dead right ear, normal left ear</td>
<td>Lateralizes to left</td>
<td>BC &gt; AC (−) right*</td>
</tr>
</tbody>
</table>

*A vibrating tuning fork on the mastoid stimulates the cochlea bilaterally, therefore in this case the left cochlea is stimulated by the Rinne test on the right (e.g. a false negative test). These tests are not valid if the ear canals are obstructed with cerumen (e.g. will create conductive loss).

**Pure Tone Audiometry**

- a threshold is the lowest intensity level at which a patient can hear the tone 50% of the time
- thresholds are obtained for each ear at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz
- air conduction thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function
- bone conduction thresholds are obtained with bone conduction oscillators which bypass the outer and middle ear

**Degree of Hearing Loss**

- determined on basis of the pure tone average (PTA) at 500, 1000, and 2000 Hz

**Figure 16** Types of hearing loss and associated audiograms of a left ear

**PURE TONE PATTERNS**

1. **Conductive Hearing Loss** (Figure 16B and 16C)
   - BC in normal range
   - AC outside of normal range
   - gap between AC and BC thresholds >10 dB (an air-bone gap)

2. **Sensorineural Hearing Loss** (Figure 16D and 16E)
   - both air and bone conduction thresholds below normal
   - gap between AC and BC <10 dB (no air-bone gap)

3. **Mixed Hearing Loss**
   - both air and bone conduction thresholds below normal
   - gap between AC and BC thresholds >10 dB (an air-bone gap)
**Speech Audiometry**

**Speech Reception Threshold**
- lowest hearing level at which patient is able to repeat 50% of two syllable words which have equal emphasis on each syllable (spondee words)
- SRT and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB; if not, suspect a retrocochlear lesion or functional hearing loss
- used to assess the reliability of the pure tone audiometry

**Speech Discrimination Test**
- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at 40 dB above the patient's SRT, therefore degree of hearing loss is taken into account
- rollover effect: a decrease in discrimination as sound intensity increases; typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears, as asymmetry may indicate a retrocochlear lesion
- best predictor of hearing aid response: a poor discrimination score indicates significant neural degeneration and hearing aids may not be the best option for the patient

**Impedance Audiometry**

**Tympanogram**
- the Eustachian tube equalizes the pressure between the external and middle ear
- tympanograms graph the compliance of the middle ear system against a pressure gradient ranging from to –400 to +200 mmH2O
- tympanogram peak occurs at the point of maximum compliance: where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range: –100 to +50 mmH2O

Figure 17. Tympanograms

**Static Compliance**
- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0 3-1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of >2 cc in children and >2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

**Acoustic Stapedial Reflexes**
- stapedius muscle contracts in response to loud sound
- acoustic reflex threshold = 70-100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
  - if reflex is absent without conductive or severe sensorineural loss, suspect CN VII lesion
- acoustic reflex decay test = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
  - normally, little reflex decay occurs at 500 and 1000 Hz
  - with cochlear hearing loss, acoustic reflex thresholds are 25-60 dB
  - with retrocochlear hearing loss (acoustic neuroma), absent acoustic reflexes or marked reflex decay (>50%) within 5 s
Auditory Brainstem Response

- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (see Order of Neural Pathway sidebar on OT9; this test can be used to determine the site of lesion)
- delay in brainstem response suggests cochlear or retrocochlear abnormalities
- does not require volition or co-operation of patient (therefore, of value in children and malingers)

Otoacoustic Emissions

- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- often used in newborn screening
- can be used to uncover normal hearing in malingering patients
- absence of emissions can be due to hearing loss or fluid in the middle ear

Aural Rehabilitation

- dependent on degree of hearing loss, communicative requirements, motivation, expectations, and physical and mental abilities
- negative prognostic factors
  - poor speech discrimination
  - narrow dynamic range (recruitment)
  - unrealistic expectations
- types of hearing aids
  - BTE: behind-the-ear (with occlusive mould or open fit which allows natural sound to pass – for milder hearing losses)
  - ITE: in-the-ear, placed in concha
  - ITC: in-the-canal, placed entirely in ear canal
  - CIC: contained-in-canal, placed deeply in ear canal
  - bone conduction – bone-anchored hearing aid (BAHA): attached to the skull
- contralateral routing of signals (CROS)
- assistive listening devices
  - direct/indirect audio output
  - infrared, FM radio, or induction loop systems
  - telephone, television, or alerting devices
- cochlear implants
  - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
  - for profound bilateral sensorineural hearing loss not rehabilitated with conventional hearing aids
  - established indication: post-lingually deafened adults, pre-and post-lingually deaf children

Vertigo

Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
- vertigo is produced by peripheral (inner ear) or central (brainstem cerebellum) stimulation
- it is important to distinguish vertigo from other potential causes of "dizziness" (see Figure 11, OT6)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Peripheral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbalance</td>
<td>Moderate-severe</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Severe</td>
<td>Variable</td>
</tr>
<tr>
<td>Auditory Symptoms</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Neurologic Symptoms</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Compensation</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Unidirectional</td>
<td>Bidirectional</td>
</tr>
<tr>
<td></td>
<td>Horizontal or rotatory</td>
<td>Horizontal or vertical</td>
</tr>
</tbody>
</table>
Table 6. Differential Diagnosis of Vertigo Based on History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
<th>Hearing Loss</th>
<th>Tinnitus</th>
<th>Aural Fullness</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Paroxysmal Positional Vertigo (BPPV)</td>
<td>Seconds</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ménière’s Disease</td>
<td>Minutes to hours</td>
<td>Un/bilateral, fluctuating</td>
<td>+</td>
<td>Pressure/warmth</td>
<td>–</td>
</tr>
<tr>
<td>Labyrinthitis/Vestibular Neuritis</td>
<td>Hours to days</td>
<td>Unilateral</td>
<td>± Whistling</td>
<td>–</td>
<td>May have recent AOM</td>
</tr>
<tr>
<td>Acoustic Neuroma</td>
<td>Chronic</td>
<td>Progressive</td>
<td>+</td>
<td>–</td>
<td>Ataxia CN VII palsy</td>
</tr>
</tbody>
</table>

Table 7. Differential Diagnosis of Vertigo Based on Time Course

<table>
<thead>
<tr>
<th>Time Course</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent, lasting</td>
<td>BPPV</td>
</tr>
<tr>
<td>Single episode, lasting minutes to hours</td>
<td>Migraine, transient ischemia of the labyrinth or brainstem</td>
</tr>
<tr>
<td>Recurrent to hours</td>
<td>Ménière’s</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Vestibular neuritis, MS, brainstem/cerebellum infarct</td>
</tr>
<tr>
<td>Acoustic neuroma</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

**Benign Paroxysmal Positional Vertigo**

**Definition**
- acute attacks of transient rotatory vertigo lasting seconds to minutes, initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)
- most common form of positional vertigo (50% of patients with peripheral vestibular dysfunction)

**Etiology**
- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
  - can affect each of the 3 semicircular canals, although the posterior canal is affected in >90% of cases
  - causes: head injury, viral infection (URTI), degenerative disease, idiopathic
  - results in slightly different signals being received by the brain from the two balance organs, resulting in sensation of movement

**Diagnosis**
- history (time course, provoking factors, associative symptoms)
  - positive Dix-Hallpike maneuver (sensitivity 82%, specificity 71%)

**Dix-Hallpike Positional Testing (see website for video and illustrations)**
- the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45°, and neck extended 20° holding the position for 20 s
  - onset of vertigo and rotary nystagmus indicate a positive test for the dependent side
  - other diagnostic testing is not indicated in posterior canal BPPV

**Treatment**
- reassure patient that process resolves spontaneously
  - particle repositioning maneuvers
  - Epley maneuver (performed by MD or by patient with the help of devices such as the DizzyFIX™)
  - Brandt-Daroff exercises (performed by patient)
  - surgery for refractory cases
  - an i-emetics for N/V
  - drugs to suppress the vestibular system delay eventual recovery and are therefore not used

**Ménière’s Disease (Endolymphatic Hydrops)**

**Definition**
- episodic attacks of tinnitus, hearing loss, aural fullness, and vertigo lasting minutes to hours

**Proposed Etiology**
- inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth

**Epidemiology**
- peak incidence 40-60 yr
  - bilateral in 35% of cases
Clinical Features
- episodic vertigo, fluctuating low frequency SNHL, tinnitus, and aural fullness
- ± drop attacks (Tumarkin crisis), ± N/V
- vertigo disappears with time (min to h), but hearing loss remains
- early in the disease: fluctuating SNHL
- later stages: persistent tinnitus and progressive hearing loss
- attacks come in clusters and can be debilitating to the patient
- triggers: high salt intake, caffeine, stress, nicotine, and alcohol

Treatment
- acute management may consist of bed rest, antiemetics, antivertiginous drugs (e.g. beta-histine [Serc®], meclizine, dimenhydramine), and anticholinergics (e.g. scopolamine)
- long-term management may include
  - medical
    - low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
    - Serc® prophylactically to decrease intensity of attacks
    - intratympanic gentamicin to destroy vestibular end-organ, results in complete SNHL
    - intratympanic glucocorticoids (e.g. dexamethasone) may improve vertigo symptoms
  - surgical
    - selective vestibular neurectomy or labyrinthectomy
    - potential benefit for endolymphatic sac decompression or sacculotomy
- must monitor opposite ear, as bilaterality occurs in 35% of cases

Vestibular Neuronitis (Labyrinthitis)

Definition
- acute onset of disabling vertigo often accompanied by N/V and imbalance without hearing loss that resolves over days, leaving a residual imbalance that lasts days to weeks
- vestibular neuronitis: inflammation of the vestibular portion of CN VIII
- labyrinthitis: inflammation of both vestibular and cochlear portions

Etiology
- thought to be due to a viral infection (e.g. measles, mumps, herpes zoster) or post-viral syndrome
- only ~30% of cases have associated URTI symptoms
- labyrinthitis may occur as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures

Clinical Features
- acute phase
  - severe vertigo with N/V and imbalance lasting 1-5 d
  - irritative nystagmus (fast phase towards the offending ear)
  - ataxia: patient tends to veer towards affected side
  - tinnitus and hearing loss in labyrinthitis
- convalescent phase
  - imbalance and motion sickness lasting days to weeks
  - spontaneous nystagmus away from affected side
  - gradual vestibular adaptation requires weeks to months

Treatment
- acute phase
  - bed rest, antivertiginous drugs
  - corticosteroids (methylprednisolone) ± antivirals
  - bacterial infection: treat with IV antibiotics, drainage of middle ear, ± mastoidectomy
- convalescent phase
  - progressive ambulation, especially in the elderly
  - vestibular exercises: involve eye and head movements, sitting, standing, and walking

Acoustic Neuroma (Vestibular Schwannoma)

Definition
- schwannoma of the vestibular portion of CN VIII

Pathogenesis
- starts in the internal auditory canal and expands into cerebellopontine angle (CPA), compressing cerebellum and brainstem
- when associated with type 2 neurofibromatosis (NF2): bilateral acoustic neuromas, juvenile cataracts, meningiomas, and ependymomas

Clinical Features
- usually presents with unilateral SNHL (chronic) or tinnitus
- dizziness and unsteadiness may be present, but true vertigo is rare as tumour growth occurs slowly, and thus compensation occurs
• facial nerve palsy and trigeminal (V1) sensory deficit (corneal reflex) are late complications
• risk factors: exposure to loud noise, childhood exposure to low-dose radiation, history of parathyroid adenoma

**Diagnosis**
- MRI with gadolinium contrast (gold standard)
- audiogram (to assess SNHL)
- poor speech discrimination relative to the hearing loss
- stapedial reflex absent or significant reflex decay
- ABR: increase in latency of the 5th wave
- vestibular tests: normal or asymmetric caloric weakness (an early sign)

**Treatment**
- expectant management if tumour is very small, or in elderly
- definitive management is surgical excision
- other options: gamma knife, radiation

---

**Diseases of the External Ear**

**Cerumen Impaction**

**Etiology**
- ear wax: a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

**Risk Factors**
- hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

**Clinical Features**
- hearing loss (conductive)
- ± tinnitus, vertigo, otalgia, aural fullness

**Treatment**
- water or ceruminolytic drops (bicarbonate solution, olive oil, glycerine, Cerumenol®, Cerumenex®)
- manual debridement (by MD)
Exostoses

**Definition**
- bony protuberances in the external auditory canal composed of lamellar bone

**Etiology**
- possible association with swimming in cold water

**Clinical Features**
- usually an incidental finding
  - if large, they can cause cerumen impaction or otitis externa

**Treatment**
- no treatment required unless symptomatic

Otitis Externa

**Definition**
- inflammation of external auditory canal or auricle

**Etiology**
- bacterial (90% of OE): *Pseudomonas aeruginosa, Pseudomonas vulgaris, E. coli, S. aureus*
  - fungal: *Candida albicans, Aspergillus niger*

**Risk Factors**
- associated with swimming (“swimmer’s ear”)
- mechanical cleaning (Q-tips®), skin dermatitis, aggressive scratching
- devices that occlude the ear canal: hearing aids, headphones, etc.
- allergic contact dermatitis, dermatologic conditions (psoriasis, atopic dermatitis)

**Clinical Features**
- **acute**
  - pain aggravated by movement of auricle (traction of pinna or pressure over tragus)
  - otorrhea (sticky, yellow purulent discharge)
  - conductive hearing loss ± aural fullness 2° to obstruction of external canal by swelling and purulent debris
  - posterior auricular lymphadenopathy
  - complicated OE exists if the pinna and/or the periauricular soft tissues are erythematous and swollen
- **chronic**
  - pruritus of external ear ± excoriation of ear canal
  - atrophic and scaly epidermal lining, ± otorrhea, ± hearing loss
  - wide meatus but no pain with movement of auricle
  - tympanic membrane appears normal

**Treatment**
- clean ear under magnification with irrigation, suction, dry swabbing, and C&S
- bacterial etiology
  - antipseudomonal otic drops (e.g. ciprofloxacin) or a combination of antibiotic and steroid (e.g. Cipro HC®)
  - do not use aminoglycoside if the tympanic membrane (TM) is perforated, because of the risk of ototoxicity
  - introduction of fine gauze wick (pope wick) if external canal edematous
  - ± 3% acetic acid solution to acidify ear canal (low pH is bacteriostatic)
  - systemic antibiotics if either cervical lymphadenopathy or cellulitis is present
- fungal etiology
  - repeated debridement and topical antifungals (gentian violet, Mycostatin® powder, boric acid, Locacorten®, Vioform® drops)
  - ± analgesics
- chronic otitis externa (pruritus without obvious infection) → corticosteroid alone (e.g. diprosalic acid)

Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

**Definition**
- osteomyelitis of the temporal bone

**Epidemiology**
- occurs in elderly diabetics and immunocompromised patients

**Etiology**
- rare complication of otitis externa
- *Pseudomonas* infection in 99% of cases
Clinical Features
• otalgia and purulent otorrhea that is refractory to medical therapy
• granulation tissue on the floor of the auditory canal

Complications
• cranial nerve palsy (most commonly CN VII>CN X>CN XI)
• systemic infection, death

Management
• imaging: high resolution temporal bone CT scan, gadolinium-enhanced MRI, technetium scan
• requires hospital admission, debridement, IV antibiotics, hyperbaric O2
• may require OR for debridement of necrotic tissue/bone

Diseases of the Middle Ear

Acute Otitis Media and Otitis Media with Effusion
• see Pediatric Otolaryngology, OT38

Chronic Otitis Media
Definition
• an ear with TM perforation in the setting of recurrent or chronic ear infections

Benign
• dry TM perforation without active infection

Chronic Serous Otitis Media
• continuous serous drainage (straw-coloured)

Chronic Suppurative Otitis Media
• persistent purulent drainage through a perforated TM

Cholesteatoma
Definition
• a cyst composed of keratinized desquamated epithelial cells occurring in the middle ear, mastoid, and temporal bone
• two types: congenital and acquired

Congenital
• presents as a “small white pearl” behind an intact tympanic membrane (anterior and medial to the malleus) or as a conductive hearing loss
• believed to be due to aberrant migration of external canal ectoderm during development
• not associated with otitis media/Eustachian tube dysfunction

Acquired (more common)
• primary cholesteatoma
  • frequently associated with retraction pockets in the pars flaccida (may lead to attic cholesteatomas, which are difficult to visualize)
  • often has crusting or desquamated debris on lateral surface
• secondary cholesteatoma
  • pearly mass evident behind TM, frequently associated with marginal perforation
  • may appear as skin that have replaced the mucosa of the middle ear
• the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

Clinical Features
• history of otitis media (especially if unilateral), ventilation tubes, ear surgery
• symptoms
  • progressive hearing loss (predominantly conductive, although may get sensorineural hearing loss in late stage)
  • otalgia, aural fullness, fever
• signs
  • retraction pocket in TM, may contain keratin debris
  • TM perforation
  • granulation tissue, polyp visible on otoscopy
  • malodorous, unilateral otorrhea

Mechanisms of Cholesteatoma Formation
• Epithelial migration through TM perforation (2nd acquired)
• Invagination of TM (1st acquired)
• Metaplasia of middle ear epithelium or basal cell hyperplasia (congenital)
Complications

Table 8. Complications of Cholesteatoma

<table>
<thead>
<tr>
<th>Local</th>
<th>Intracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ossicular erosion: conductive hearing loss</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Inner ear erosion: SNHL, dizziness, and/or labyrinthitis</td>
<td>Sigmoid sinus thrombosis</td>
</tr>
<tr>
<td>Temporal bone infection: mastoiditis, petrositis</td>
<td>Intracranial abscess (subdural, epidural, cerebellar)</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td></td>
</tr>
</tbody>
</table>

Investigations

- audiogram and CT scan

Treatment

- there is no conservative therapy for cholesteatoma
- surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction

Mastoiditis

Definition

infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two weeks after onset of untreated or inadequately treated acute suppurative otitis media
- more common in children than adults

Etiology

- acute mastoiditis caused by the same organisms as AOM: S. pneumoniae, H. influenzae, M. catarrhalis, S. pyogenes, S. aureus, P. aeruginosa

Clinical Features

- otorrhea
- tenderness to pressure over the mastoid
- retroauricular swelling with protruding ear
- fever, hearing loss, ± TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)

Treatment

- IV antibiotics with myringotomy and ventilation tubes – usually all that is required acutely
- cortical mastoidectomy
  - debridement of infected tissue allowing aeration and drainage
- indications for surgery
  - failure of medical treatment after 48 h
  - symptoms of intracranial complications
  - aural discharge persisting for 4 wk and resistant to antibiotics

Otosclerosis

Definition

- fusion of stapes footplate to oval window so that it cannot vibrate

Etiology

- autosomal dominant, variable penetrance approximately 40%
- F>M, progresses during pregnancy (hormone responsive)

Clinical Features

- progressive conductive hearing loss first noticed in teens and 20s (may progress to sensorineural hearing loss if cochlea involved)
- ± pulsatile tinnitus
- tympanic membrane normal ± pink blush (Schwartz's sign) associated with the neovascularization of otosclerotic bone
- characteristic dip at 2000 Hz (Carhart's notch) on audiogram (see Figure 16C, OT10)

Treatment

- monitor with serial audiograms if coping with loss
- hearing aid (air conduction, bone conduction, BAHA)
- stapedectomy or stapledotomy (with laser or drill) with prosthesis is definitive treatment

Complications of AOM are rare due to rapid and effective treatment of AOM with antibiotics

Otosclerosis is the 2nd most common cause of conductive hearing loss in 15-50 yr old (after cerumen impaction)
Diseases of the Inner Ear

Congenital Sensorineural Hearing Loss

Hereditary Defects
- non-syndrome associated (70%)
  - often idiopathic, autosomal recessive
  - connexin 26 (GJB2) most common
- syndrome associated (30%)
  - Waardenburg: white forelock, heterochromia iridis (each eye different color), wide nasal bridge, and increased distance between medial canthi
  - Pendred: deafness associated with thyroid gland disorders, SLC26A4 gene enlarged vestibular aqueducts
  - Treacher-Collins: first and second branchial cleft anomalies
  - Alport: hereditary nephritis

Prenatal TORCH Infections
- toxoplasmosis, others (e.g. HIV, syphilis), rubella, CMV, HSV

Perinatal
- Rh incompatibility
- anoxia
- hyperbilirubinemia
- birth trauma (hemorrhage into inner ear)

Postnatal
- meningitis, mumps, measles

High Risk Factors (for hearing loss in newborns)
- low birth weight/prematurity
- perinatal anoxia (low APGARs)
- kernicterus: bilirubin >25 mg/dL
- craniofacial abnormality
- family history of deafness in childhood
- 1st trimester illness: TORCH infections
- neonatal sepsis
- ototoxic drugs
- perinatal infection, including post-natal meningitis
- consanguinity
- 50-75% of newborns with SNHL have at least one of the above risk factors and 90% of these have spent time in the NICU

Treatment
- presence of any risk factor: ABR study performed before leaving NICU and at 3 mo adjusted age
- early rehabilitation improves speech and school performance

Presbycusis

Definition
- SNHL associated with aging (starting in 5th and 6th decades)

Etiology
- hair cell degeneration
- age related degeneration of basilar membrane, possibly genetic etiology
- cochlear neuron damage
- ischemia of inner ear

Clinical Features
- progressive, bilateral hearing loss initially at high frequencies, then middle frequencies
- loss of discrimination of speech, especially with background noise present – patients describe people as mumbling
- recruitment phenomenon: inability to tolerate loud sounds
- tinnitus

Treatment
- hearing aid if patient has difficulty functioning, hearing loss >30-35 dB, and good speech discrimination
- ± lip reading, auditory training, auditory aids (doorbell and phone lights)
Sudden Sensorineural Hearing Loss

Clinical Features
- presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, aural fullness
- usually idiopathic, rule out other causes
  - autoimmune causes (e.g. ESR, rheumatoid factor, ANA)
  - MRI to rule out tumour and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)

Treatment
- intratympanic or oral corticosteroids within 3 d of onset: prednisone 1 mg/kg/d for 10-14 d

Prognosis
- depends on degree of hearing loss
- 70% resolve within 10-14 d
- 20% experience partial resolution
- 10% experience permanent hearing loss

Autoimmune Inner Ear Disease

Etiology
- idiopathic
- may be associated with systemic autoimmune diseases (e.g. rheumatoid arthritis, SLE), vasculitides (e.g. GPA, polyarteritis nodosa), and allergies

Epidemiology
- most common between ages 20-50

Clinical Features
- rapidly progressive or fluctuating bilateral SNHL
- ± tinnitus, aural fullness, vestibular symptoms (e.g. ataxia, disequilibrium, vertigo)

Investigations
- autoimmune workup: CBC, ESR, ANA, rheumatoid factor

Treatment
- high dose corticosteroids: treat early for at least 30 d
- consider cytotoxic medication for steroid non-responders

Drug Ototoxicity

Aminoglycosides
- streptomycin and gentamicin (vestibulotoxic), kanamycin, and tobramycin (cochleotoxic)
- toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
- destroys sensory hair cells: outer first, inner second (therefore, otoacoustic emissions are lost first)
- high frequency hearing loss develops earliest
- ototoxicity occurs days to weeks post-treatment
- must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
- q24h dosing recommended (with amount determined by creatinine clearance)
- aminoglycoside toxicity displays saturable kinetics, therefore, once daily dosing presents less risk than divided daily doses
- duration of treatment is the most important predictor of ototoxicity
  - treatment: immediately stop aminoglycosides

Salicylates
- hearing loss with tinnitus, reversible if discontinued

Antimalarials (Quinines)
- hearing loss with tinnitus
- reversible if discontinued but can lead to permanent loss

Others
- many antineoplastic agents are ototoxic (weigh risks vs. benefits)
- loop diuretics
Noise-Induced Sensorineural Hearing Loss

Pathogenesis
- 85-90 dB over months or years or single sound impulses >135 dB can cause cochlear damage
- bilateral SNHL initially and most prominently at 4000 Hz (resonant frequency of the temporal bone), known as “boilermaker’s notch” on audiogram, extends to higher and lower frequencies with time (see Figure 16D, OT10)
- speech reception not altered until hearing loss >30 dB at speech frequency, therefore considerable damage may occur before patient complains of hearing loss
- difficulty with speech discrimination, especially in situations with competing noise

Phases of Hearing Loss
- dependent on: intensity of sound and duration of exposure
  - temporary threshold shift
    - when exposed to loud sound, decreased sensitivity or increased threshold for sound
    - may have associated aural fullness and tinnitus
  - with removal of noise, hearing returns to normal
  - permanent threshold shift
    - hearing does not return to previous state

Treatment
- hearing aid
- prevention
  - ear protectors: muffs, plugs
  - limit exposure to noise with frequent rest periods
  - regular audiologic follow-up

Temporal Bone Fractures

Table 9. Features of Temporal Bone Fractures

<table>
<thead>
<tr>
<th></th>
<th>Transverse (1)</th>
<th>Longitudinal (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extension</td>
<td>Into bony labyrinth and internal auditory meatus</td>
<td>Into middle ear</td>
</tr>
<tr>
<td>Incidence</td>
<td>10-20%</td>
<td>70-90%</td>
</tr>
<tr>
<td>Etiology</td>
<td>Frontal/occipital trauma</td>
<td>Lateral skull trauma</td>
</tr>
<tr>
<td>CN Pathology</td>
<td>CN VII palsy (50%)</td>
<td>CN VII palsy (10-20%)</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>SNHL due to direct cochlear injury</td>
<td>CHL secondary to ossicular injury</td>
</tr>
<tr>
<td>Vestibular Symptoms</td>
<td>Sudden onset vestibular symptoms due to direct semicircular canal injury</td>
<td>Rare</td>
</tr>
<tr>
<td>Other Features</td>
<td>Intact external auditory meatus, TM ± hemotympanum</td>
<td>Torn TM or hemotympanum</td>
</tr>
<tr>
<td></td>
<td>Spontaneous nystagmus</td>
<td>Bleeding from external auditory canal</td>
</tr>
<tr>
<td></td>
<td>CSF leak in Eustachian tube to nasopharynx ± rhinorrhea (risk of meningitis)</td>
<td>Step format on in external auditory canal</td>
</tr>
<tr>
<td></td>
<td>Battle’s sign = mastoid ecchymoses</td>
<td>CSF otitis</td>
</tr>
<tr>
<td></td>
<td>Raccoon eyes = periorbital ecchymoses</td>
<td>Battle’s sign = mastoid ecchymoses</td>
</tr>
</tbody>
</table>

- characterized as longitudinal or transverse relative to the long axis of the petrous temporal bone
- temporal bone fractures are rarely purely transverse or longitudinal (often a mixed picture)

Diagnosis
- otoscopy
- do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
- CT head
- audiometry, facial nerve tests (for transverse fractures), Schirmer’s test (of lacrimation), stapedial reflexes if CN VII palsy
- if suspecting CSF leak: look for halo sign, send fluid for β-2 transferrin or β trace protein (prostaglandin D synthase)

Treatment
- ABCs
- medical: expectant, prevent otogenic meningitis
- surgical: explore temporal bone; indications:
  - CN VII palsy (immediate and complete)
  - gunshot wound
  - depressed fracture of external auditory meatus
  - early meningitis (mastoidectomy)
  - bleeding intracranially from sinus
  - CSF otitis (may resolve spontaneously)

Hemotympanum can be indicative of temporal bone trauma

Signs of Basilar Skull Fracture
- Battle’s Sign
- Raccoon Eyes
- CSF Rhinorrhea/Otorrhea
- Cranial Nerve Involvement:
  - facial palsy → CN V, I
  - vestibular → CN V, VI
  - facial numbness → CN V
Complications
- AOM ± labyrinthitis ± mastoiditis
- meningitis/epidural abscess/brain abscess
- post-traumatic cholesteatoma

Facial Nerve (CN VII) Paralysis

Peripheral Facial Paralysis (PFP)
- mononeuropathy of the facial nerve where there is weakening in the facial muscles, which alters facial symmetry and functions
- can have a detectable cause (secondary facial nerve palsy) or may be idiopathic (primary)

Etiology
- supranuclear and nuclear (MS, poliomyelitis, cerebral tumours)
- infranuclear

Treatment
- treat according to etiology, plus provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, gold weighting of upper lid
- facial paralysis that does not resolve with time or with medical treatment will often be referred for possible reanimation techniques to restore function
- common reanimation techniques include
  - direct facial nerve anastomosis
  - interpositional grafts
  - anastomosis to other motor nerves
  - muscle transpositions

Table 10. Differential Diagnosis of Peripheral Facial Paralysis (PFP)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incidence</th>
<th>Findings</th>
<th>Investigations</th>
<th>Treatment, Follow-up, and Prognosis (Px)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell’s Palsy</td>
<td>80-90% of PFP</td>
<td>Hx Acute onset&lt;br&gt;Numbness of ear&lt;br&gt;Schirmer’s test&lt;br&gt;Recurrence (12%)&lt;br&gt;+ Ftx (14%)&lt;br&gt;Hyperacusis (30%)</td>
<td>Stapedial reflex absent&lt;br&gt;Audiology normal (or baseline)&lt;br&gt;EMG – best measure for prognosis&lt;br&gt;Topognostic testing&lt;br&gt;MRI with gadolinium – enhancement of CN VII and VIII&lt;br&gt;High resolution CT</td>
<td>Rx Protect the eye to prevent exposure keratitis with patching or tarsorrhaphy&lt;br&gt;Systemic steroids may lessen degeneration and hasten recovery&lt;br&gt;Consider antiviral (acyclovir)&lt;br&gt;F/U Spontaneous remission should begin within 3 wk of onset&lt;br&gt;Delayed (3-6 mo) recovery portends at least some functional loss&lt;br&gt;Px: ENOG testing between day 3-14 of onset:&lt;br&gt;&lt;90% degeneration=high likelihood of recovery&lt;br&gt;90% + no voluntary EMG motor unit potentials= surgical decompression&lt;br&gt;Poorer if hyperacusis, &gt;60 yr, DM, HTN, severe pain</td>
</tr>
<tr>
<td>Ramsay Hunt Syndrome (Herpes Zoster Oticus)</td>
<td>4.5-9% of PFP</td>
<td>Hx Hyperacusis&lt;br&gt;SNHL&lt;br&gt;Severe pain of pinna, mouth, or face</td>
<td>Stapedial reflex absent&lt;br&gt;Audiology SNHL&lt;br&gt;Viral ELISA studies to confirm&lt;br&gt;MRI with gadolinium (85% of facial nerves enhance)</td>
<td>Rx Avoid touching lesions to prevent spread of infection&lt;br&gt;Systemic steroids can relieve pain, vertigo avoid postherpetic neuralgia&lt;br&gt;Acyclovir may lessen pain, aid healing of vesicles&lt;br&gt;F/U: 2-4 wk&lt;br&gt;Px Poorer prognosis than Bell’s palsy; 22% recover completely, 66% incomplete paralysis, 10% complete paralysis</td>
</tr>
<tr>
<td>Varicella zoster infection of CN VII/VIII</td>
<td>&gt;60 yr</td>
<td>Hx Vesicles on pinna, external canal (erupt 3-7 d after onset of pain)&lt;br&gt;Associated herpes zoster ophthalmicus (uveitis, keratoconjunctivitis, optic neuritis, or glaucoma)</td>
<td>Stapedial reflex absent&lt;br&gt;Audiology SNHL&lt;br&gt;Viral ELISA studies to confirm&lt;br&gt;MRI with gadolinium (85% of facial nerves enhance)</td>
<td>Rx Protect the eye to prevent exposure keratitis with patching or tarsorrhaphy&lt;br&gt;Systemic steroids may lessen degeneration and hasten recovery&lt;br&gt;Consider antiviral (acyclovir)&lt;br&gt;F/U Spontaneous remission should begin within 3 wk of onset&lt;br&gt;Delayed (3-6 mo) recovery portends at least some functional loss&lt;br&gt;Px: ENOG testing between day 3-14 of onset:&lt;br&gt;&lt;90% degeneration=high likelihood of recovery&lt;br&gt;90% + no voluntary EMG motor unit potentials= surgical decompression&lt;br&gt;Poorer if hyperacusis, &gt;60 yr, DM, HTN, severe pain</td>
</tr>
<tr>
<td>TEMPORAL BONE FRACTURE</td>
<td>*rarely a patient has a single type of fracture</td>
<td>Hx Blow to side of head&lt;br&gt;P/E Trauma to side of head&lt;br&gt;Neuro findings consistent with epidural/subdural bleed</td>
<td>Skull X-rays CT head</td>
<td>Px Injury usually due to stretch or impingement; may recover with time</td>
</tr>
<tr>
<td>Longitudinal (80%)</td>
<td>20% have PFP</td>
<td>Hx Blow to side of head&lt;br&gt;P/E Trauma to side of head&lt;br&gt;Neuro findings consistent with epidural/subdural bleed</td>
<td>Skull X-rays CT head</td>
<td>Px Nerve transection more likely</td>
</tr>
<tr>
<td>Transverse (10%)</td>
<td>40% have PFP</td>
<td>Hx Blow to frontal or occipital area&lt;br&gt;P/E Trauma to front or back of head</td>
<td>Skull X-rays CT head</td>
<td>Px Nerve transection more likely</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Variable (depending on level of injury)</td>
<td>Wait for lidocaine to wear off EMG</td>
<td>Exploration if complete nerve paralysis&lt;br&gt;No exploration if any movement present&lt;br&gt;Source: Paul Warrick, MD</td>
<td></td>
</tr>
</tbody>
</table>
Rhinitis

Definition
- inflammation of the lining (mucosa) of the nasal cavity

Table 11. Classification of Rhinitis

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perennial non-allergic</td>
<td>Rhinitis medicamentosa</td>
</tr>
<tr>
<td>Asthma, ASA sensitivity</td>
<td>Topical decongestants</td>
</tr>
<tr>
<td>Allergic</td>
<td>Hormonal</td>
</tr>
<tr>
<td>Seasonal</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Perennial</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Atrophic</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Primary: Klebsiella ozena (especially in elderly)</td>
<td>Idiopathic vasomotor</td>
</tr>
<tr>
<td>Acquired: post-surgery if too much mucosa or turbinates has been resected</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Viral: e.g. rhinovirus, influenza, parainfluenza, etc.</td>
<td></td>
</tr>
<tr>
<td>Bacterial: e.g. S. aureus</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
</tr>
<tr>
<td>Granulomatous: TB, syphilis, leprosy</td>
<td></td>
</tr>
<tr>
<td>Non infectious</td>
<td></td>
</tr>
<tr>
<td>Sarcoiosis</td>
<td></td>
</tr>
<tr>
<td>GPA</td>
<td></td>
</tr>
<tr>
<td>Irritant</td>
<td></td>
</tr>
<tr>
<td>Dust</td>
<td></td>
</tr>
<tr>
<td>Chemicals</td>
<td></td>
</tr>
<tr>
<td>Pollution</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Nasal Discharge: Character and Associated Conditions

<table>
<thead>
<tr>
<th>Character</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery/mucoid</td>
<td>Allergic, viral, vasomotor, CSF leak (halo sign)</td>
</tr>
<tr>
<td>Mucopurulent</td>
<td>Bacterial, foreign body</td>
</tr>
<tr>
<td>Serosanguinous</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Bloody</td>
<td>Trauma, neoplasia, bleeding disorder, hype tension/vascular disease</td>
</tr>
</tbody>
</table>

Allergic Rhinitis (i.e. Hay Fever)

Definition
- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds

Etiology
- when allergens contact the respiratory mucosa, specific IgE antibody is produced in susceptible hosts
- concentration of allergen in the ambient air correlates directly with the rhinitis symptoms

Epidemiology
- age at onset usually <20 yr
- more common in those with a personal or family history of allergies/atopy

Clinical Features
- nasal: obstruction with pruritus, sneezing
- clear rhinorrhea (containing increased eosinophils)
- itching of eyes with tearing
- frontal headache and pressure
- mucosa: swollen, pale, “boggy”
- seasonal (summer, spring, early autumn)
  - pollens from trees
  - lasts several weeks, disappears, and recurs the following year at same time
- perennial
  - inhaled: house dust, wool, feathers, foods, tobacco, hair, mould
  - ingested: wheat, eggs, milk, nuts
  - occurs intermittently for years with no pattern or may be constantly present

Complications
- chronic sinusitis/polyps
- serous otitis media

Rhinitis medicamentosa: rebound congestion due to the overuse of intranasal vasoconstrictors; for prevention, use of these medications for only 5-7 days is recommended

Congestion reduces nasal airflow and allows the nose to repair itself (i.e. washes away the irritants). Treatment should focus on the initial insult rather than target this defense mechanism.
Diagnosis
- history
- direct exam
- allergy testing

Treatment
- education: identification and avoidance of allergen
- nasal irrigation with saline
- antihistamines (e.g. diphenhydramine, fexofenadine)
- oral decongestants (e.g. pseudoephedrine, phenylpropanolamine)
- topical decongestant (may lead to rhinitis medicamentosa)
- other topicals: steroids (fluticasone), disodium cromoglycate, antihistamines, ipratropium bromide
- oral steroids if severe
- desensitization by allergen immunotherapy

**Vasomotor Rhinitis**

Definition
- neurovascular disorder of nasal parasympathetic system (vidian nerve) affecting mucosal blood vessels
- nonspecific reflex hypersensitivity of nasal mucosa

Etiology
- temperature change
- alcohol, dust, smoke
- stress, anxiety, neurosis
- endocrine: hypothyroidism, pregnancy, menopause
- parasympathomimetic drugs
- beware of rhinitis medicamentosa: reactive vasodilation due to prolonged use (>5 d) of nasal drops and sprays (Dristan®, Otrivin®)

Clinical Features
- chronic intermittent nasal obstruction, varies from side to side
- rhinorrhea: thin, watery
- mucosa and turbinates: swollen
- nasal allergy must be ruled out

Treatment
- elimination of irritant factors
- parasympathetic blocker (Atrovent® nasal spray)
- steroids (e.g. beclomethasone, fluticasone)
- surgery (often of limited lasting benefit): electrocautery, cryosurgery, laser treatment, or removal of inferior or middle turbinates
- vidian neurectomy (rarely done)
- symptomatic relief with exercise (increased sympathetic tone)

**Rhinosinusitis**

Definition
- inflammation of the mucosal lining of the sinuses and nasal passages

Pathogenesis of Rhinosinusitis
- ostial obstruction or dysfunctional cilia permit stagnant mucous and, consequently, infection
- all sinuses drain to a common prechamber under the middle meatus called the osteomeatal complex

Classification
- acute: <4 wk
- subacute: 4-8 wk
- chronic: >8-12 wk
## Table 13. Etiologies of Rhinosinusitis

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ostial Obstruction</td>
<td>Inflammation URTI, Allergy, Mechanical Septal deviation, Turbinate hypertrophy, Polyps, Tumours, Adenoid hypertrophy, Foreign body, Congenital abnormalities (e.g. cleft palate)</td>
</tr>
<tr>
<td>Immune</td>
<td>PA, Lymphoma, leukemia, Immunosuppressed patients (e.g. neutropenics, diabetics, HIV)</td>
</tr>
<tr>
<td>Direct Extension</td>
<td>Cystic fibrosis, Immotile cilia (e.g. Kartagener’s)</td>
</tr>
</tbody>
</table>

### Acute Bacterial Rhinosinusitis

**Definition**
- bacterial infection of the paranasal sinuses and nasal passages lasting >7 d
- clinical diagnosis requiring ≥2 major symptoms, and at least one of the symptoms is either nasal obstruction or purulent/dischoured nasal discharge

**Major Symptoms (at least 2 of PODS, 1 must be O or D)**
- **P** Facial Pain/Pressure/fullness
- **O** Nasal Obstruction
- **D** Purulent/dischoured nasal Discharge
- **S** Hyposmia/anosmia (Smell)

**Minor Symptoms**
- Headache
- Halitosis
- Fatigue
- Dental pain
- Cough
- Ear pain/fullness

**Etiology**
- bacteria: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis*, *S. aureus*, anaerobes (dental)
- children are more prone to a bacterial etiology, but viral i. still more common
- maxillary sinus most commonly affected
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless, black or pale mucosa on examination)

**Clinical Features**
- sudden onset of:
  - nasal blockage/congestion and/or purulent nasal discharge/posterior nasal drip
  - ± facial pain or pressure, hyposmia, sore throat
  - persistent/worsening symptoms >5-7 d or presence of purulence for 3-4 d with high fever
  - speculum exam: erythematous mucosa, mucopurulent discharge, pus originating from the middle meatus
  - predisposing factors: viral URTI, allergy, dental disease, anatomical defects
  - differentiate from acute viral rhinosinusitis (course: <10 d, peaks by 3 d)

**Diagnosis**
- along with clinical criteria, can confirm radiographically and/or endoscopically using antral puncture for bacterial cultures

**Management**
- depends on symptom severity (i.e. intensity/duration of symptoms, impact on quality of life)
  - mild/moderate: INCS
    - if no response within 72 h, add antibiotics
  - severe: INCS + antibiotics
    - antibiotics
      - 1st line: amoxicillin x 10 d (TMP-SMX or macrolide if penicillin allergy)
      - if no response to 1st line antibiotics within 72 h, switch to 2nd line
        - 2nd line: fluoroquinolones or amoxicillin-clavulanic acid
      - adjuvant therapy (saline or HOCL (pediatric sinusitis) irrigation, analgesics, oral/topical decongestant) may provide symptomatic relief
      - CT indicated only if complications are suspected

**Acute Rhinosinusitis Complications**
- Consider hospitalization if any of the following are suspected
  - Orbital (Chandler’s classification)
    - Preseptal cellulitis
    - Subperiosteal abscess
    - Orbital abscess
    - Cavernous sinus thrombosis
  - Intracranial
    - Meningitis
    - Abscess
  - Bony
    - Subperiosteal frontal bone abscess (“Pott’s Puffy tumour”)
    - Osteomyelitis
  - Neurologic
    - Superior orbital fissure syndrome (CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypoesthesia)
    - Orbital apex syndrome (as above, plus neuritis, papilledema, decreased visual acuity)

**Use of Single Dose Azithromycin as Treatment of Acute Bacterial Rhinosinusitis**

*Otolaryngol Head Neck Surg 2005;133(2):194-200*

**Summary:** Single-dose azithromycin microspheres were comparable to 10 days of levofloxacin and may be a safe and effective treatment for acute bacterial rhinosinusitis.

**Results:** An international, multicentre, double-blind, double-dummy RCT comparing single dose azithromycin vs. 10-day levofloxacin group for treatment of acute bacterial rhinosinusitis. Clinical success was 94.5% (242/256) in the azithromycin group and 92.8% (233/251) in the levofloxacin group.
Chronic Rhinosinusitis

Definition
• inflammation of the mucosa of paranasal sinuses and nasal passages >8-12 wk
• diagnosis requires ≥2 major symptoms for >8-12 wk and ≥1 objective finding of inflammation of the paranasal sinuses (CT/endoscopy)

Etiology
• unclear etiology but the following may contribute or predispose
  • inadequate treatment of acute rhinosinusitis
  • bacterial colonization/biofilms
    ■ S. aureus, enterobacteriaceae, Pseudomonas, S. pneumoniae, H. influenzae, β-hemolytic Streptococci
  • fungal infection (e.g. Aspergillus, Zygomycetes, Candida)
  • anatomic abnormality (e.g. lost ostia patency, deviated septum – predisposing factors)
  • allergy/allergic rhinitis
  • ciliary disorder (e.g. cystic fibrosis, Kartagener syndrome)
  • chronic inflammatory disorder (e.g. GPA)
  • untreated dental disease

Clinical Features (similar to acute, but less severe) - at least 2 of CPODS for >8-12 wk
• facial Congestion/fullness
• facial Pain/Pressure
• chronic nasal Obstruction
• purulent anterior/posterior nasal Discharge
• hyposmia/anosmia (Smell)
• others: halitosis, chronic cough, maxillary dental pain

Management
• identify and address contributing or predisposing factors
• obtain CT or perform endoscopy
• if polyps present: INCS, oral steroids ± antibiotics (if signs of infection), refer to otolaryngologist/H&N surgeon
• if polyps absent: INCS, antibiotics, saline irrigation, oral steroids (severe cases)
• antibiotics for 3-6 wk
  ■ amoxillin-clavulanic acid, fluoroquinolone (moxifloxacin), macrolide (clarithromycin), clindamycin, Flagyl® (metronidazole)
• surgery if medical therapy fails or fungal sinusitis FESS, balloon sinoplasty

Complications
• same as acute sinusitis, mucocele

Epistaxis

Blood Supply to the Nasal Septum (see Figure 4, OT3)
1. Superior posterior septum
   • internal carotid → ophthalmic → anterior/posterior ethmoidal
2. Posterior septum
   • external carotid → internal maxillary → sphenopalatine artery → nasopalatine
3. Lower anterior septum
   • external carotid → facial artery → superior labial artery → nasal branch
   • external carotid → internal maxillary → descending palatine → greater palatine
• these arteries all anastomose to form Kiesselbach’s plexus, located at Little’s area (anterior-inferior portion of the cartilaginous septum)
• bleeding from above middle turbinate is internal carotid, from below is external carotid
### Table 14. Etiology of Epistaxis

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>(most common)</td>
</tr>
<tr>
<td>Fractures: facial, nasal</td>
<td>Benign: polyps, inverting papilloma, angiofibroma</td>
</tr>
<tr>
<td>Self-induced: digital, foreign body</td>
<td>Malignant: SCC, esthesioneuroblastoma (olfactory neuroblasia)</td>
</tr>
<tr>
<td>Iatrogenic: nasal, sinus, orbit surgery</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Barometric changes</td>
<td>Rhinitis: allergic, non-allergic</td>
</tr>
<tr>
<td>Nasal dryness: dry air ± septal deformities</td>
<td>Infections: bacterial, viral, fungal</td>
</tr>
<tr>
<td>Septal perforation</td>
<td></td>
</tr>
<tr>
<td>Chemical: cocaine, nasal sprays, ammonia, etc.</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
</tr>
<tr>
<td>Coagulopathies</td>
<td></td>
</tr>
<tr>
<td>Meds: anticoagulants, NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Hemophilias, von Willebrand’s</td>
<td></td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td></td>
</tr>
<tr>
<td>Liver failure, uremia</td>
<td></td>
</tr>
<tr>
<td>Vascular: HTN, atherosclerosis, Osler-Weber-Rendu</td>
<td>(hereditary hemorrhagic telangiectasia)</td>
</tr>
<tr>
<td>Others: GPA, SLE</td>
<td></td>
</tr>
</tbody>
</table>

**Investigations**
- CBC, PT/PTT (if indicated)
- X-ray, CT as needed

**Treatment**
- locate bleeding and achieve hemostasis

1. **ABCs**
- lean patient forward to minimize swallowing blood and avoid airway obstruction
- apply constant firm pressure for 20 min on cartilaginous part of nose (not bony pyramid)
- if significant bleeding, assess vitals for signs of hemorrhagic shock ± IV NS, cross-match blood

2. **Determine Site of Bleeding**
- anterior/posterior hemorrhage defined by location in relationship to bony septum
- visualize nasal cavity with speculum
- use cotton pledget with topical lidocaine ± topical decongestant (i.e. Otrivin*) to help identify area of bleeding (often anterior septum)
- if suspicious bleeding disorder, coagulation workup (platelet number and platelet function assay)

3. **Control the Bleeding**
- first-line: topical vasoconstrictors (Otrivin*)
  - if first-line fails and bleeding adequately visualized, cauterize with silver nitrate
  - **do not cauterize both sides of the septum** at one time due to risk of septal perforation from loss of septal blood supply
  A. **Anterior hemorrhage treatment**
    - if failure to achieve hemostasis with cauterization
      - place anterior pack* with half inch Vaseline-soaked ribbon gauze strips layered from nasal floor toward nasal roof and extending to posterior choanae, or lubricated absorbable packing (i.e. Gelfoam wrapped in Surgicel*) for 2-3 d
      - can also attempt packing with Merocel* or nasal tampons of different shapes
      - can also apply Floseal* (hemostatic matrix consisting of topical human thrombin and cross-linked gelatin) if other methods fail
  B. **Posterior hemorrhage treatment**
    - if unable to visualize bleeding source, then usually posterior source
      - place posterior pack* using a Foley catheter, gauze pack, or Epistat* balloon
      - subsequently, layer anterior packing bilaterally
      - admit to hospital with packs in for 3-5 d
      - watch for complications: hypoxemia (naso-pulmonic reflex), toxic shock syndrome (Rx: remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration
  C. **If anterior/posterior packs fail to control epistaxis**
    - ligation or embolization of culprit arterial supply by interventional radiology
    - ± septoplasty

*antibiotics for any posterior pack or any pack left for >48 h because of risk of toxic shock syndrome

**Special Cases**
- Adolescent male with unilateral recurrent epistaxis - consider juvenile nasopharyngeal angiofibroma (JNA); this is the most common benign tumour of the nasopharynx.
- Thrombocytopenic patients: use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

**4. Prevention**
- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of HTN and coagulopathies
Hoarseness

Definitions
- **Hoarseness**: change in voice quality, ranging from voice harshness to voice weakness; reflects abnormalities anywhere along the vocal tract from oral cavity to lungs
- **Dysphonia**: a general alteration in voice quality
- **Aphonia**: no sound emanates from vocal folds

Acute Laryngitis

**Definition**
- <2 wk inflammatory changes in laryngeal mucosa

**Etiology**
- Viral: influenza, adenovirus, HSV
- Bacterial: Group A Streptococcus
- Mechanical: acute voice strain → submucosal hemorrhage → vocal cord edema → hoarseness
- Environmental: toxic fume inhalation

**Clinical Features**
- URTI symptoms, hoarseness, aphonia, cough attacks, ± dyspnea
- True vocal cords erythematous/edematous with vascular injection and normal mobility

**Treatment**
- Usually self-limited, resolves within ~1 wk
- Voice rest
- Humidification
- Hydration
- Avoid irritants (e.g., smoking)
- Treat with antibiotics if there is evidence of coexistent bacterial pharyngitis

Chronic Laryngitis

**Definition**
- >2 wk inflammatory changes in laryngeal mucosa

**Etiology**
- Repeated attacks of acute laryngitis
- Chronic irritants (dust, smoke, chemical fumes)
- Chronic voice strain
- Chronic rhinosinusitis with postnasal drip
- Chronic EtOH use
- Esophageal disorders: GERD, Zenker’s diverticulum, hiatus hernia
- Systemic: allergy, hypothyroidism, Addison’s disease

**Clinical Features**
- Chronic dysphonia: rule out malignancy
- Cough, globus sensation, frequent throat clearing 2° to GERD
- Laryngoscopy: cords erythematous, thickened with ulceration/granuloma formation, and normal mobility

**Treatment**
- Remove offending irritants
- Treat related disorders (e.g., antisecretory therapy for GERD)
- Speech therapy with voice rest
- ± Antibiotics ± steroids to decrease inflammation
- Laryngoscopy to rule out malignancy

Vocal Cord Polyps

**Definition**
- Structural manifestation of vocal cord irritation
- Acutely, polyp forms 2° to capillary damage in the subepithelial space during extreme voice exertion

**Etiology**
- Most common benign tumour of vocal cords
- Voice strain (muscle tension dysphonia)
- Laryngeal irritants (GERD, allergies, tobacco)
Epidemiology
- 30-50 yr of age
- M>F

Clinical Features
- hoarseness, aphonia, cough attacks ± dyspnea
- pedicled or sessile polyp on free edge of vocal cord
- typically, polyp asymmetrical, soft, and smooth
- more common on the anterior 1/3 of the vocal cord
- intermittent respiratory distress with large polyps

Treatment
- avoid irritants
- endoscopic laryngeal microsurgical removal if persistent or if high risk of malignancy

Vocal Cord Nodules

Definition
- vocal cord callus
- i.e. "screamer's or singer's nodules"

Etiology
- early nodules occur 2° to submucosal hemorrhage
- mature nodules result from hyalinization, which occurs with long-term voice abuse
- chronic voice strain
- frequent URTI, smoke, EtOH

Epidemiology
- frequently in singers, children, bartenders, and school teachers
- F>M

Clinical Features
- hoarseness worst at end of day
- on laryngoscopy
  - often bilateral
  - at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords – point of maximal cord vibration
- chronic nodules may become fibrotic, hard, and white

Treatment
- voice rest
- hydration
- speech therapy
- avoid irritants
- surgery rarely indicated for refractory nodules

Benign Laryngeal Papillomas

Etiology
- HPV types 6, 11
- possible hormonal influence, possibly acquired during delivery

Epidemiology
- biphasic distribution: 1) birth to puberty (most common laryngeal tumour) and 2) adulthood

Clinical Features
- hoarseness and airway obstruction
  - can seed into tracheobronchial tree
  - highly resistant to complete removal
- some juvenile papillomas resolve spontaneously at puberty
- may undergo malignant transformation
- laryngoscopy shows wart-like lesions in supraglottic larynx and trachea

Treatment
- microdebridement or CO2 laser
- adjuvants under investigation: interferon, cidofovir, acyclovir
- HPV vaccine may prevent/decrease the incidence, but more research is needed

Laryngeal Carcinoma

- see Neoplasms of the Head and Neck, OT34
**Salivary Glands**

### Sialadenitis

**Definition**
- inflammation of salivary glands

**Etiology**
- viral most common (mumps)
- bacterial causes: *S. aureus, S. pneumoniae, H. influenzae*
- obstructive vs. non-obstructive
  - obstructive infection involves salivary stasis and bacterial retrograde flow

**Predisposing Factors**
- HIV
- anorexia/bulimia
- Sjögren’s syndrome
- Cushing’s, hypothyroidism, DM
- hepatic/renal failure
- meds that increase stasis: diuretics, TCAs, β-blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)

**Clinical Features**
- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- ± fever
- ± leukocytosis
- ± suppurative drainage from punctum of the gland

**Investigations**
- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

**Treatment**
- bacterial: treat with cloxacillin ± abscess drainage, sialogogues
- viral: no treatment

### Sialolithiasis

**Definition**
- ductal stone (mainly hydroxyapatite) in adults, sand/sludge in children, leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

**Risk Factors**
- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, diabetes, EtOH, hypercalcemia, psychiatric medication)

**Clinical Features**
- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculus

**Investigations**
- U/S ± sialogram

**Treatment**
- may resolve spontaneously
- encourage salivation to clear calculus
- massage, analgesia, antibiotics, sialogogues (e.g. lemon wedges, sour lemon candies), warm compresses
- remove calculi endoscopically, by dilating duct or orifice, or by excision through floor of the mouth
- gland preserving surgery has long-term symptom improvement and favourable gland retention rates

### Salivary Gland Neoplasms

**Etiology**
- anatomic distribution
  - parotid gland: 70-85%
  - submandibular gland: 8-15%
  - sublingual gland: 1%
  - minor salivary glands, most concentrated in hard palate: 5-8%
neck masses

• malignant (see Table 15, OT31 and Table 16, OT35)
• benign
  • benign mixed (pleomorphic adenoma): 80%
  • Warthin’s tumour (5-10% bilateral, M>F): 10%
  • cysts, lymph nodes, and adenomas: 10%
  • oncocytoma: <1%

Epidemiology
• 3-6% of all head and neck neoplasms in adults
• mean age at presentation: 55-65
• M=F

Parotid Gland Neoplasms

Clinical Features
• 80% benign (pleomorphic adenoma: most common), 20% malignant (mucoepidermoid: most common)
• if bilateral, suggests benign process (Warthin’s tumour, Sjögren’s, bulimia, mumps) or possible lymphoma
• facial nerve involvement (i.e. facial paralysis): increases risk of malignancy

Investigations
• FNA biopsy
• CT, U/S, or MRI to determine extent of tumour

Treatment
• treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
• pleomorphic adenomas are excised due to risk of malignant transformation (5% risk over prolonged period of time)
• superficial tumour
  • superficial parotidectomy above plane of CN VII ± radiation
  • incisional biopsy contraindicated
• deep lesion
  • near-total parotidectomy sparing as much of CN VII as possible
  • if CN VII involved, then it is removed and cable grafted
• complications of parotid surgery
  • hematoma, infection, salivary fistula, temporary facial paresis, Frey’s syndrome (gustatory sweating)

Prognosis
• benign: excellent, <5% of pleomorphic adenomas may recur
• malignant: dependent on stage and type of malignancy (see Table 16, OT35)

Approach to a Neck Mass

• ensure that the neck mass is not a normal neck structure (hyoid, transverse process of C1 vertebra, prominent carotid bulb)
• any neck mass persisting for >2 wk should be investigated for possible neoplastic causes

Table 15. Acquired Causes of Neck Lumps According to Age

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Possible Causes of Neck Lump</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>1. Inflammatory 2. Congenital 3. Neoplastic</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1. Neoplastic 2. Inflammatory 3. Congenital</td>
</tr>
</tbody>
</table>

Differential Diagnosis
• congenital
  • lateral (branchial cleft cyst, lymphatic/venous/venolymphatic malformation)
  • midline (thyroglossal duct cyst, dermoid cyst, laryngocele, thyroid/thymus anomaly, vascular malformation)
• infectious/inflammatory
  • reactive lymphadenopathy (2° to tonsillitis, pharyngitis)
  • infectious mononucleosis
  • Kawasaki, Kikuchi, Kimura, Cat-scratch disease, Castleman’s
  • HIV
  • salivary gland calculi, sialadenitis
  • thyroiditis

DDx Parotid Tumour
Benign
• Pleomorphic adenoma
• Warthin’s tumour (more common in men)
• Benign lymphoepithelial cysts (viral etiology e.g. HIV)
• Oncocytoma

Malignant
• Mucoepidermoid carcinoma
• Adenoid cystic carcinoma
• Acinic cell carcinoma

Frey’s syndrome is a post-operative complication characterized by gustatory sweating. It is due to aberrant innervation of cutaneous sweat glands by parasympathetic nerve fibres that are divided during surgery.
Congenital Neck Masses

- granulomatous disease
  - mycobacterial infections
  - sarcoidosis
- neoplastic
  - lymphoma
  - salivary gland tumours
  - thyroid tumours
  - metastatic malignancy (“unknown primary”)

**Evaluation**

**Investigations**
- history and physical (including nasopharynx and larynx)
- all other investigations and imaging are dependent upon clinical suspicion following history and physical
- laboratory investigations
  - WBC: infection vs. lymphoma
  - Mantoux TB test
  - thyroid function tests and scan
- imaging
  - neck U/S
  - CT scan
  - angiography: vascularity and blood supply to mass
  - biopsy: for histologic examination
    - FNA: least invasive
    - needle biopsy
    - open biopsy: for lymphoma
- identification of possible primary tumour (rule out a metastatic lymph node from an “unknown primary”)
  - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
  - biopsy of normal tissue of nasopharynx, tonsils, base of tongue, and hypopharynx
  - primary identified 95% of time → stage and treat
  - primary occult 5% of time: excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (squamous cell carcinoma)

**Congenital Neck Masses**

**Brachial Cleft Cysts/Sinuses/Fistulae**

**Embryology**
- at the 6th wk of development, the 2nd branchial arch grows over the 3rd and 4th arches and fuses with the neighbouring caudal pre-cardial swelling, forming the cervical sinus
- 3 types of malformations
  1. branchial fistula: persistent communication between skin and GI tract
  2. branchial sinus: blind-ended tract opening to skin
  3. branchial cyst: persistent cervical sinus with no external opening

**Clinical Features**
- 2nd branchial cleft malformations most common
  - sinuses and fistulae present in infancy as a small opening anterior to the sternocleidomastoid muscle
  - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following a URTI
- 1st branchial cleft malformations present as sinus/fistula or cyst in preauricular area or on face over angle of mandible
- 3rd branchial cleft malformations present as recurrent thyroiditis or thyroid abscess and have a tract leading usually to the left pyriform sinus. Air on CT scan in or near the thyroid gland is pathognomonic for this anomaly
- there is controversy whether or not 4th branchial cleft anomalies exist, as they may be remnants of the thyrothyroidic axis

**Treatment**
- surgical removal of cyst or fistula tract
- if infected: allow infection to settle before removal (antibiotics may be required)

<table>
<thead>
<tr>
<th>Inflammatory vs. Malignant Neck Masses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>History</td>
</tr>
<tr>
<td>H&amp;N infection</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>CA risk factors</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Physical</td>
</tr>
<tr>
<td>Tender</td>
</tr>
<tr>
<td>Rubbery</td>
</tr>
<tr>
<td>Rock hard</td>
</tr>
<tr>
<td>Mobile</td>
</tr>
</tbody>
</table>
Thyroglossal Duct Cysts

Embryology
- thyroid originates as ventral midline diverticulum at base of tongue, caudal to junction of 3rd and 4th branchial arches (foramen cecum), and migrates down to inferior aspect of neck
- thyroglossal duct cysts are vestigial remnants of this tract

Clinical Features
- usually presents in childhood or during 20-40s as a midline cyst that enlarges with URTI and elevates with swallowing and tongue protrusion

Treatment
- pre-operative antibiotics to reduce inflammation (infection before surgery is a well-described cause of recurrence)
- small potential for neoplastic transformation, so complete excision of cyst and issue around tract up to foramen cecum at base of tongue, with removal of central portion of hyoid bone (Sistrunk procedure) recommended
Lymphatic, Venous, or Mixed Venolymphatic Malformations

Definition
- lymphatic malformation arising from vestigial lymph channels of neck

Clinical Features
- commonly identified in many fetuses, but regress before birth and never cause a clinical problem
- usually present by age 2
- can be macrocystic (composed of large thin-walled cysts, usually below level of mylohyoid muscle) or microcystic (composed of minute cysts, usually above level of mylohyoid muscle)
- usually painless, soft, compressible
- infection or trauma causes a sudden increase in size

Treatment
- can regress spontaneously after bacterial infection, therefore do not plan surgical intervention until several months after infection
- macrocystic lesions can be treated by sclerotherapy or surgical excision
- microcystic lesions are difficult to treat, but can be debulked if it will not cause loss of function of normal structures, or injected with sclerotherapy in surrounding tissues

Neoplasms of the Head and Neck

Pre-Malignant Disease
- leukoplakia
  - hyperkeratosis of oral mucosa
  - risk of malignant transformation 5-20%
- erythroplakia
  - red superficial patches adjacent to normal mucosa
  - commonly associated with epithelial dysplasia
  - associated with carcinoma in situ or invasive tumour in 40% of cases
- dysplasia
  - histopathologic presence of mitoses and prominent nucleoli
  - involvement of entire mucosal thickness = carcinoma in situ
  - associated progression to invasive cancer in 15-30% of cases

Investigations
- initial metastatic screen includes CXR
- scans of liver, brain, and bone only if clinically indicated
- CT scan is superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI is superior to discriminate tumour from mucus and to detect bone marrow invasion
- ± PET scans

Treatment
- treatment depends on
  - histologic grade of tumour
  - stage
  - physical and psychological health of patient
  - facilities available
  - expertise and experience of the medical and surgical oncology team
- in general
  - 1st surgery for malignant oral cavity tumours with radiotherapy reserved for salvage or poor prognostic indicators
  - 1st radiotherapy for nasopharynx, oropharynx, hypopharynx, larynx malignancies with surgery reserved for salvage
  - palliative chemotherapy for metastatic or incurable disease
  - concomitant chemotherapy increases survival in advanced disease
  - chemotherapy has a role as induction therapy prior to surgery and radiation
  - panendoscopy to detect primary disease when lymph node metastasis is identified
  - anti-EGFR treatment (cetuximab, panitumumab) has a role as concurrent therapy with radiation for SCC of the head and neck (for advanced local and regional disease)

Prognosis
- synchronous tumours occur in 9-15% of patients
- late development of 2nd primary is most common cause of post treatment failure after 36 mo
## Table 16. Quick Look-Up Summary of Head and Neck Malignancies – Etiology and Epidemiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Epidemiology</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Cavity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% SCC others: sarcoma, melanoma, minor salivary gland tumour</td>
<td>Mean age: 50-60 yr M&gt;F</td>
<td>Smoking/ETOH Poor oral hygiene Lichen planus, chronic inflammation Sun exposure – lip HPV infection</td>
</tr>
<tr>
<td><strong>Nose and Paranasal Sinus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-80% SCC Adenocarcinoma (2nd most common) and mucoepidermoid 99% in maxillary/ethmoid sinus 10% of nose and paranasal sinus tumours arise from minor salivary glands</td>
<td>Mean age: 50-70 yr Rare tumours ↓ incidence in last 5-10 yr</td>
<td>Wood/shoe/textile industry Hardwood dust (nasal/ethmoid sinus) Nickel, chromium (maxillary sinus) Air pollution Chronic rhinosinusitis</td>
</tr>
<tr>
<td><strong>Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx, and Larynx)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td></td>
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<tr>
<td>90% SCC ~10% lymphoma</td>
<td>Mean age: 50-59 yr M:F = 2.4:1 Incidence 0.8 per 100,000 100x increased incidence in Southern Chinese</td>
<td>Epstein-Barr virus (EBV) Salted fish Nickel exposure Poor oral hygiene Genetic – Southern Chinese</td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% SCC – poorly differentiated Up to 70% of oropharyngeal cancer (OPC) attributable to HPV</td>
<td>Mean age: 50-70 yr Patients with HPV+ OPC are approximately 10 yrs younger Prevalence of HPV+ OPC has increased by 225% from 1988 to 2004. M:F = 4:1</td>
<td>Smoking/ETOH HPV 16 infection: increased sexual encounters, specifically oral sex</td>
</tr>
<tr>
<td><strong>Hypopharynx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% SCC 3 sites 1. pyriform sinus (60%) 2. post-cricoid (30%) 3. post pharyngeal wall (10%)</td>
<td>Mean age: 50-70 yr M:F = 8-10% of all H&amp;N cancer</td>
<td>Smoking/ETOH</td>
</tr>
<tr>
<td><strong>Larynx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC most common 3 sites 1. supraglottic (30-35%) 2. glottic (60-65%) 3. subglottic (1%)</td>
<td>Mean age: 45-75 yr M:F = 10:1 45% of all H&amp;N cancer</td>
<td>Smoking/ETOH HPV 16 infection strongly associated with the risk of laryngeal squamous cell cancers</td>
</tr>
<tr>
<td><strong>Salivary Gland</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% mucoepidermoid 30% adenoid cystic 5% acinic cell 5% malignant mixed 5% lymphoma</td>
<td>Mean age: 55-65 yr M:F = 3-6% of all H&amp;N cancer Percentage of malignant tumours n each gland: Parotid 15-25% Submandibular 37-43% Minor salivary &gt;80%</td>
<td></td>
</tr>
<tr>
<td><strong>Thyroid (90% benign – 10% malignant)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80% papillary 5-15% follicular 5% medullary &lt;5% anaplastic 1-5% hürthle cell 1-2% metastatic</td>
<td>Children Adults &lt; 30 or &gt;60 yr Nodules more common in females Malignancy more common in males</td>
<td>Radiation exposure Family history – papillary CA or multiple endocrine neoplasia – MEN II Older age Male Papillary – Gardner’s, Cowden’s, familial adenomatous polyposis (FAP)</td>
</tr>
<tr>
<td><strong>Parathyroid</strong></td>
<td>Mean age: 44-55 yr Rare tumour</td>
<td></td>
</tr>
</tbody>
</table>
## Table 17. Quick Look-Up Summary of Head and Neck Malignancies – Diagnosis and Treatment

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Cavity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic neck mass (30%)</td>
<td>Biopsy</td>
<td>1st surgery</td>
<td>5 yr survival</td>
</tr>
<tr>
<td>Non-healing ulcer ± bleeding</td>
<td>CT</td>
<td>local resection</td>
<td>T1/T2: 75%</td>
</tr>
<tr>
<td>Dysphagia, xerostomia, dysphonia</td>
<td></td>
<td>± neck dissection</td>
<td>T3/T4: 30-35%</td>
</tr>
<tr>
<td>Oral, palatal, oropharyngeal</td>
<td></td>
<td>± reconstruction</td>
<td>Poor prognostic indicators</td>
</tr>
<tr>
<td>(pre-malignant changes or CIS)</td>
<td></td>
<td>2nd radiation</td>
<td>Depth of invasion, close surgical margins location (tongue worse than floor of mouth)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cervical nodes, extra-capsular spread</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nose and Paranasal Sinus</strong></td>
<td></td>
<td>Surgery and radiation</td>
<td>5 yr survival: 30-60%</td>
</tr>
<tr>
<td>Early Symptoms</td>
<td>CT/MRI</td>
<td>Chemoradiation</td>
<td>Poor prognosis 2nd to late presentation</td>
</tr>
<tr>
<td>Unilateral nasal obstruction</td>
<td>Biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis, rhinorrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd to invasion of nose, orbit, nerves, oral cavity, skin, skull base, cribriform plate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical nodes (60-90%)</td>
<td>Nasopharyngoscopy</td>
<td>1st radiation, chemoradiation</td>
<td>5 yr survival</td>
</tr>
<tr>
<td>Nasal obstruction, epistaxis</td>
<td>Biopsy</td>
<td>Surgery for limited or recurrent disease</td>
<td>T1: 79%</td>
</tr>
<tr>
<td>Unilateral otitis media ± hearing loss</td>
<td>CT/MRI</td>
<td></td>
<td>T2: 72%</td>
</tr>
<tr>
<td>CN III to VII, IX to XII (25%)</td>
<td></td>
<td></td>
<td>T3: 50-60%</td>
</tr>
<tr>
<td>Proptosis, voice change, dysphagia</td>
<td></td>
<td></td>
<td>T4: 36-42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia, odynophagia</td>
<td>Biopsy</td>
<td>1st radiation</td>
<td>5 yr survival</td>
</tr>
</tbody>
</table>
| Ulcerated/enlarged tonsil | Determine HPV status via RT-PCR | 2nd surgery | T1: 53%
| Fixed tongue/trismus/dysarthria | positive if presence of HPV DNA and p16 expression | local resection | T2/T3: 36-39%
| Oral, palatal, oropharyngeal | CT | ± neck dissection | T4: >40% (surgery with radiation)
| (pre-malignant changes or CIS) | | ± reconstruction | Control rate early lesions >90% (radiation)
| | | | 10 to 12% of small lesions fail radiotherapy |
| | | | |
| **Hypopharynx** | | | |
| Dysphagia, odynophagia, globus | Pharyngoscopy | 1st radiation | 5 yr survival |
| Hoarseness | Biopsy | 2nd surgery | T1: 53%
| Cervical lymphadenopathy | CT | local resection | T2/T3: 36-39%
| | | ± neck dissection | T4: 24%
| | | ± reconstruction | |
| | | | |
| **Larynx** | | | |
| Dysphagia, odynophagia, globus | Laryngoscopy | 1st radiation | 5 yr survival |
| Hoarseness | Biopsy | 2nd surgery | T4: >40% (surgery with radiation)
| Dyspnea/stridor | CT/MRI | local resection | Control rate early lesions >90% (radiation)
| Cough/hemoptysis | | ± neck dissection | 10 to 12% of small lesions fail radiotherapy |
| Cervical nodes (rare with glottic CA) | | ± reconstruction | |
| | | | |
| **Salivary Gland** | | | |
| Painless mass (occ. pain is possible) | FNA | 1st surgery | 5 yr survival |
| CN VII palsy | MRI/CT/U/S | ± neck dissection | T1: 53%
| Cervical lymphadenopathy | | Post-operative radiotherapy | T2/T3: 36-39%
| Rapid growth | | Chemotherapy if unresectable | T4: 24%
| Invasion of skin | | | |
| Constitutional signs/symptoms | | | |
| | | | |
| **Thyroid** | | | |
| Thyroid mass, cervical nodes | FNA | 1st surgery | Recurrences occur within 5 yr |
| Vocal cord paralysis | U/S | for intermediate and high risk | Need long-term follow-up: clinical exam, thyroglobulin |
| Hyper/hypo thyroidism | | well differentiated thyroid cancer | |
| Dysphagia | | | |
| | | | |
| **Parathyroid** | | | |
| Increased serum Ca²⁺ | Sestamibi | Wide surgical excision | Recurrence rates |
| Neck mass | | Post-operative monitoring of serum Ca²⁺ | 1 yr: 27% |
| Bone disease, renal disease | | | 5 yr: 82%
| Pancreatitis | | | 10 yr: 91%
| | | Mean survival: 6-7 yr | |

Note: TMN stage (I, II, III, IV)
Thyroid Carcinoma

Table 18. Bethesda Classification of Thyroid Cytology

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic or unsatisfactory</td>
<td>Unknown</td>
</tr>
<tr>
<td>Benign</td>
<td>0·3%</td>
</tr>
<tr>
<td>Follicular lesion of undetermined significance/</td>
<td>5·15%</td>
</tr>
<tr>
<td>Atypia of undetermined significance</td>
<td></td>
</tr>
<tr>
<td>Follicular/hürthle cell neoplasms</td>
<td>15·30%</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60·75%</td>
</tr>
<tr>
<td>Malignant</td>
<td>97·99%</td>
</tr>
</tbody>
</table>

Table 19. Thyroid Carcinoma

<table>
<thead>
<tr>
<th>Papillary</th>
<th>Follicular</th>
<th>Medullary</th>
<th>Anaplastic</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (% of all thyroid cancers)</td>
<td>70·80%</td>
<td>10·15%</td>
<td>1 to 2%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Route of Spread</td>
<td>Lymphatic</td>
<td>Hematogenous</td>
<td>Lymphatic and hematogenous</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Histology</td>
<td>Orphan Annie nuclei</td>
<td>Papillary architecture</td>
<td>Amyloid</td>
<td>Giant cells</td>
</tr>
<tr>
<td></td>
<td>Psammoma bodies</td>
<td></td>
<td>May secrete calcitonin, prostaglandins,</td>
<td>Spindle cells</td>
</tr>
<tr>
<td></td>
<td>Papillary architecture</td>
<td></td>
<td>ACTH, serotonin, kallikrein, or bradykinin</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Ps – Papillary cancer</td>
<td>Fs – Follicular cancer</td>
<td>Fs – Medullary cancer</td>
<td>Usually non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Popular (most common)</td>
<td>For away mets</td>
<td>Multiple endocrine neoplasia (MEN Ia or Iib)</td>
<td>Rapidly enlarging thyroid mass</td>
</tr>
<tr>
<td></td>
<td>Palpable lymph nodes</td>
<td>Female (3:1)</td>
<td>aMyloid</td>
<td>Hx of Hashimoto’s thyroiditis increases</td>
</tr>
<tr>
<td></td>
<td>Positive 18F uptake</td>
<td>NOT FNA (cannot be diagnosed by FNA)</td>
<td>Medullary node dissection</td>
<td>60x</td>
</tr>
<tr>
<td></td>
<td>Positive prognosis</td>
<td>Favourable prognosis</td>
<td>Rule out lymphoma</td>
<td>4:1 female predominance dysphagia, dyspnea, stridor, hoarseness, neck pain, facial edema, accompanied by “B” symptoms*</td>
</tr>
<tr>
<td></td>
<td>Post-operative 18F scan to</td>
<td></td>
<td>More common in elderly</td>
<td>Usually non-surgical Combined radiation</td>
</tr>
<tr>
<td></td>
<td>guide treatments</td>
<td></td>
<td>70% in women</td>
<td>Chemotherapy (CHOP**)</td>
</tr>
<tr>
<td>Prognosis</td>
<td>98% at 10 yr</td>
<td>92% at 10 yr</td>
<td>50% at 10 yr</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Small tumours: Near total</td>
<td>Small tumours: Near total</td>
<td>Total thyroidectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>thyroidecctomy or lobectomy</td>
<td>thyroidecctomy or lobectomy/</td>
<td>Median and/or lateral compartment node</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse/bilateral: Total</td>
<td>isthmoctomy</td>
<td>neck dissection (based on serum calcitonin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>thyroidecctomy ± neck</td>
<td>Large/diffuse tumours: Total thyroidecctomy</td>
<td>Modified neck dissection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dissection ± post-operative 18F treatment</td>
<td></td>
<td>Post-ope ative thyroxine, radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>Tracheostomy</td>
<td>Screen relatives</td>
<td>Tracheostomy</td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>Subtotal thyroidectomy,</td>
<td></td>
<td>Screen relatives</td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>radiation, chemotherapy,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>palliative care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>Small tumours: Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>thyroidectomy ± external beam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>Non-surgical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>Combined radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powere</td>
<td>Chemotherapy (CHOP**)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* B symptoms = fever, night sweats, chills, weight loss > 10% in 6 mo
** CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

Approach to Thyroid Nodule
- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- intermediate-high suspicion nodule >1 cm and low suspicion nodule >1.5 cm should undergo FNA
- nodules <1 cm with clinical symptoms or lymphadenopathy may require further evaluation
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule

Table 20. Management of the Thyroid Nodule

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioiodine therapy</td>
<td>For the treatment of hyperthyroidism or as adjuvant treatment after surgery in the treatment of intermediate-high risk papillary or follicular carcinoma</td>
</tr>
<tr>
<td>Chemotherapy and/or radiotherapy</td>
<td>Recurrent/residual medullary CA, anaplastic CA or thyroid lymphoma</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Nodule that is suspicious on FNA cytology</td>
</tr>
<tr>
<td></td>
<td>Malignancy other than anaplastic CA or thyroid lymphoma</td>
</tr>
<tr>
<td></td>
<td>Mass that on FNA is benign but increasing in size on serial imaging and/or &gt;3-4 cm in size</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism not amenable to medical therapy</td>
</tr>
</tbody>
</table>

* U/S findings: cyst c: risk of malignancy < 1%; solid risk of malignancy - 10%; solid with cystic c: imprints: risk of malignancy same as if solid
Acute Otitis Media

Definition
all of: presence of middle ear effusion (MEE); presence of middle ear inflammation (MEI); acute onset of symptoms of MEE and MEI

Epidemiology
- most frequent diagnosis in sick children visiting clinicians' offices and most common reason for antibiotic administration
- peak incidence between 6–15 mo; ~85% of children have >1 episode by 3 yr old
- seasonal variability: peaks in winter

Etiology
- primary defect causing AOM: Eustachian tube dysfunction/obstruction → stasis/colonization by pathogens
- bacterial: *S pneumoniae*, non-typable *H. influenzae*, *M. catarrhalis*, Group A *Streptococcus*, *S. aureus*
- viral: RSV, influenza, parainfluenza, adenovirus
- commonly due to bacterial/viral co-infection

Predisposing Factors
- Eustachian tube dysfunction/obstruction
  - swelling of tubal mucosa
  - upper respiratory tract infection (URTI)
  - allergic rhinitis
  - chronic rhinosinusitis
- obstruction/infiltration of Eustachian tube ostium
  - tumour: nasopharyngeal carcinoma (adults)
  - adenoid hypertrophy (by maintaining a source of infection rather than obstruction)
  - barotrauma (sudden changes in air pressure)
- inadequate tensor palati function: cleft palate (even after repair)
- abnormal Eustachian tube
  - Down syndrome (horizontal position of Eustachian tube), Crouzon syndrome, cleft palate, and Apert syndrome
- disruption of action of:
  - cilia of Eustachian tube: Kartagener’s syndrome
  - mucus secreting cells
  - capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, cystic fibrosis

Risk Factors
- non-modifiable: young age, family history of OM, prematurity, orofacial abnormalities, immunodeficiencies, Down syndrome, race, and ethnicity
- modifiable: lack of breastfeeding, day care attendance, household crowding, exposure to cigarette smoke and air pollution, pacifier use

Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features
- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers
  - ear-tugging (this alone is not a good indicator of pathology)
  - hearing loss, balance disturbances (rare)
  - irritable, poor sleeping
  - vomiting and diarrhea
  - anorexia
- otoscopy of TM
  - hyperemia
  - bulging, pus may be seen behind TM
  - loss of landmarks: handle and long process of malleus not visible

Clinical Assessment of AOM in Pediatrics
*JAMA* 2010;304:2161-69
In assessment of AOM in pediatrics, ear pain is the most useful symptom with a likelihood ratio (LR) between 3.0-7.3. Useful otoscopic signs include erythema (LR 8.4, 95% CI 7-11), cloudy (LR 51, 95% CI 36-73), and immobile tympanic membrane (LR 31, 95% CI 26-37) on pneumatic otoscopy.
Diagnosis

- **history**
  - acute onset of otalgia or ear tugging in a preverbal child
  - otorrhea, decreased hearing
  - unexplained irritability, fever, upper respiratory symptoms, poor sleeping, anorexia, N/V, and diarrhea
- **physical**
  - febrile
  - MEE on otoscopy: immobile tympanic membrane, acute otorrhea, loss of bony landmarks, opacification of TM, air-fluid level behind TM
- **MEI on otoscopy:** bulging TM with marked discolouration (hemorrhagic, red, grey, or yellow)

Management

- supportive care and symptom management: maintain hydration, analgesic, and antipyretic (acetaminophen, ibuprofen)
- watchful waiting: in a generally healthy child >6 mo of age with unilateral non-severe suspected AOM
  - without MEE, OR with MEE but non-bulging or mildly erythematous TM
  - consider viral etiology
  - reassess in 24-48 h if not clinically improved (or earlier if worsening)
  - mildly ill (alert, responsive, no rigors, mild otalgia, fever <39°C, <48 h illness) with MEE present
  - AND bulging TM
  - recommend analgesia
    - observe and follow-up in 24-48 h – if not improved or worsening, treat with antimicrobials
  - antimicrobials indicated: infants <6 mo of age, or in a generally healthy child >6 mo of age with suspected AOM and the following features
    - moderately or severely ill (irritable, difficulty sleeping, poor antipyretic response, severe otalgia
      OR fever ≥39°C OR >48 h of symptoms
    - treat with antimicrobials: 10 d course if 6-24 mo, 5 d if ≥2 yr old
    - perforated TM with purulent drainage
    - treat with antimicrobials for 10 d
    - referral to otolaryngology for myringotomy and tympanostomy tubes may be warranted for recurrent infections

Treatment

- antimicrobial agents for AOM
  - 5 d course of appropriate dose antimicrobial recommended for most ≥ 2 yr old with uncomplicated AOM.
  - 10 d course for 6-24 mo, and perforated TM or recurrent AOM
  - 1st line treatment (no penicillin allergy)
    - amoxicillin: 5 d course of 45-60 mg/kg/d divided 3x/d, or 75-90 mg/kg/d divided 2x/d
  - 2nd line treatment
    - cefprozil: 30 mg/kg/d divided 2x/d
    - cefuroxime axetil: 30 mg/kg/d divided 2-3x/d (1st line for penicillin allergy)
    - ceftriaxone: 50 mg/kg IM (or IV) x 3 doses (1st line for penicillin allergy)
    - azithromycin: 10 mg/kg OD x 1 dose, then 5 mg/kg OD x 4 doses
    - clarithromycin: 15 mg/kg/d divided 2x/d
  - if initial therapy fails (i.e. no symptomatic improvement after 2-3 d)
    - amoxicillin-clavulanate: 45-60 mg/kg/d (7:1 formulation, 400 mg/5 mL suspension) for 10 d for child weighing ≤35 kg, or 500 mg tablets TID for 10 d for child weighing >35 kg
    - if AOM-related symptoms do not resolve with amoxicillin-clavulanate, a course of ceftriaxone 50 mg/kg/d IM (or IV) OD x 3 doses could be considered

Complications

- extracranial
  - hearing loss and speech delay (secondary to persistent MEE), TM perforation, extension of supplicative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction, persistent effusion (often leading to hearing loss)
- intracranal
  - meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis, facial nerve paralysis
- other
  - mastoiditis, labyrinthitis, sigmoid sinus thrombophlebitis

Otitis Media with Effusion

Definition

- presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology

- most common cause of pediatric hearing loss
- not exclusively a pediatric disease
- frequently follows AOM in children
- middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10% (i.e. 90% of children clear the fluid within 3 mo – observe for 3 mo before considering myringotomy and tubes)
Risk Factors
- same as AOM

Clinical Features
- conductive hearing loss ± tinnitus
  - confirm with audiogram and tympanogram (flat) (see Figure 16B, OT10 and Figure 17B, OT11)
- fullness – blocked ear
  ± pain, low grade fever
- otoscopy of tympanic membrane
  - discoloration – amber or dull grey with "glue" ear
  - meniscus fluid level behind TM
  - air bubbles
  - retraction pockets/TM atelectasis
  - most reliable finding with pneumatic otoscopy is immobility

Treatment
- expectant: 90% resolve by 3 mo
  - watchful waiting for 3 mo from onset, or 3 mo from diagnosis if onset unknown
  - document hearing loss with audiogram
  - no clinical evidence that antihistamines, decongestants, or antibiotics clear disease faster
  - recommend against intranasal or systemic steroids, systemic antibiotics, antihistamines, decongestants for OME treatment
  - surgery: myringotomy ± ventilation tubes to equalize pressure and drain ear (tympanostomy tubes recommended) ± adenoidectomy (not recommended in <4 yr old unless nasal obstruction, chronic adenoiditis; recommended in ≥ 4 yr old)

Complications of Otitis Media with Effusion
- hearing loss, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma, especially when retraction pockets involve pars flaccida
- retraction of tympanic membrane, atelectasis, ossicular fixation

Adenoid Hypertrophy
- size peaks at age 5 and resolves by age 12
- increase in size with repeated URTI and allergies

Clinical Features
- nasal obstruction
  - adenoid facies (open mouth, high arched palate, narrow midface, malocclusion)
  - history of hypernasal voice and snoring
  - long-term mouth breather; minimal air escape through nose
- choanal obstruction
  - chronic rhinosinusitis/rhinitis
  - obstructive sleep apnea
- chronic inflammation
  - nasal discharge, post nasal drip, and cough
  - cervical lymphadenopathy

Diagnosis
- enlarged adenoids on nasopharyngeal exam (usually with flexible nasopharyngoscope)
- enlarged adenoid shadow on lateral soft tissue x-ray

Complications
- Eustachian tube obstruction leading to serous otitis media
  - interference with nasal breathing, necessitating mouth-breathing
- malocclusion
- sleep apnea/respiratory disturbance
- orofacial developmental abnormalities

Adenoidectomy
Indications for Adenoidectomy
- chronic upper airway obstruction with sleep disturbance/apnea ± cor pulmonale
- chronic nasopharyngitis resistant to medical treatment
- chronic serous otitis media and chronic supplicative otitis media (with 2nd set of tubes)
- recurrent acute otitis media resistant to antibiotics
- suspicion of nasopharyngeal malignancy
- persistent rhinorrhea secondary to nasal obstruction
Contraindications
• uncontrollable coagulopathy
• recent pharyngeal infection
• conditions that predispose to velopharyngeal insufficiency (cleft palate, impaired palatal function, or enlarged pharynx)

Complications
• bleeding, infection
• velopharyngeal insufficiency (hypernasal voice or nasal regurgitation)
• scarring of Eustachian tube orifice

Sleep-Disordered Breathing in Children

Definition
• spectrum of sleep-related breathing abnormalities ranging from snoring to OSA

Epidemiology
• peak incidence between 2-8 yr when tonsils and adenoids are the largest relative to the pharyngeal airway

Etiology
• due to a combination of anatomic and neuromuscular factors
  • adenotonsillar hypertrophy
  • craniofacial abnormalities
  • neuromuscular hypotonia (i.e. cerebral palsy, Down syndrome)
  • obesity

Clinical Features
• heavy snoring, mouth breathing pauses or apnea, enuresis, excessive daytime sleepiness, behavioural/learning problems, diagnosis of ADHD, morning headache, failure to thrive, sleeping with neck hyperextended, cyanosis

Investigations
• flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
• polysomnography (apnea-hypopnea index >1/h considered abnormal)
  • children: Mild OSA ≥1 to <5/h; Moderate OSA ≥5 to <10/h; Severe OSA ≥10/h
  • adults: Mild OSA 5.1-15/h; Moderate OSA 15.1-30/h; Severe OSA >30.1/h

Treatment
• nonsurgical: CPAP, BiPAP, sleep hygiene, weight loss in overweight/obese child with OSA
• medication: topical nasal steroids and leukotriene-receptor antagonists for mild OSA or residual sleep-disordered breathing post-adenotonsillectomy
• surgical: bilateral tonsillectomy and adenoidectomy is first surgery of choice
  • if persistent obstructive sleep apnea following tonsillectomy and adenoidectomy, consider adenoid regrowth
  • if these fail and not tolerant of PAP therapy, consider lingual tonsillectomy, midline glossectomy, or other surgeries targeting areas of resistance as required (STAR surgery); surgery may be guided by Drug-Induced Sleep Endoscopy (DISE) or CINE-MRI to localize site of resistance

Acute Tonsillitis
• see Pediatrics, P52

Peritonsillar Abscess (Quinsy)

Definition
• cellulitis of space behind tonsillar capsule extending onto soft palate, leading to abscess

Etiology
• bacterial: Group A strep (GAS) (50% of cases), S. pyogenes, S. aureus, H. influenzae, and anaerobes

Epidemiology
• can develop from acute tonsillitis with infection spreading into plane of tonsillar bed
• unilateral
• most common in 15-30 yr age group

Clinical Features
• trismus (due to irritation and reflex spasm of the medial pterygoid) is the most reliable indicator of peritonsillar abscess
• fever and dehydration
• sore throat, dysphagia, and odynophagia
• extensive peritonsillar swelling but tonsil may appear normal
- edema of soft palate
- uvular deviation
- dysphonia (edema → failure to elevate palate) 2° to CN X involvement
- unilateral referred otalgia
- cervical lymphadenitis

**Complications**
- aspiration pneumonia 2° to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

**Treatment**
- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 d if cultures positive for GAS
- add PO/IV metronidazole or clindamycin x 10 d if culture positive for Bacteroides
- consider tonsillectomy after second episode

**Other Sources of Parapharyngeal Space Infections**
- pharyngitis
- acute suppurative parotitis (see Salivary Glands, OT30)
- AOM
- mastoiditis (Bezold's abscess)
- odontogenic infection

---

### Tonsillectomy

**Absolute Indications**
- most common indication: sleep-disordered breathing
- 2nd most common indication: recurrent throat infections
- tonsillar hypertrophy causing upper airway obstruction, obstructive sleep apnea, severe dysphagia, or cardiopulmonary complications such as cor pulmonale
- suspicion of malignancy (e.g. lymphoma, squamous cell carcinoma)
- orofacial/dental deformity
- hemorrhagic tonsillitis

**Relative Indications (To Reduce Disease Burden)**
- recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 yr, or at least 3 episodes per year for 3 yr, with documentation in the medical record for each episode of sore throat and 1 or more of the following: temperature >38.3 °C, cervical adenopathy, tonsillar exudate, or positive test for Group A β-hemolytic *Streptococcus* (Paradise Criteria)
- chronic tonsillitis with halitosis (bad breath) or sore throat ± tonsilloliths (clusters of material that form in the crevices of the tonsils)
- complications of tonsillitis: quinsy/peritonsillar abscess, parapharyngeal abscess, retropharyngeal abscess
- failure to thrive

**Relative Contraindications**
- velopharyngeal insufficiency: overt or submucous/covert cleft of palate, impaired palatal function due to neurological or neuro-muscular abnormalities
- hematologic: coagulopathy, anemia
- infectious: active local infection without urgent obstructive symptoms

**Complications**
- hemorrhage: primary (within 24 h); secondary (within first 7-10 d)
- odynophagia and/or otalgia; dehydration 2° to odynophagia
- infection
- atlantoaxial subluxation (Grisel's syndrome) - rare

---

### Airway Problems in Children

**DIFFERENTIAL DIAGNOSIS BY AGE GROUP**

**Neonates (Obligate Nose Breeders)**
- extralaryngeal
  - choanal atresia (e.g. CHARGE syndrome)
  - nasopharyngeal dermoid, glioma, encephalocele
  - glossoptosis: Pierre-Robin sequence, Down syndrome, lymphatic malformation, hemangioma
• laryngeal
  ▪ laryngomalacia: most common cause of stridor in children
  ▪ vocal cord palsy (due to trauma or Arnold-Chiari malformation)
  ▪ glottic web
  ▪ subglottic stenosis
  ▪ laryngeal cleft
  ▪ laryngocele
• tracheal
  ▪ tracheoesophageal fistula
  ▪ tracheomalacia
  ▪ vascular rings
  ▪ complete tracheal rings

2-3 Months
• congenital
  ▪ laryngomalacia
  ▪ vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
  ▪ laryngeal papilloma
• acquired
  ▪ subglottic stenosis: post-intubation
  ▪ tracheal granulation: post-intubation
  ▪ tracheomalacia: post-tracheotomy and TEF repair

Infants – Sudden Onset
• foreign body aspiration
• croup
• bacterial tracheitis
• caustic ingestion
• epiglottitis

Children and Adults
• infection
  ▪ Ludwig’s angina
  ▪ peritonsillar/parapharyngeal abscess
  ▪ retropharyngeal abscess
• neoplastic
  ▪ squamous cell carcinoma (SCC) (adults): larynx, hypopharynx
  ▪ retropharyngeal: lymphoma, neuroblastoma
  ▪ nasopharyngeal: carcinoma, rhabdomyosarcoma
• allergic
  ▪ angioneurotic edema
  ▪ polyps (suspect cystic fibrosis in children)
• trauma
  ▪ laryngeal fracture, facial fracture
  ▪ burns and lacerations
  ▪ post-intubation
  ▪ caustic ingestion
• congenital
  ▪ lingual thyroglossal duct cyst
  ▪ lingual tonsil hypertrophy
  ▪ lingual thyro de

**Signs of Airway Obstruction**

**Stridor**
• note quality, timing (inspiratory or expiratory)
• body position important
  ▪ lying prone: double aortic arch
  ▪ lying supine: laryngomalacia, glossoptosis
• site of stenosis
  ▪ vocal cords or above: inspiratory stridor
  ▪ subglottis and extrathoracic trachea: biphasic stridor
  ▪ distal tracheobronchial tree: expiratory stridor

**Respiratory Distress**
• nasal flaring
• supraclavicular and intercostal indrawing
• sternal retractions
• use of accessory muscles of respiration
• tachypnea
• cyanosis
• altered LOC
Feeding Difficulty and Aspiration
- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- laryngeal cleft → aspiration pneumonia
- TEF

Acute Laryngotracheobronchitis (Croup)

Definition
- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining and associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space is narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

Etiology
- viral: parainfluenzae I (most common), II, III, influenza A and B, RSV

Clinical Features
- age: 4 mo-5 yr
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea lion bark)
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- "steeple-sign" on AP X-ray of neck
- if recurrent croup, think subglottic stenosis

Treatment
- racemic epinephrine via MDI q1-2h prn (only if in respiratory distress)
- systemic corticosteroids (e.g. dexamethasone 0.5 mg/kg, prednisone)
- adequate hydration
- close observation for 3-4 h
- intubation if severe (use smaller endotracheal tube than expected for age)
- hospitalize if poor response to steroids after 4 h and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)
- if recurrent episodes of croup-like symptoms, perform high kV croup series X-ray (AP and lat) when well to rule out underlying subglottic stenosis and consider bronchoscopy for definitive diagnosis

Acute Epiglottitis

Definition
- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

Etiology
- H. influenzae type b
- relatively uncommon condition due to Hib vaccine

Clinical Features
- any age most commonly 1-4 yr
- rapid onset
- toxic-looking, fever, anorexia, restlessness
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up ("tripod" posture), open mouth, drooling, tongue protruding, sore throat, dysphagia

Investigations and Management
- investigations and physical exam may lead to complete obstruction, thus preparations for intubation or tracheotomy must be made prior to any manipulation
- stat ENT/anesthesia consult(s)
- WBC (elevated), blood and pharyngeal cultures after intubation
- lateral neck radiograph (only done if patient stable)

Treatment
- secure airway
- IV access with hydration
- antibiotics: IV cefuroxime, cefotaxime, or ceftriaxone
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis

When managing epiglottitis, it is important not to agitate the child, as this may precipitate complete obstruction

Thumb sign: cherry-shaped epiglottic swelling seen on lateral neck radiograph
Subglottic Stenosis

Congenital
- Diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage)

Acquired
- Following prolonged, repeated, or traumatic intubation
  - Most commonly due to endotracheal intubation; nasal intubation is less traumatic and preferred in long-term intubation, as it puts less pressure on the subglottis (tube sits at different orientation) and there is less movement
  - Subglottic stenosis is related to duration of intubation and pressure of the endotracheal tube cuff
- Can also be due to foreign body, infection (e.g., TB, diphtheria, syphilis), or chemical irritation

Clinical Features
- Biphasic stridor
- Respiratory distress
- Recurrent/prolonged croup

Diagnosis
- Rigid laryngoscopy and bronchoscopy

Treatment
- If soft stenosis: divide tissue with knife or laser, dilate with balloon ± steroids
- If firm stenosis: laryngotracheoplasty

Laryngomalacia

- Short aryepiglottic folds, omega-shaped epiglottis, pendulous mucosa
- Caused by indrawing of supraglottis on inspiration, leading to laryngopharyngeal reflux of acid

Clinical Features
- High-pitched inspiratory stridor at 1-2 wk
- Stridor is constant or intermittent and more pronounced supine and following URTI
- Usually mild but can be associated with cyanosis or feeding difficulties when severe, leading to failure to thrive

Treatment
- Observation ± proton pump inhibitor (to break the acid reflux cycle that leads to edema and worse airway obstruction) is usually sufficient, as symptoms spontaneously subside by 12-18 mo in >90% of cases
- If severe, division of the aryepiglottic folds (supraglottoplasty) provides relief

Foreign Body

Ingested
- Usually stuck at cricopharyngeus muscle
- Coins, toys, batteries (emergency)
- Presents with drooling, dysphagia, stridor if very large

Aspirated
- Usually stuck at right main bronchus
- Peanuts, carrot, apple core, popcorn, balloons
- Presentation
  - Stridor if lodged in trachea
  - Unilateral “asthma” if bronchial, therefore often misdiagnosed as asthma
  - If totally occludes airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax, death

Diagnosis and Treatment
- Sudden onset, not necessarily febrile or elevated WBC
- Any patient with suspected foreign body should be kept NPO immediately
- Older patient: inspiratory-expiratory chest X-ray (if patient is stable)
- Younger patient: right and left decubitus chest X-rays. Lack of lung deflation while resting on dependent side suggests foreign body blocking bronchus
- Bronchoscopy or esophagoscopy with removal

Batteries MUST be ruled out as a foreign body (vs. coins) as they are lethal and can erode through the esophagus. Batteries have a halo sign around the rim on AP x-ray and a step deformity on lateral x-ray
**Deep Neck Space Infection**

- most commonly arise from an infection of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
- often a rapid onset and may progress to fatal complications

**Etiology**
- usually mixed aerobes and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes

**Clinical Features**
- sore throat or pain and trismus
- dysphagia and odynophagia
- stridor and dyspnea
- late findings may include dysphonia and hoarseness
- swelling of the face and neck, erythema
- asymmetry of the oropharynx with purulent oral discharge
- lymphadenopathy

**Diagnosis**
- lateral cervical view plain radiograph
- CT
- MRI

**Treatment**
- secure the airway
- surgical drainage
- maximum doses of IV systemic antimicrobials regimens according to the site of infection

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**Table 21. Antibiotics**

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin (Amox®, Amoxi®, Amox®)</td>
<td>Adult: 500 mg PO tid Children: 75-90 mg/kg/d in 2 divided doses</td>
<td>Streptococcus, Pneumococcus, H. influenzae, Proteus coverage</td>
<td>May cause rash in patients with infectious mononucleosis</td>
</tr>
<tr>
<td>piperacillin with tazobactam (Zosyn®)</td>
<td>3 g PO q6h</td>
<td>Gram-positive and negative aerobes and anaerobes plus Pseudomonas coverage</td>
<td>May cause pseudomembranous colitis</td>
</tr>
<tr>
<td>ciprofloxacin (Cipro®, Citoxan®)</td>
<td>500 mg PO bid</td>
<td>Pseudomonas, Streptococci, MRSA, and most Gram-negative; no anaerobic coverage</td>
<td>Animal studies suggest that systemic quinolones may cause cartilage necrosis in children</td>
</tr>
<tr>
<td>erythromycin (Erythrocin®, EryPed®, Staticin®, T-Stat®, Erybid®, Novorythro Encap®)</td>
<td>500 mg PO qid</td>
<td>Alternative to penicillin</td>
<td>Ototoxic</td>
</tr>
</tbody>
</table>

**Table 22. Otic Drops**

<table>
<thead>
<tr>
<th>Generic Name (B and Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciprofloxacin (CiproDex®)</td>
<td>4 gtt in affected ear bid</td>
<td>For otitis externa and complications of otitis media Pseudomonas, Streptococci, MRSA, and most Gram-negative; no anaerobic coverage</td>
<td></td>
</tr>
<tr>
<td>neomycin, polymyxin B sulfate, and hydrocortisone (Cortisporin Otic®)</td>
<td>5 gtt in affected ear tid</td>
<td>For otitis externa Used for inflammatory conditions which are currently infected or at risk of bacterial infections</td>
<td>May cause hearing loss if placed in inner ear</td>
</tr>
<tr>
<td>hydrocortisone and acetic acid (VoSol HC®)</td>
<td>5-10 gtt in affected ear tid</td>
<td>For otitis media</td>
<td>Bactericidal by lowering pH</td>
</tr>
<tr>
<td>tobramycin and dexamethasone (TobraDex®)</td>
<td>5-10 gtt in affected ear bid</td>
<td>For chronic suppurative otitis media</td>
<td>Risk of vestibular or cochlear toxicity</td>
</tr>
</tbody>
</table>
### Table 23. Nasal Sprays

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>flunisolide (Rhinalar®)</td>
<td>Allergic rhinitis</td>
<td>Requires up to 4 wk of consistent use to have effect</td>
</tr>
<tr>
<td>budesonide (Rhinocort®)</td>
<td>Chronic sinusitis</td>
<td>Long-term use</td>
</tr>
<tr>
<td>triamcinolone (Nasacort®)</td>
<td></td>
<td>Dries nasal mucosa; may cause minor bleeding</td>
</tr>
<tr>
<td>beclomethasone (Beconase®)</td>
<td></td>
<td>Patient should stop if epistaxis</td>
</tr>
<tr>
<td>mometasone furoate, monohydrate (Nasonex®)</td>
<td></td>
<td>May sting</td>
</tr>
<tr>
<td>fluticasone furoate (Avamys®)</td>
<td></td>
<td>Flonase® and Nasonex® not absorbed systemically</td>
</tr>
<tr>
<td><strong>Antihistamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levocarbastine (Livostin®)</td>
<td>Allergic rhinitis</td>
<td>Immediate effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If no effect by 3 d then discontinue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use during allergy season</td>
</tr>
<tr>
<td><strong>Decongestant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>xylometazoline (Otr vin®)</td>
<td>Acute sinusitis</td>
<td>Careful if patient has hypertension</td>
</tr>
<tr>
<td>oxymetazoline (Dristan®)</td>
<td>Rhinitis</td>
<td>If short-term use (&lt;5 d)</td>
</tr>
<tr>
<td>phényléphrine (Neosynephrine®)</td>
<td></td>
<td>If long-term use, can cause decongestant addiction (i.e. rhinitis medicamentosa)</td>
</tr>
<tr>
<td><strong>Antibiotic/Decongestant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>framycetin, gramicidin, phényléphrine (Soframycin®)</td>
<td>Acute sinusitis</td>
<td></td>
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<tr>
<td><strong>Anticholinergic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipratropium bromide (Atrovent®)</td>
<td>Vasomotor rhinitis</td>
<td>Careful not to spray into eyes as can cause burning or precipitation of narrow angle glaucoma</td>
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<tr>
<td></td>
<td></td>
<td>Increased rate of epistaxis when combined with topical nasal steroids</td>
</tr>
<tr>
<td><strong>Lubricants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saline, NeilMed®, Rhinaris®</td>
<td>Dry nasal mucosa</td>
<td>Use prn</td>
</tr>
<tr>
<td>Secaris®, Polysporin®, Vaseline®</td>
<td></td>
<td>Rhinaris® and Secaris® may cause stinging</td>
</tr>
</tbody>
</table>

Source: Dr. MM Carr
**Acronyms**

- GASTRO : Gastroenterology
- CARD : Cardiology
- GENETIC : Genetics, Dysmorphisms, and Metabolism
- ONCO : Oncology
- INFECT : Infectious Diseases

**Pediatric Quick Reference Values**

- 3

**Primary Care**

- 3

1. Visit Overview
2. Routine Immunization
3. Growth and Development
4. Nutrition
5. Injury Prevention Counselling

**Common Complaints**

- 8

1. Breath Holding Spells
2. Circumcision
3. Crying/Fussing Child
4. Infantile Colic
5. Dentition and Caries
6. Enuresis
7. Encopresis
8. Toilet Training
9. Failure to Thrive
10. Obesity
11. Poison Prevention
12. Rashes
13. Sleep Disturbances
14. Sudden Infant Death Syndrome

**Child Abuse and Neglect**

- 14

1. Physical Abuse
2. Sexual Abuse
3. Neglect

**Adolescent Medicine**

- 15

**Cardiology**

- 16

1. Congenital Heart Disease
2. Atrioventricular Canal (AVM) Heart Disease
3. Cyanotic Congenital Heart Disease
4. Congestive Heart Failure
5. Dysrhythmias
6. Heart Murmurs
7. Infective Endocarditis

**Development**

- 22

1. Approach to Global Developmental Delay
2. Intellectual Disability
3. Language Delay
4. Specific Learning Disorder
5. Fetal Alcohol Spectrum Disorder
6. Attention Deficit Hyperactivity Disorder
7. Autism Spectrum Disorder
8. Motor Delay

**Endocrinology**

- 25

1. Antidiuretic Hormone
2. Diabetes Mellitus
3. Growth
4. Hypercalciemia/Hypocalciemia/Rickets
5. Hyperthyroidism and Hypothyroidism
6. Sexual Development

**Gastroenterology**

- 32

1. Vomiting
2. Gastroesophageal Reflux
3. Tracheoesophageal Fistula
4. Pyloric Stenosis
5. Duodenal Atresia
6. Malrotation of the Intestine
7. Diarrhea
8. Gastroenteritis
9. Toddler’s Diarrhea
10. Lactase Deficiency (Lactose Intolerance)
11. Irritable Bowel Syndrome
12. Celiac Disease
13. Milk Allergy (MA) and Cow’s Milk Protein Allergy
14. Inflammatory Bowel Disease
15. Cystic Fibrosis
16. Constipation
17. Abdominal Pain
18. Chronic Abdominal Pain
19. Abdominal Mass
20. Upper Gastrointestinal Bleeding
21. Lower Gastrointestinal Bleeding

**Genetics, Dysmorphisms, and Metabolism**

- MG4

1. Congenital Anomalies
2. Approach to the Dysmorphic Child
3. Genetic Syndromes
4. Metabolic Diseases

**Hematology**

- 40

1. Approach to Anemia
2. Physiologic Anemia
3. Iron Deficiency Anemia
4. Vitamin K Deficiency
5. Anemia of Chronic Disease
6. Sickle Cell Disease
7. Thalassemia
8. Hereditary Spherocytosis
9. Glucose-6-Phosphate Dehydrogenase Deficiency
10. Bleeding Disorders
11. Immune Thrombocytopenic Purpura
12. Hemophilia
13. von Willebrand’s Disease

**Oncology**

- 43

1. Lymphadenopathy
2. Leukemia
3. Lymphoma
4. Brain Tumours
5. Wilms’ Tumour (Nephroblastoma)
6. Neuroblastoma
7. Bone Tumours
8. Cancer Predisposition Syndromes

**Infectious Diseases**

- 46

1. Fever
2. Acute Otitis Media
3. Otitis Media with Effusion
4. Gastroenteritis
<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td></td>
</tr>
<tr>
<td>HIV Infection</td>
<td></td>
</tr>
<tr>
<td>Infectious Pediatric Exanthems</td>
<td></td>
</tr>
<tr>
<td>Infectious Mononucleosis</td>
<td></td>
</tr>
<tr>
<td>Infectious Pharyngitis/Tonsillitis</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Periorbital (Preseptal) and Orbital Cellulitis</td>
<td></td>
</tr>
<tr>
<td>Sexually Transmitted Infection</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>58</td>
</tr>
<tr>
<td>Neonatology</td>
<td>58</td>
</tr>
<tr>
<td>Gestational Age and Size</td>
<td></td>
</tr>
<tr>
<td>Routine Neonatal Care</td>
<td></td>
</tr>
<tr>
<td>Neonatal Resuscitation</td>
<td></td>
</tr>
<tr>
<td>Common Conditions of Neonates</td>
<td>60</td>
</tr>
<tr>
<td>Apnea</td>
<td></td>
</tr>
<tr>
<td>Bleeding Disorders in Neonates</td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia</td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td></td>
</tr>
<tr>
<td>Diaphragmatic Hernia</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Intraventricular Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td></td>
</tr>
<tr>
<td>Persistent Pulmonary Hypertension of the Newborn</td>
<td></td>
</tr>
<tr>
<td>Respiratory Distress in the Newborn</td>
<td></td>
</tr>
<tr>
<td>Retinopathy of Prematurity</td>
<td></td>
</tr>
<tr>
<td>Sepsis in the Neonate</td>
<td></td>
</tr>
<tr>
<td>Skin Conditions of the Neonate</td>
<td></td>
</tr>
<tr>
<td>Fluids and Electrolytes</td>
<td>69</td>
</tr>
<tr>
<td>Approach to Infant/Child with Dehydration</td>
<td></td>
</tr>
<tr>
<td>Nephrology</td>
<td>71</td>
</tr>
<tr>
<td>Common Pediatric Renal Diseases</td>
<td></td>
</tr>
<tr>
<td>Hemolytic Uremic Syndrome</td>
<td></td>
</tr>
<tr>
<td>Nephritic Syndrome</td>
<td></td>
</tr>
<tr>
<td>Nephrotic Syndrome</td>
<td></td>
</tr>
<tr>
<td>Hypertension in Childhood</td>
<td></td>
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### Acronyms

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<td>ABG</td>
<td>arterial blood gas</td>
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<td>ACE</td>
<td>angiotensin converting enzyme</td>
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<td>ALL</td>
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<td>ALPS</td>
<td>autoimmune lymphoproliferative syndrome</td>
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<td>ANA</td>
<td>antinuclear antibody</td>
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<td>ARMD</td>
<td>alcohol-related neurodevelopmental disorder</td>
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<td>arteriovenous malformation</td>
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<td>BHR</td>
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<td>CAS</td>
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<td>CHD</td>
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<td>CML</td>
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<td>CMV</td>
<td>cytomegalovirus</td>
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<td>CP</td>
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<td>CPS</td>
<td>Canadian Pediatric Society</td>
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<td>diabetic ketoacidosis</td>
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<td>DMARD</td>
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<td>DS</td>
<td>Down syndrome</td>
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<td>echocardiogram</td>
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<td>EMB</td>
<td>electrolymography</td>
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<td>FSH</td>
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<tr>
<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
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<td>GA</td>
<td>gestational age</td>
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<td>GBS</td>
<td>group B streptococcus</td>
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<td>glycogen storage disease</td>
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<td>glomerulonephritis</td>
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<td>hemolytic disease of the newborn</td>
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<tr>
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<td>Haemoglobin A</td>
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<td>HbA1c</td>
<td>glycated hemoglobin</td>
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<td>Hb</td>
<td>hemoglobin</td>
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<td>HIE</td>
<td>hypoxic ischemic encephalopathy</td>
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<td>HLA</td>
<td>human leukocyte antigen</td>
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<td>human rotavirus</td>
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<td>HSD</td>
<td>Henoch-Schönlein purpura</td>
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<td>HUS</td>
<td>hemolytic uremic syndrome</td>
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<tr>
<td>IBW</td>
<td>ideal body weight</td>
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<tr>
<td>ICH</td>
<td>intracranial hemorrhage</td>
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<tr>
<td>ITP</td>
<td>immune thrombocytopenic purpura</td>
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<tr>
<td>ITU</td>
<td>intrauterine growth restriction</td>
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<tr>
<td>IVH</td>
<td>intraventricular hemorrhage</td>
</tr>
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<td>IVg</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>JIA</td>
<td>juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>LAH</td>
<td>left atrial hypertrophy</td>
</tr>
<tr>
<td>LGA</td>
<td>large for gestational age</td>
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<tr>
<td>LP</td>
<td>lumbar puncture</td>
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<tr>
<td>LLSD</td>
<td>lower left septal border</td>
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<td>LOC</td>
<td>level of consciousness</td>
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<td>LRTI</td>
<td>lower respiratory tract infection</td>
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<td>LUS</td>
<td>left upper septal border</td>
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<td>MCD</td>
<td>minimal change disease</td>
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<td>MDI</td>
<td>metastic bone disease</td>
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<td>MSU</td>
<td>maple syrup urine disease</td>
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<td>NICU</td>
<td>neonatal intensive care unit</td>
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<td>NS</td>
<td>normal saline</td>
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<tr>
<td>OCP</td>
<td>oral contraceptive pill</td>
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<td>ORT</td>
<td>oral rehydration therapy</td>
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<td>PDA</td>
<td>patent ductus arteriosus</td>
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<tr>
<td>PKU</td>
<td>phenylketonuria</td>
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<tr>
<td>PPHN</td>
<td>persistent pulmonary hypertension of newborn</td>
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<tr>
<td>PPV</td>
<td>positive pressure ventilation</td>
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<tr>
<td>PUS</td>
<td>psoriasis + UVA</td>
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<td>RAD</td>
<td>right axis deviation</td>
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<tr>
<td>RAS</td>
<td>renal artery stenosis</td>
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<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
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<td>RDS</td>
<td>respiratory distress syndrome</td>
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<tr>
<td>RF</td>
<td>rheumatoid factor</td>
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<tr>
<td>RL</td>
<td>Ringer’s lactate</td>
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<td>RSV</td>
<td>respiratory syncytial virus</td>
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<td>RSV</td>
<td>right upper septal border</td>
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<tr>
<td>RVH</td>
<td>right ventricular hypertrophy</td>
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<td>RVOT</td>
<td>right ventricular outflow tract obstruction</td>
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<td>SEM</td>
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<td>SGA</td>
<td>small for gestational age</td>
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<td>SIADH</td>
<td>syndrome of inappropriate antidiuretic hormone</td>
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<td>SVT</td>
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<td>TEF</td>
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<tr>
<td>TM</td>
<td>tympanic membrane</td>
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<td>TPN</td>
<td>total parenteral nutrition</td>
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<td>TTN</td>
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<td>UMN</td>
<td>upper motor neuron</td>
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<td>VUR</td>
<td>vesicoureteral reflux</td>
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<td>WPW</td>
<td>Wolf-Parkinson-White</td>
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### Pediatric Quick Reference Values

#### Table 1. Average Vitals at Various Ages

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<tr>
<th>Age (years)</th>
<th>Pulse (bpm)</th>
<th>Respiratory Rate (br/min)</th>
<th>sBP (mmHg)</th>
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<td>&lt;1</td>
<td>110-160</td>
<td>30-40</td>
<td>70-90</td>
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<td>1-2</td>
<td>100-150</td>
<td>25-35</td>
<td>80-95</td>
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<td>2-5</td>
<td>95-140</td>
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<tr>
<td>&gt;12</td>
<td>60-100</td>
<td>15-20</td>
<td>110-120</td>
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### Primary Care

#### Visit Overview

- **schedule**
  - newborn (within 1 wk post-discharge), 1, 2, 4, 6, 9, 12, 15, 18, 24 mo
  - annually between age 2-5; every 1-2 years between age 6-18
- **content**
  - history and physical exam including growth, development and nutrition
  - routine immunizations
  - counselling and anticipatory guidance
Routine Immunization

Table 2. Publicly Funded Immunization Schedule for Ontario, December 2016

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<thead>
<tr>
<th>Age</th>
<th>DTap-IPV</th>
<th>dtaP-IPV</th>
<th>Pneumococcal 13-valent</th>
<th>Rot-1</th>
<th>Men-C</th>
<th>MMR</th>
<th>Var</th>
<th>MMRV</th>
<th>Men-C-ACYW</th>
<th>HepB</th>
<th>HPV-4</th>
<th>Tdap</th>
<th>Inf</th>
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<td>✓ IM</td>
<td>✓ SC</td>
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<td>IM</td>
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<td>IM</td>
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<td>✓ IM</td>
<td>✓ PO</td>
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<td>✓ SC</td>
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<td>IM</td>
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<td>14-16 yr</td>
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<td></td>
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<td>IM</td>
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<td>Every autumn</td>
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<td></td>
<td>IM</td>
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</table>

IM = intramuscular; PO = per oral; SC = subcutaneous

Vaccine Adverse Reaction

DTaP-IM
- Prolonged crying
- Hypotonic unresponsive state (rare)
- Seizure on day of vaccine (rare)
- Anaphylactic reaction to neomycin or streptomycin

Rot-IM
- Cough
- Diarrhea, vomiting
- History of intussusception
- Immunocompromised
- Abdominal disorder (e.g. Meckel’s diverticulum)
- Received blood products (e.g. immunoglobulin) within 42 d

MMR
- Measles-like rash (7 14 d)
- Lymphadenopathy, arthralgia, arthritis
- Parotitis (rare)
- Especially painful injection
- Transient thrombocytopenia (1/30,000)

Var
- Mild varicella-like papules or vesicles;
- 2 wk may get local or generalized rash

HepB
- Anaphylactic reaction to Baker’s yeast

MMRV
- Same as MMR and Var vaccines

dTAP
- 1st trimester pregnancy

Inf
- Malaria, myalgia
- Febrile seizure when given with Pneu-C 13 or DTap

HPV-4*
- Urticaria, rhinitis, anaphylaxis

MenB**
- Anaphylactic reaction to MenB vaccine or its components in the past

Contraindication

- Evolving unstable neurologic disease
- Hyporesponsive/hypotonic following previous vaccine
- Anaphylactic reaction to neomycin or streptomycin
- History of intussusception
- Immunocompromised
- Abdominal disorder (e.g. Meckel’s diverticulum)
- Immunocompromised infants (except healthy HIV positive children)
- Anaphylactic reaction to gelatin
- Pregnancy
- Immunocompromised infants
- Healthy HIV positive children
- Anaphylactic reaction to gelatin
- Pregnant or planning to get pregnant within 3 mo
- Anaphylactic reaction to gelatin
- 1st trimester pregnancy
- <6 mo of age
- Immunocompromised
- Egg-allergic individuals – Live attenuated influenza vaccine is not recommended for those with an egg allergy. In these individuals, trivalent or quadrivalent vaccine can be given in environment where anaphylaxis can be managed

Vaccination in Cases of Asplenia or Hypersensitivity

- Should receive all routine immunizations, including the yearly influenza vaccine
- No vaccines are contraindicated
- Susceptible to infection by encapsulated bacteria (“SHINE KISS” – S. pneumoniae, H. influenzae, N. meningitidis, E. coli, Klebsiella, Salmonella, Group B Strept)
- Must add:
  - Meningococcal-C-Conjugate at age ≥2 yr
  - Quadravalent Men-P-ACYW at least 2 wk later
- Booster of Men-P-ACYW at age ≥2 y
- Pneumococcal polysaccharide vaccine (Pneu-P-23) at age ≥2 y
- Single booster of Pneu-P-23 at age ≥3 yr
- Consider single booster HiB at age ≥5 y

Growth and Development

Growth
- Growth is not linear
- Most rapid growth during first 2 yr and at puberty
- Tissues grow at different times
  - First 2 yr = CNS; mid-childhood = lymphoid tissue; puberty = gonads
- Measurement of growth
  - Premature infants (<37 wk) use corrected GA until age 2
  - Body proportion = upper/lower segment ratio (use symphysis pubis as midpoint)
  - Newborn = 1.7, adult male = 0.9, adult female = 1.0

Injection site
- Infants (<12 mo): anterolateral thigh
- Children (≥12 mo): anterolateral thigh

* ** Males 9-26 yrs: Currently only publically funded for men who have sex with men
** Current only publically funded for select groups (asplenia, antibody/complement deficiencies, coch ear implant recipients, HIV, close contacts with infected individuals)

Adverse Reactions Associated With Any Vaccine

- Local: induration, tenderness, redness, swelling
- Systemic: fever, rash, instability
- Allergic: urticaria, rhinitis, anaphylaxis
- Contraindications
- Moderate/severe illness
- Allergy to vaccine component
- No need to delay vaccination for mild URTI

According to the CDC, the weight of currently available scientific evidence does not support the hypothesis that MMR vaccine causes autism or IBD. The landmark paper linking autism to the MMR vaccine (Lancet 1998;351:637-641) was retracted due to false claims in the article (Lancet 2010;375:445)
Average Growth Parameters

Table 3. Parameter of Average Growth at Birth

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Growth</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>3.25 kg (7 lbs)</td>
<td>Gain 20-30 g/d (term neonate)</td>
<td>Weight loss (up to 10% of birth weight) in first 7 d of life is normal. Neonate should regain birth weight by ~10-14 d of age.</td>
</tr>
<tr>
<td>Length/Height</td>
<td>50 cm (20 in)</td>
<td>25 cm in 1st yr, 12 cm in 2nd yr, 8 cm in 3rd yr then 4-7 cm/yr until puberty</td>
<td>Measure supine length until 2 yr of age, then measure standing height.</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>35 cm (14 in)</td>
<td>2 cm/mo for 1st mo, 1 cm/mo at 3-6 mo, 0.5 cm/mo at 6-12 mo</td>
<td>Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference.</td>
</tr>
</tbody>
</table>

Reflexes

Table 4. Reflexes

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Maneuver to Elicit Reflex</th>
<th>Appropriate Reflex Response</th>
<th>Age of Disappearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moro</td>
<td>Infant placed semi-upright, head supported by examiner’s hand, sudden withdrawal of supported head with immediate return of support</td>
<td>Abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms</td>
<td>4-6 mo</td>
</tr>
<tr>
<td>Galant</td>
<td>Infant held in ventral suspension and one side of back is stroked along paravertebral line</td>
<td>Pelvis will move in the direction of stimulated side</td>
<td>2-3 mo</td>
</tr>
<tr>
<td>Grasp</td>
<td>Placement of examiner’s finger in infant’s palm</td>
<td>Flexion of infant’s finger(s)</td>
<td>3-4 mo</td>
</tr>
<tr>
<td>ATNR</td>
<td>Turn infant’s head to one side</td>
<td>“Fencing” posture (extension of ipsilateral leg and arm and flexion of contralateral arm)</td>
<td>4-6 mo</td>
</tr>
<tr>
<td>Placing</td>
<td>Dorsal surface of infant’s foot placed touching edge of table</td>
<td>Flexion followed by extension of ipsilateral limb up onto table (resembles primitive walking)</td>
<td>Variable</td>
</tr>
<tr>
<td>R rooting</td>
<td>Tactile stimulus near mouth</td>
<td>Infant turns head and opens mouth to suck on same side that cheek was stroked</td>
<td>2-3 mo</td>
</tr>
<tr>
<td>Parachute</td>
<td>Tilt infant to side while in sitting position</td>
<td>Ipsilateral arm extension, present by 6-8 mo</td>
<td>Does not disappear</td>
</tr>
</tbody>
</table>

ATNR = asymmetric tonic neck reflex

Developmental Milestones

Table 5. Developmental Milestones

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>Turns head side to side when supine</td>
<td>Hands fisted, thumb in fist</td>
<td>Cries, startles to loud noises</td>
<td>Calms when comforted</td>
</tr>
<tr>
<td>2 mo</td>
<td>Briefly raises head when prone, holds head erect when upright</td>
<td>Pulls at clothes</td>
<td>Variety of sounds (e.g. coos, gurgles)</td>
<td>Smiles responsively, recognizes and calms down to familiar voice, follows movement with eyes</td>
</tr>
<tr>
<td>4 mo</td>
<td>Lifts head and chest when prone, holds head steady when supported sitting, rolls prone to supine</td>
<td>Briefly holds object when placed in hand, reaches for midline objects</td>
<td>Turns head towards sounds</td>
<td>Laughs responsively, follows moving toy or person with eyes, responds to people with excitement (e.g. leg movement)</td>
</tr>
<tr>
<td>6 mo</td>
<td>Tripod sit, pivots in prone position</td>
<td>Ulnar or raking grasp, transfers objects from hand to hand, brings objects to mouth</td>
<td>Babbles</td>
<td>Stranger anxiety, beginning of object permanence</td>
</tr>
<tr>
<td>9 mo</td>
<td>Sits well without support, crawls, pulls to stand, stands with support</td>
<td>Early pincer grasp with straight wrist</td>
<td>“Mama, dada” – appropriate, imitates 1 word, responds to “no” regardless of tone</td>
<td>Plays games (e.g. peek-a-boo), reaches to be picked up</td>
</tr>
<tr>
<td>12 mo</td>
<td>Gets into sitting position without help, stands without support, walks while holding on</td>
<td>Neat pincer grasp, releases ball with throw</td>
<td>2 words, follows 1-step command, uses facial expression, sounds, actions to make needs known</td>
<td>Responds to own name, separation anxiety begins</td>
</tr>
</tbody>
</table>

*Use co rect: d GA until 2 yr

Safety and Efficacy of an Attenuated Vaccine Against Severe Rotavirus Gastroenteritis

Methods: Randomized, double-blind, phase 3 trial including healthy infants from Latin America and Finland, assigned to receive two oral doses of HRV vaccine versus placebo at 2 and 4 mo of age. Primary outcomes were episodes of gastrointestinal symptoms and severity. Results: 63,225 healthy infants were enrolled. The vaccine was 85% efficacious against severe rotavirus gastroenteritis and hospitalizations associated with gastroenteritis (p<0.001) and 100% efficacious against more severe gastroenteritis. Hospitalization for diarrhea of any cause was reduced by 42% (95% CI -29.53%, p=0.001). Six vaccine recipients and seven placebo recipients had definite intussusception within 31 d after each dose (risk difference -0.32/10,000 infants; 95% CI -2.91 to 2.18, p=0.78).

Conclusion: Two oral doses of the live attenuated HRV vaccine were highly efficacious in decreasing incidence of severe rotavirus and all-cause gastroenteritis, and were not associated with an increased risk of intussusception.
Nutrition

Dietary Requirements

<table>
<thead>
<tr>
<th>Weight</th>
<th>100 kcal/kg/d</th>
<th>10-20 kg</th>
<th>&gt;20 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needs</td>
<td>1,000 cal + 50 kcal/kg/d for each kg &gt;10</td>
<td>1,500 cal + 20 kcal/kg/d for each kg &gt;20</td>
<td></td>
</tr>
</tbody>
</table>

Dietary Recommendations

- 0-6 mo: breast milk or formula
  - exclusive breast milk during first 6 mo recommended over formula unless contraindicated
  - breastfed infants require supplements: vitamin D (400 IU/d), fluoride (after 6 mo if not sufficient in water), iron (6-12 mo, only if not receiving fortified cereals/meat/meat alternatives)
- >6 mo: solid food introduction – do not delay beyond 9 mo
- 2-3 new foods per wk, wait at least 2 d in between each food to allow time for adverse reaction identification
  - common allergens: eggs, milk, mustard, peanuts, seafood, seaweed, soy, tree nut, wheat
- early introduction of highly allergenic foods is recommended
- offer lumpy, soft-cooked, pureed, mashed textured foods
- 9-24 mo: switch to homogenized (3.25%) milk, offer 16 oz/d to non-breastfeeding infant
- offer vegetables, fruit, grains, and full-fat milk in any order after iron-rich foods are given
- provide up to 3 large feedings (meals) with 1-2 smaller feedings (snacks), depending on child’s hunger/satiety cues
- encourage self-feeding and introduce open cup (should be done by 18 mo)
- foods to avoid
  - honey until past 12 mo (risk of botulism)
  - added sugar, salt
  - excessive milk (i.e. no more than 750 mL or 24 oz/d after 1 yr)
  - limit juice intake (not nutritious, too much sugar), maximum 4-6 oz (1/2 cup) daily anything that is a choking hazard (chunks, round foods like grapes)
  - 2-6 yr: switch to 2% milk (500 mL/day)
  - can maintain breastfeeding during this time complementary to solids

Breastfeeding

- content of breast milk
  - colostrum (first few days): clear, rich in nutrients (i.e. high protein, low fat), immunoglobulin
  - mature milk: 70:30 whey:casein ratio, fat from dietary butterfat, carbohydrate from lactose
- advantages
  - easily digested, low renal solute load
  - immunologic
    - contains IgA, macrophages, active lymphocytes, lysozymes, lactoferrin (which inhibits E. coli growth in intestine)
    - lower pH promotes growth of Lactobacillus in GI tract

Table 5. Developmental Milestones (continued)

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mo</td>
<td>Walks without support, crawls up stairs/steps</td>
<td>Picks up and eats finger foods, scribbles, stacks 2 blocks</td>
<td>4-5 words, points to needs/wants</td>
<td>Looks to see how others react (e.g. after falling)</td>
</tr>
<tr>
<td>18 mo</td>
<td>Runs, walks forward pulling toys or carrying objects</td>
<td>Tower of 3 cubes, scribbling, eats with spoon</td>
<td>10 words, follows simple commands</td>
<td>Shows affection towards others, points to show interest in something</td>
</tr>
<tr>
<td>24 mo</td>
<td>Climbs up and down steps with 2 feet per step, runs, kicks ball</td>
<td>Tower of 6 cubes, undresses</td>
<td>2-3 word phrases, uses &quot;I, me, you&quot;, 50% intelligible, understands 2-step commands</td>
<td>Parallel play, helps to dress</td>
</tr>
<tr>
<td>3 yr</td>
<td>Rides tricycle, climbs up 1 foot per step, down 2 feet per step, stands on one foot briefly</td>
<td>Copies a circle, turns pages one at a time, puts on shoes, dress/undress fully except buttons</td>
<td>Combines 3 or more words into sentence, recognizes color, numbers, prepositions, plurals, counts to 10, 75% intelligible</td>
<td>Knows sex and age, shares some of the time, plays make-believe games</td>
</tr>
<tr>
<td>4 yr</td>
<td>Hops on 1 foot, climbs down 1 foot per step</td>
<td>Copies a cross, uses scissors, buttons clothes</td>
<td>Speech 100% intelligible, uses past tense, understands 3-part directions</td>
<td>Cooperative play, fully toilet-trained by day, tries to comfort someone who is upset</td>
</tr>
<tr>
<td>5 yr</td>
<td>Skips, rides bicycle</td>
<td>Copies a triangle and square, prints name, ties shoelaces</td>
<td>Fluent speech, future tense, alphabet, retells sequence of a story</td>
<td>Cooperates with adult requests most of the time</td>
</tr>
</tbody>
</table>
- parent-child bonding
- economical, convenient
- maternal contraindications
  - chemotherapy or radioactive compounds
  - HIV/AIDS, active untreated TB, herpes in breast region
  - >0.5 g/kg/d of alcohol or illicit drugs
  - medications known to cross to breast milk
  - OCPs are not a contraindication to breastfeeding (estrogen may decrease lactation, but is not dangerous to infant)
  - MotherRisk® Program – valuable research and counselling on reproductive risk or safety of drugs and chemicals
- breastfeeding jaundice (first 1-2 wk): due to lack of maternal milk production and subsequent infant dehydration (see jaundice, P69)
- breast milk jaundice (0.3% of newborns, persists up to 4-6 mo): rare, glucuronyl transferase inhibitor in breast milk inhibits conjugation of bilirubin, increases enterohepatic circulation of bilirubin
  - baby presents healthy and thriving, and jaundice (secondary to unconjugated bilirubin) resolves
- poor weight gain: consider dehydration or FIT
- oral candidiasis (thrush): treat baby with antifungal such as nystatin; can occur in breast or bottle-fed infants

### Table 6. Common Formulas Compared to Breast Milk

<table>
<thead>
<tr>
<th>Type of Nutrition</th>
<th>Indications</th>
<th>Content (as compared to breast milk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s Milk-Based</td>
<td>Prematurity</td>
<td>Lower whey:casein ratio</td>
</tr>
<tr>
<td>(Enfamil®, Similac®)</td>
<td>Transition into breastfeeding</td>
<td>Plant fats instead of dietary butterfat</td>
</tr>
<tr>
<td>Fortified Formula</td>
<td>Low birth weight</td>
<td>Higher calories and vitamins A, C, D, K</td>
</tr>
<tr>
<td></td>
<td>Prematurity</td>
<td>May only be used in hospital due to risk of fat-soluble vitamin toxicity</td>
</tr>
<tr>
<td>Soy Protein</td>
<td>Galactosemia</td>
<td>Com syrup solids or sucrose in place of lactose</td>
</tr>
<tr>
<td>(Isomil®, Prosobee®)</td>
<td>Desire for vegetarian/vegan diet*</td>
<td></td>
</tr>
<tr>
<td>Partially Hydrolyzed Proteins</td>
<td>Delayed gastric emptying</td>
<td>Protein is 100% whey with no casein</td>
</tr>
<tr>
<td>(Good Start®)</td>
<td>Risk of cow milk protein allergy</td>
<td></td>
</tr>
<tr>
<td>Protein Hydrolysate</td>
<td>Malabsorption</td>
<td>Protein is 100% casein with no whey</td>
</tr>
<tr>
<td>(Nutramigen®, Alimentum®,</td>
<td>Food allergy</td>
<td>Com syrup solids, sucrose, or tapioca starch instead of lactose</td>
</tr>
<tr>
<td>Pregestimil®, Portagen®)</td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>Food allergy</td>
<td>Free amine acids (no protein)</td>
</tr>
<tr>
<td>(Neocate®, PurAminoTM)</td>
<td>Short gut</td>
<td>Com syrup solids instead of lactose</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Inborn errors of metabolism</td>
<td>Various different compositions for children with galactosemia, propionic acidemia, etc.</td>
</tr>
</tbody>
</table>

*10-35% of children with cow’s milk protein allergy also have reactions to soy-based formula

### Signs of Inadequate Intake

- <1 wet diaper per/d of age for first wk
- <7 feeds/d
- Sleepy or lethargic, sleeping throughout the night <6 wk
- Weight loss >10% of birth weight
- Jaundice

### Table 7. Injury Prevention Counselling

- injuries are the leading cause of death in children >1 yr of age
- main causes: motor vehicle crashes, burns, drowning, falls, choking, infanticide

<table>
<thead>
<tr>
<th>0-6 mo</th>
<th>6-12 mo</th>
<th>1-2 yr</th>
<th>2-5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not leave alone on bed, on changing table, or in tub</td>
<td>Install star barriers</td>
<td>Never leave unattended</td>
<td>Bicycle helmet</td>
</tr>
<tr>
<td>Keep crib rails up</td>
<td>Discourage use of walkers</td>
<td>Keep pot handles turned to back of stove</td>
<td>Never leave unsupervised at home, driveway or pool</td>
</tr>
<tr>
<td>Check water temperature before bathing</td>
<td>Avoid play areas with sharp-edged tables and corners</td>
<td>Caution with whole grapes, nuts, raw carrots, hotdogs, etc. due to choking hazard</td>
<td>Teach bike safety, stranger safety, and street safety</td>
</tr>
<tr>
<td>Do not hold hot liquid and infant at the same time</td>
<td>Cover electrical outlets</td>
<td>No running while eating</td>
<td>Swimming lessons (&gt;4 yr), sunscreen (from 6 mo), fences around pools</td>
</tr>
<tr>
<td>Check milk temperature before feeding</td>
<td>Unplug appliances when not in use</td>
<td>Appropriate car seats</td>
<td>Appropriate car seats</td>
</tr>
<tr>
<td>Appropriate car seats are required before leaving hospital</td>
<td>Keep small objects, plastic bags, cleaning products, and medications out of reach</td>
<td>Supervise during feeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supervise during feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appropriate car seats</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: This list is not exhaustive. For more details, see Rourke Baby Record (http://www.rourkebymbrecord.ca/pdf/RBR2011Ont_Eng.pdf)
**Breath Holding Spells**

- epidemiology: 0.1-5% of healthy children 6 mo-4 yr of age, usually start during first year of life
- etiology: child is provoked (usually by anger, injury, or fear) → holds breath and becomes silent → spontaneously resolves or loses consciousness
- types
  - cyanotic (more common), usually associated with anger/frustration
  - pallid, usually associated with pain/surprise
- management
  - usually resolves spontaneously and rarely progresses to seizure
  - help child control response to frustration and avoid drawing attention to spell
  - may be associated with iron deficiency anemia, improves with supplemental iron

**Circumcision**

- elective procedure
  - not covered by OHIP in Ontario, but recent evidence shows show risks vs. benefit → not clearly different; no clear position by CPS in 2015 statement
  - often for religious or culture reasons
  - beneficial: prevention of phimosis and slightly reduced incidence of UTI, STI, balanitis, cancer of the penis
  - complications (<1%): local infection, bleeding, urethral injury
  - contraindications: presence of genital abnormalities (e.g. hypospadias) or known bleeding disorder

**Crying/Fussing Child**

- history
  - description of baseline feeding, sleeping, crying patterns
  - infectious symptoms: fever, tachypnea, rhinorrhea, ill contacts
  - feeding intolerance: gastroesophageal reflux with esophagitis, N/V, diarrhea, constipation
  - trauma
  - recent immunizations (vaccine reaction) or medications (drug reactions), including maternal drugs taken during pregnancy (neonatal withdrawal syndrome) and drugs that may be transferred via breast milk
  - inconsistent history, pattern of numerous emergency department visits, high-risk social situations all raise concern of maltreatment

**Table 8. Physical Exam and Differential Diagnosis**

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Possible Examination Findings</th>
<th>Possible Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEENT</td>
<td>Bulging fontanelle, bulging and erythematous TM</td>
<td>Meningitis, shaken baby syndrome, hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Blepharospasm tearing</td>
<td>Corneal abrasion, glaucoma</td>
</tr>
<tr>
<td></td>
<td>Retinal hemorrhage</td>
<td>Shaken baby syndrome</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal infections</td>
<td>Thrush, gingivostomatitis, herpangina, otitis media</td>
</tr>
<tr>
<td>Neurological</td>
<td>Irritability or lethargy</td>
<td>Meningitis, shaken baby syndrome</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Poor perfusion</td>
<td>Sepsis, anomalous coronary artery, meningitis, myocarditis, CHF</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachycardia</td>
<td>Pneumonia, CHF</td>
</tr>
<tr>
<td></td>
<td>Grunting</td>
<td>Respiratory disease, response to pain</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Mass, empty RLQ</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Scrotal swelling</td>
<td>Incarcerated hernia, testicular torsion</td>
</tr>
<tr>
<td></td>
<td>Penile/clitoral swelling</td>
<td>Hair tourniquet</td>
</tr>
<tr>
<td>Rectal</td>
<td>Anal fissure</td>
<td>Constipation or diarrhea</td>
</tr>
<tr>
<td></td>
<td>Hemocult positive stool</td>
<td>Intussusception, NEC, volvulus</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Point tenderness or decreased movement</td>
<td>Fracture, syphilis, osteomyelitis, toe/finger hair tourniquet</td>
</tr>
</tbody>
</table>

**Infantile Colic**

- definition: unexplained paroxysms of irritability and crying for ≥3 h/d, ≥3 d/wk for ≥3 wk in an otherwise healthy, well-fed baby (rule of 3s)
- epidemiology: 10% of infants; usual onset 10 d to 3 mo of age with peak at 6-8 wk
- etiology: unknown. Theories: alterations in fecal microflora, cow’s milk intolerance, GI immaturity or inflammation, poor feeding, maternal smoking
Common Complaints

- diagnosis of exclusion: rule out otitis media, cow's milk intolerance, GI problem, fracture

**management**
- parental relief, rest, and reassurance
- hold baby, soother, car ride, music, vacuum, check diaper
- some evidence for probiotics
- maintain breastfeeding but eliminate allergens (cow's milk protein, eggs, wheat and nuts) from mother's diet
- try casein hydrolysate formula (Nutramigen®)
- time – all resolve, most in the first 3-6 mo of life, no long-term adverse effects

**Dentition and Caries**

**Dentition**
- primary dentition (20 teeth)
  - first tooth at 5-9 mo (lower incisor), then 1/mo
  - 6-8 central teeth by 1 yr
  - assessment by dentist 6 mo after eruption of first tooth and certainly by 1 yr of age (Grade B recommendation)
- secondary dentition (32 teeth)
  - first adult tooth is 1st molar at 6 yr, then lower incisors

**Caries**
- milk caries: decay of superior front teeth and back molars in first 4 yr of life
- cause: often due to prolonged feeding (e.g. put to bed with bottle, prolonged breastfeeding)
- prevention
  - no bottle at bedtime, clean teeth after last feed
  - minimize juice and sweetened pacifier
  - clean teeth with soft damp cloth or toothbrush and water
  - water fluoridation

**Enuresis**

**Definition**
- involuntary urinary incontinence by day and/or night in child >5 yr

**General Approach**
- should be evaluated if dysuria, change in colour, odour, stream, secondary or diurnal, change in gait, stool incontinence

**Primary Nocturnal Enuresis**
- definition: involuntary loss of urine at night, bladder control has never been attained
- epidemiology: boys > girls; 10% of 6 yr olds, 3% of 12 yr olds, 1% of 18 yr olds
- etiology: developmental disorder or maturational lag in bladder control while asleep
- management
  - time and reassurance (~20% resolve spontaneously each yr)
  - behaviour modification (limiting fluids, voiding prior to sleep), bladder retention exercises, scheduled toileting overnight has limited effectiveness
  - conditioning: "wet" alarm wakes child upon voiding (70% success rate)
  - medications (for children >7 yr, considered second line therapy, may be used for sleepovers/camp): DDAVP oral tablets (similar success rate as "wet" alarm therapy but higher relapse rate), imipramine ('Tofranil®') (rarely used, lethal if overdose, SE: cardiac toxicity, anticholinergic effects)

**Secondary Enuresis**
- definition: involuntary loss of urine at night, develops after child has sustained period of bladder control (>6 mo)
- etiology: inorganic regression due to stress or anxiety (e.g. birth of sibling, significant loss, family discord, sexual abuse), secondary to organic disease (UTI, DM, DI, sleep apnea, neurogenic bladder, CP, seizures, pinworms)
- management: treat underlying cause

**Diurnal Enuresis**
- definition: daytime wetting (60-80% also wet at night)
- etiology: micturition deferral (holding urine until last minute) due to psychosocial stressor (e.g. shy), structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders, DM
- management: treat underlying cause, behavioural (scheduled toileting, double voiding, good bowel program, sitting backwards on toilet, charting/incentive system, relaxation/biofeedback), pharmacotherapy

**Antidiuretic Hormone Regulation in Primary Nocturnal Enuresis**

**Arch Dis Child** 1995;73(6):508-11

**Purpose:** To evaluate the efficacy of DDAVP for the treatment of primary nocturnal enuresis.

**Methods:** Children with primary nocturnal enuresis were compared with a corresponding control group. Diurnal and nocturnal urine production, ADH secretion, and plasma osmolality were determined.

**Results:** Ten children (mean age 10.5 years) with primary nocturnal enuresis were compared to a control group of eight patients. No differences in urine production, ADH levels during day and night, or plasma osmolality were found. However, the enuretic children required a markedly greater ADH output (2.87 pg/ml/mmol/kg vs. 0.56 in controls; p<0.01).

**Conclusion:** ADH secretion is a function of plasma osmolality. Urine production is not increased at night in individuals with primary nocturnal enuresis because of lower ADH secretion.

**Treatment for primary nocturnal enuresis**

should not be considered until 7 yr of age due to high rate of spontaneous cure
**Encopresis**

- **definition** fecal incontinence in a child >4 yr old, at least once per mo for 3 mo
- **prevalence**: 1-1.5% of school-aged children (rare in adolescence); M:F = 6:1 in school-aged children
- **causes**: chronic constipation (retentive encopresis), Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, anorectal malformations, bowel obstruction

**Retentive Encopresis**

- **definition**: child holds bowel movement develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
- **etiology**
  - physical: painful stooling often secondary to constipation
  - emotional: disturbed parent-child relationship, coercive toilet training, social stressors
- **clinical presentation**
  - history
    - crosses legs or stands on toes to resist urge to defecate
    - distressed by symptoms, soiling of clothes
    - toilet training coercive or lacking in motivation
    - may show oppositional behaviour
    - abdominal pain
  - physical exam
    - digital rectal exam or abdo x-ray: large fecal mass in rectal vault
    - anal fissures (result from passage of hard stools)
  - palpable stool in LLQ
- **management**
  - complete clean-out of bowel: PEG 3350 given orally is most effective, enemas and suppositories may be second line therapies, but these are invasive and often less effective
  - maintenance of regular bowel movements (see Constipation Treatment, P36)
  - assessment and guidance regarding psychosocial stressors
  - behavioural modification
- **complications**: recurrence, toxic megacolon (requires >3-12 mo to treat) bowel perforation

**Toilet Training**

- 90% of children attain bladder control before bowel control
- generally, females train earlier than males
- 25% by 2 yr (in North America), 98% by 3 yr have daytime bladder control
- signs of toilet readiness
  - ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several h (large enough bladder), can recognize need to go, able to remove clothing

**Failure to Thrive**

- **definition** weight <3rd percentile, falls across two major percentile curves, or <80% of expected weight for height and age
- inadequate caloric intake most common factor in poor weight gain
- may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
- factors affecting physical growth: genetics, intrauterine factors, nutrition, endocrine hormones, chronic infections/diseases, psychosocial factors
- **clinical presentation**
  - history
    - nutritional intake
    - current symptoms
    - past illnesses
    - family history: growth, puberty, parental height and weight including mid-parental height
    - psychosocial history
  - physical exam
    - growth parameters, plotted: height, weight, head circumference, arm span
    - vital signs
    - complete head to toe exam
    - dysmorphic features or evidence of chronic disease
    - upper to lower segment ratio
    - sexual maturity staging
    - signs of maltreatment or neglect
- **investigations** (as indicated by clinical presentation)
  - CBC, blood smear, electrolytes, T4, TSH
  - bone age x-ray
  - chromosomes/karyotype
  - chronic illness: chest (CXR, sweat Cl–), cardiac (CXR, ECG, Echo), GI (celiac screen, inflammatory markers, malabsorption), renal (urinalysis), liver (enzymes, albumin)

**Mid-Parental Height**

- Boys target height = (father ht + mother ht + 13) / 2
- Girls target height = (father ht + mother ht - 13) / 2
- **Note**: height should be taken in cm

**Clinical Signs of FTT**

- **SMALL KID**
  - Subcutaneous fat loss
  - Muscle atrophy
  - Alopecia
  - Lethargy
  - Lagging behind normal
  - Kwashiorkor
  - Infection (recurrent)
  - Dermatitis
Table 9. Failure to Thrive Patterns

<table>
<thead>
<tr>
<th>Growth Parameters</th>
<th>Suggestive Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Wt</td>
<td>Normal Ht</td>
</tr>
<tr>
<td></td>
<td>Normal HC</td>
</tr>
<tr>
<td></td>
<td>Caloric insufficiency</td>
</tr>
<tr>
<td></td>
<td>Decreased intake</td>
</tr>
<tr>
<td>Decreased Wt</td>
<td>Decreased Ht</td>
</tr>
<tr>
<td></td>
<td>Normal HC</td>
</tr>
<tr>
<td></td>
<td>Structural dystrophies</td>
</tr>
<tr>
<td></td>
<td>Endocrine disorder</td>
</tr>
<tr>
<td>Decreased Wt</td>
<td>Decreased Ht</td>
</tr>
<tr>
<td></td>
<td>Decreased HC</td>
</tr>
<tr>
<td></td>
<td>Intrauterine insult</td>
</tr>
<tr>
<td></td>
<td>Genetic abnormality</td>
</tr>
</tbody>
</table>

BA = bone age; CA = chronological age; HC = head circumference; Ht = height; Wt = weight

Etiology
- an interplay between pathophysiology and psychosocial influences. Investigations should assess:
  - complex factors in the parent-child relationship
    - dietary intake, knowledge about feeding, improper mixing of formula
    - feeding environment
    - parent-child interaction, attachment
    - child behaviours, hunger/satiety cues
    - postpartum depression
    - social factors: stress, poverty, neglect, child/domestic abuse, parental substance abuse, restricted diets
  - inadequate caloric intake: inadequate milk supply/latching, mechanical feeding difficulty (cleft palate), oromotor dysfunction, toxin-induced anorexia
  - inadequate absorption: biliary atresia, celiac, IBD, CF; inborn errors of metabolism, milk protein allergy, pancreatic cholestatic conditions
  - increased metabolism: chronic infection, CF, lung disease from prematurity, hyperthyroidism, asthma, IBD, malignancy, renal failure

Management
- most as outpatient using multidisciplinary approach: primary care physician, dietitian, psychologist, social work, CAS
- medical: oromotor problems, iron-deficiency anemia, gastro-esophageal reflux
- nutritional: educate about age-appropriate foods, calorie boosting, mealtime schedules and environment; goal to reach 90–110% IBW, correct nutritional deficiencies, and promote catch-up growth/development
- behavioural: positive reinforcement, mealtime environment

Energy Requirements
- see Nutrition, P6

Obesity
- definition: overweight is BMI >85th percentile; obesity is BMI >95th percentile for age and height
- risk factors: genetic predisposition (e.g. both parents obese – 80% chance of obese child)
- etiology: organic causes are rare (<5%), but may include Prader-Willi, Carpenter, Turner, Cushing syndromes, hypothyroidism
- complications: association with HTN, dyslipidemia, slipped capital femoral epiphysis, type 2 DM, asthma, obstructive sleep apnea, gynecostasia, polycystic ovarian disease, early menarche, irregular menses, psychological trauma (e.g. bullying, decreased self-esteem, unhealthy coping mechanisms, depression)
- childhood obesity often persists into adulthood
- investigations: BP pulse, screen lipid profile
- management:
  - encouragement and reassurance; engagement of entire family
  - diet: qualitative changes (do not encourage weight loss, but allow for linear growth to catch up with weight), special diets used by adults and very low calorie diets are not encouraged
  - behaviour modification: increase activity, change eating habits/meal patterns, limit juice/sugar drinks, ensure adequate sleep
  - education: multidisciplinary approach, dietitian, counselling
  - surgery and pharmacotherapy are rarely used in children
  - increase physical activity (1 h/d), reduce screen time (<2 h/d)
  - in children with risk factors/complications: AST/ALT and diabetes screening, small changes in energy expenditure and intake (lose 1 lb/mo)
  - long term goal: maintain BMI <85th percentile

Poison Prevention
- keep all types of medicines, vitamins, and chemicals locked up in a secure container
- potentially dangerous: medications, illicit drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- keep alcoholic beverages out of reach: 3 oz hard liquor can kill a 2 yr old
- always read labels before administering medicine to ensure correct medication drug and dose and/or speak with a pharmacist or healthcare provider
Rashes

Table 10. Common Pediatric Rashes

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Differential Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaper Dermatitis</td>
<td>Irritant contact dermatitis</td>
<td>Eliminate direct skin contact with urine and feces, allow periods of rest</td>
</tr>
<tr>
<td></td>
<td>Shiny, red macules/patches, no skin fold involvement</td>
<td>without a diaper, frequent diaper changes, topical barriers (petrolatum,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>zinc oxide or paste), short-term low-potency topical corticosteroids (severe</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>Yellow, greasy macules/plaques on erythema, scales</td>
<td>Short-term, moisturisers, topical antifungal (ketoconazole), low-potency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>topical corticosteroids</td>
</tr>
<tr>
<td>Candidal dermatitis</td>
<td>Erythematous macerated papules/plaques, satellite lesions,</td>
<td>Antifungal agents (e.g. clotrimazole, nystatin)</td>
</tr>
<tr>
<td></td>
<td>involvement</td>
<td></td>
</tr>
</tbody>
</table>

Other Dermatitis

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Differential Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis</td>
<td>Erythematous, papules/plaques, oozing, excoriation,</td>
<td>Eliminate exacerbating factors, maintain skin hydration (daily baths and</td>
</tr>
<tr>
<td></td>
<td>lichenification, classic areas of involvement</td>
<td>moisturisers), corticosteroids, topical calcineurin inhibitor (2nd line)</td>
</tr>
<tr>
<td>Nummular dermatitis</td>
<td>Annular erythematous plaques, oozing, crusting</td>
<td>Avoid irritant if identified, potent topical steroid in emollient base,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>short-term systemic steroids ± antibiotics (severe)</td>
</tr>
<tr>
<td>Allergic contact</td>
<td>Red papules/plaques/vesicles/bulla only in area of allergen</td>
<td>Mild: soothing lotion (e.g. calamine lotion)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td></td>
<td>Moderate: low-to-intermediate potency topical corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe: systemic corticosteroids and antihistamine</td>
</tr>
<tr>
<td>Irritant contact</td>
<td>Morphology depends on irritant</td>
<td>Avoid skin contact</td>
</tr>
<tr>
<td>Dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyshidrotic dermatitis</td>
<td>Papulovesicular, cracking/fissuring, hands and feet</td>
<td>Mild/moderate: medium/potent topical corticosteroids</td>
</tr>
<tr>
<td></td>
<td>(‘tapioca pudding’)</td>
<td>Severe: systemic corticosteroids, local PUVA or UVA treatments</td>
</tr>
</tbody>
</table>

Infectious

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Differential Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scabies</td>
<td>Polymorphic (red excoriated papules/nodules, burrows), in</td>
<td>Permethrin (Nix®) 5% cream for patient and family (2 applications, 1 wk</td>
</tr>
<tr>
<td></td>
<td>web spaces/folds, very pruritic</td>
<td>apart)</td>
</tr>
<tr>
<td></td>
<td>Often affects multiple family members</td>
<td></td>
</tr>
<tr>
<td>Impetigo</td>
<td>Honey-coloured crusts or superficial bullae</td>
<td>Topical antibiotics if mild: fucidic acid or mupirocin cream; Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>antibiotics if severe (e.g. cephalaxin/erythromycin)</td>
</tr>
<tr>
<td>Tinea corporis</td>
<td>Round erythematous plaques, central clearing and scaly border</td>
<td>Topical anti-fungal for skin, systemic anti-fungals for nails/head</td>
</tr>
</tbody>
</table>

Pediatric Exanthems (see Infectious Pediatric Exanthems, P50)

Drug Reactions (see Dermatology, D21)

Acne (see Dermatology, D11)

Sleep Disturbances

Types of Sleep Disturbances

- insufficient sleep quantity
  - difficulty falling asleep (e.g. limit setting sleep disorder)
  - preschool and older children
  - bedtime resistance
  - due to caregiver’s inability to set consistent bedtime rules and routines
  - often exacerbated by child’s oppositional behaviours

- poor sleep quality
  - frequent arousals (e.g. sleep-onset association disorder)
  - infants and toddlers
  - child learns to fall asleep only under certain conditions or associations (e.g. with parent, held, rocked or fed, with light on, in front of television), and loses ability to self-soothe
  - during the normal brief arousal periods of sleep (q90-120 min), child cannot fall back asleep because same conditions are not present

- obstructive sleep apnea
- epidemiology: 1-5% of preschool aged children, more common in African American children
- definition: partial or intermittent complete airway obstruction during sleep causing disrupted ventilation and sleep pattern
- features: snoring/gasping/noisy breathing during sleep and irritable/tired/hyperactive during the day
- sequelae: cardiovascular (HTN/LV remodelling due to sympathetic activation), growth, cognitive, and behavioural deficits

Daily Sleep Requirement

- <6 mo: 16 h
- 6 mo: 14.5 h
- 12 mo: 13.5 h
- 2 yr: 13 h
- 4 yr: 11.5 h
- 6 yr: 9.5 h
- 12 yr: 8.5 h
- 18 yr: 8 h

Nap Patterns

- 2/d at 1 yr
- /d at 2 yr: 2-3 h
- 0.5/d at 5 yr: 1.7 h
Common Complaints

- risk factors: adenotonsillar hypertrophy, craniofacial abnormalities, obesity
- investigation: polysomnography is gold standard for diagnosis but not required (expensive, inaccessible)
- management: adenotonsillectomy and weight management are first-line tx, follow-up for residual OSA. Watchful waiting acceptable in mild-moderate cases
  - adenotonsillectomy does not improve executive function/attention but improves behaviour, QOL, polysomnographic findings
  - use CPAP if adenotonsillectomy is contraindicated (cleft palate/bleeding disorder/acute tonsillitis), OSA w/ minimal adenotonsillar tissue, residual OSA
  - avoid pollutants/tobacco smoke, allergens
  - avoid use of corticosteroids and antibiotics
- parasomnias
  - episodic nocturnal behaviours (e.g. sleepwalking, sleep terrors, nightmares)
  - often involves cognitive disorientation and autonomic/skeletal muscle disturbance

Management of Sleep Disturbances

- set strict bedtimes and "wind-down" routines
- do not send child to bed hungry
- positive reinforcement for: limit setting sleep disorder
- always sleep in own bed, in a dark, quiet, and comfortable room
- do not use bedroom for timeouts
- systematic ignoring and gradual extinction for: sleep-onset association disorder

Nightmares

- epidemiology: common in boys, 4-7 yr old
- associated with REM sleep (anytime during night)
- features: upon awakening, child is alert and clearly recalls frightening dream ± associated with daytime stress/anxiety
- management: reassurance

Night Terrors

- epidemiology: 15% of children have occasional episodes
- abrupt sitting up, eyes open, screaming
- clinical features: occurs in early hours of sleep, stage 4 of sleep; signs of panic and autonomic arousal, no memory of event, inconsolable, stress/anxiety can aggravate them
- course: remits spontaneously at puberty
- management: reassurance for parents, ensure child is safe (e.g. if sleepwalks)

Sudden Infant Death Syndrome

Definition

- sudden and unexpected death of an infant <12 mo of age in which the cause of death cannot be found by history, examination, or a thorough postmortem and death scene investigation

Epidemiology

- 0.5/1,000 (leading cause of death between 1-12 mo of age); M:F = 3:2
- more common in children placed in prone position
- in full term infants, peak incidence is 2-4 mo, 95% of cases occur by 6 mo
- increase in deaths during peak RSV season
- most deaths occur between midnight and 8 AM

Risk Factors

- prematurity (<37 wk), early bed sharing (<12 wk), alcohol use during pregnancy, soft bedding, low birthweight, bed sharing, Aboriginals ethnicity, male, no prenatal care, smoking in household, prone sleep position, poverty
- risk of SIDS is increased 3-5x in siblings of infants who have died of SIDS
- bedsharing: sleeping on a sofa, sleeping with an infant after consumption of alcohol/street drugs or extreme fatigue, sleeping on a surface with a fixed wall (couch/sofa), infant sleeping with someone other than primary caregiver

Prevention

- "Back to Sleep, Front to Play" (place infant on back when sleeping)
- avoid sharing bed with infant
- allow supervised play time daily in prone position ("tummy time")
- alarms, monitors not recommended – increase anxiety, do not prevent life-threatening events
- avoid overheating and overdressing
- appropriate infant bedding (firm mattress, avoid loose bedding, pillows, stuffed animals, and crib bumper pads)
- no smoking
- exclusive breastfeeding in first mo
- pacifiers appear to have a protective effect; do not reinsert if falls out during sleep
- infant monitors do not reduce incidence

Brief Resolved Unexplained Events (BRUE)

A group of conditions often marked by an episode of apnea, cyanosis, change in tone, or change in mental status occurring in a child, when an observer fears the child may be dying. There is no clear connection between most BRUEs and SIDS. Evaluating for a cause of the BRUE (e.g. infection, cardiac, neurologic) is guided by history, physical exam, and period of observation
# Child Abuse and Neglect

**Definition**
- an act of commission (physical, sexual, or psychological abuse) or omission (neglect) by a caregiver that harms a child

**Legal Duty to Report**
- upon reasonable grounds to suspect abuse and/or neglect, physicians are required by legislation to contact the CAS to personally disclose all information relevant to the child safety concern
- duty to report overrides patient confidentiality; physician is protected against liability

**Ongoing Duty to Report**
- if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the CAS must be made

**Risk Factors**
- environmental factors: social isolation, poverty, domestic violence
- caregiver factors: personal history of abuse, psychiatric illness, postpartum depression, substance abuse, single parent family, poor social and vocational skills, below average intelligence
- child factors: difficult temperament, disability, special needs (e.g. developmental delay), premature

**Management of Physical Abuse, Child Abuse, and Neglect**
- report all suspicions to CAS; request emergency visit if imminent risk to child or any siblings in the home
- acute medical care: hospitalize for medical evaluation or treatment of injuries if indicated
- arrange consultation to social work and appropriate follow-up
- may need to discharge child directly to CAS or to responsible guardian under CAS supervision

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## Physical Abuse

**History**
- history that is not compatible with physical findings or with child's developmental capabilities
- history not reproducible or changes dramatically over time
- delay in seeking medical attention that is unexplained by other factors
- assess previous trauma or hospitalizations
- ask FHx: bleeding disorder, bone disorder, metabolic conditions
- ask developmental history

**Physical Exam**
- physical findings not explained by underlying medical condition
- growth parameters including past recorded parameters (weight, height, head circumference)
- multiple injuries not explained by accidental injury or child's development level
- patterned skin injuries: belt buckle, hand prints, burns that do not match provided history
- injury location: bruises; on areas with abundant soft-tissue cushioning, such as abdomen, buttocks, genitalia, fleshy part of cheek or on ears, neck or feet; fractures; posterior rib/metaphyseal/scapular/vertebral/sternal fractures (more suspicious for non-accidental injuries); bruises that do not fit described cause; immersion burns (e.g. hot water)
- altered mental status: head injury, poisoning
- eyes – retinal hemorrhages
- scalp – patchy hair loss from traumatic alopecia or severe malnutrition
- oral exam – check the frenula for tears
- head trauma is the leading cause of death in child maltreatment (e.g. acceleration-deceleration forces [shaking], direct force application [blow or impact])
- consider “red herrings” (e.g. slate grey macule/congenital dermal melanocytosis vs. bruises)

**Investigations**
- document all injuries on a body diagram: type, location, size, shape, colour, pattern
- photography of skin injuries is ideal (police or hospital photography preferred; do not use physician’s personal camera)
- rule out medical causes of bruising/fracture with appropriate investigations (e.g. blood disorders or rickets):
  - if fractures evident: Ca++, Mg++, PO43-, ALP, PTH, Vitamin D, albumin
  - if bruising present: CBC, INR, PT, von Willebrand factor, factors VIII/IX
- screen for abdominal trauma
  - transaminases and amylase if elevated: abdo CT recommended
  - renal function – electrolytes, urinalysis
    - toxicity screen – overdose or poisoning
- skeletal survey in children <2 yr; select imaging based on history in children >5 yr
- neuroimaging: CT and/or MRI - dilated eye examination by pediatric ophthalmologist to rule out retinal haemorrhage if subdural hemorrhage detected on head imaging

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**Medical Assessment of Bruising in Suspected Child Maltreatment Cases**

Paediatr Child Health 2013;18(8):433-7
CPS Position Statement: While bruises are most often due to minor accidental injury, they may also signal underlying medical illness or inflicted injury. Knowing when to assess bruises in the context of maltreatment can be challenging. The following are red flags for inflicted injury in such bruising cases:
- Babies not yet cruising
- Present on ears, neck, feet, buttocks or torso
- Not on the front of the body and/or overlying bone
- Unusually large or numerous
- Clustered or patterned
- Not fitting with the described causal mechanism
Sexual Abuse

Epidemiology
- peak ages at 2-6 yr and 12-16 yr, most do not report until adulthood
- as adults: more likely to develop obesity, sexual problems, IBS, fibromyalgia, STI, substance use disorder.
  More likely to experience intimate partner violence and sexual assault
- in decreasing order: family member, non-relative known to victim, stranger

History
- do not take a sexual abuse history from a young child; this must be done by trained personnel (e.g. during a forensic interview)
- psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of trust, low self-esteem, school failure, sexually aggressive behaviour, advanced sexual knowledge, sexual preoccupation or play

Physical Exam
- recurrent UTIs, pregnancy, STIs, vaginitis, vaginal bleeding, pain, genital injury, enuresis
  - anogenital exam performed along with head-to-toe physical for physical trauma
  - instrumentation not required for anogenital exam, speculum contraindicated in prepubertal girls
  - most victims have normal anogenital exam – cannot rule out sexual abuse if exam is negative

Investigations
- depend on presentation, age, sex, and pubertal development of child
  - sexual assault examination kit within 24 h if prepubertal, within 72 h if pubertal
  - rule out STI, UTI, pregnancy (consider STI prophylaxis or emergency contraception)
  - rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)
  - investigations to rule out drug and alcohol screen e.g. Rohypnol, 'Liquid G,' etc.

Neglect

Definition
- omissions in care by parents or caregiver that leads in actual or potential harm

History
- from child and each caregiver separately (if possible)

Physical Exam
- head to toe (do not force), growth parameters, nutrition status
  - dental care
  - emotional state

Investigations
- blood tests to rule out medical conditions (e.g. thrombocytopenia or coagulopathy)

Adolescent Medicine

Adolescent History (HEEADSSS)
- tailor your history according to the clinical context

Home: Who do you live with? What kind of place do you live in? Do you get along with your parents and/or siblings?

Education/Employment: What grade are you in? What are your favourite subjects? What was your average on your last report card (ask for changes)? How much school have you missed this past year? Do you work (if so, how much)? Do you get along with teachers/employers?

Eating: Tell me about your meals/snacks in a typical day. Have you ever gone on a diet? What are your favourite and least favourite foods? (see Psychiatry, Eating Disorders, PS30)

Activities: What do you do after school? On the weekends? How much time do you spend on the computer/watching TV every day? Do you use social media (i.e. Facebook, Twitter, Instagram, etc.)? What do you do with your friends outside of school?

Drugs: Which seems to be more popular at your school, alcohol or drugs? How often do you drink/smoke marijuana take other drugs? Do you smoke cigarettes? When you drink, do you usually get drunk? Have you ever passed out or not been able to remember what happened while you were drinking? Has anything bad ever happened to you while you were drunk or stoned? (see Psychiatry, Substance Abuse, PS21)
Sexuality: Are you romantically interested in anyone? When you think about having sex with someone, do you think about females, males, or both? Have you ever had sex with anyone? Whether the answer is yes or no, the next question is: What activities would you include in the term ‘having sex’? What do you do to prevent getting a STI/getting pregnant/getting someone pregnant? Has anyone ever given you money, drugs, or other stuff in exchange for sex? (see Gynecology, Sexually Transmitted Infections, GY27)

Suicidality/Depression: On a scale of 1 to 10, where 1 is so sad that you might kill yourself and 10 is the happiest you could be, where are you most days? Have you lost interest in activities that you used to enjoy? Do you often have trouble sleeping (Is there a difference between school days and the weekend)? Have you ever thought seriously about suicide? Did you make a plan? (see Psychiatry, Depression/Suicide, PS10, PS4)

Safety/Violence: Do you ever get into a car with a driver who has been drinking? Do you always wear a seatbelt/bicycle helmet? Are you being bullied at school? Has anyone ever touched you in an unwanted way?

See Normal and Abnormal Pubertal Development, P30

Cardiology

Congenital Heart Disease

PRENATAL CIRCULATION

Before Birth
- shunting deoxygenated blood
  - ductus arteriosus: connection between pulmonary artery and aorta
  - shunting oxygenated blood
  - foramen ovale: connection between right and left atria
  - ductus venosus: connection between umbilical vein and inferior vena cava

At Birth
- with first breath, lungs open up → pulmonary resistance decreases → pulmonic blood flow increases
- separation of low resistance placenta → systemic circulation becomes a high resistance system → ductus venosus closure
- increased pulmonic flow → increased left atrial pressures → foramen ovale closure
- increased oxygen concentration in blood after first breath → decreased prostaglandins → ductus arteriosus closure
- closure of fetal shunts and changes in vascular resistance → infant circulation assumes normal adult flow

Epidemiology
- 8/1,000 live births have CHD, which may present as a heart murmur, heart failure, or cyanosis; VSD is the most common lesion
**Investigations**
- Echo, ECG, CXR
- pre and postductal oxygen saturations, 4 limb BPs, hyperoxia test

**CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE**
- cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 30 g/dL
- acyanotic heart disease (i.e. L to R shunt, obstruction occurring beyond lungs): blood passes through pulmonic circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis
- cyanotic heart disease (i.e. R to L shunt): blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis

**Figure 2. Common congenital heart diseases**

### Acyanotic Congenital Heart Disease

1. **LEFT-TO-RIGHT SHUNT LESIONS**
   - extra blood is displaced through a communication from the left to the right side of the heart → increased pulmonary blood flow → increased pulmonary pressures
   - shunt volume is dependent upon three factors: (1) size of defect, (2) pressure gradient between chambers or vessels, and (3) peripheral outflow resistance
   - untreated shunts can result in pulmonary vascular disease, left ventricular dilatation and dysfunction, right ventricular HTN and RVH, and ultimately R to L shunts

   **Atrial Septal Defect**
   - 3 types: *ostium primum* (common in DS), *ostium secundum* (most common type, 50-70%), *sinus* *venous* (defect located at entry of superior vena cava into right atrium)
   - **epidemiology:** 6-8% of congenital heart lesions, common in patients with certain congenital disorders (e.g. Down’s syndrome, fetal alcohol syndrome)
   - **natural history**
     - 80-100% spontaneous closure rate if ASD diameter <8 mm
     - if remains patent, CHF and pulmonary HTN can develop in adult life
   - **clinical presentation**
     - history: often asymptomatic in childhood
     - physical exam: grade 2-3/6 pulmonic outflow murmur, widely split and fixed S2
     - children with large ASDs may have signs of heart failure (tachypnea, FTT, hepatomegaly, pulmonary rales/retractions)
   - **investigations**
     - ECG: RAD, mild RVH, RBBB
     - CXR: increased pulmonary vasculature, cardiac enlargement
     - Echo: test of choice
   - **management:** elective surgical or catheter closure between 2-5 yr of age

   **Ventricular Septal Defect**
   - most common congenital heart defect (30-50%)
   - small VSD (majority)
     - **clinical presentation**
       - history: asymptomatic, normal growth and development
       - physical exam: early systolic to holosystolic murmur, best heard at LLSB, thrill
     - **investigations:** ECG and CXR are normal; Echo to confirm diagnosis
     - **management:** most close spontaneously
   - moderate-to-large VSD
     - epidemiology: CHF by 2 mo; late secondary pulmonary HTN if left untreated
     - **clinical presentation**

### Cyanotic (5 “T” lesions)

**Congenital Heart Disease**

<table>
<thead>
<tr>
<th>Acyanotic</th>
<th>Obstructive</th>
<th>Cyanotic (5 “T” lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L → R shunt</td>
<td>Coarctation of the aorta</td>
<td>R → L shunt</td>
</tr>
<tr>
<td>ASD</td>
<td>Aortic stenosis</td>
<td>TOF</td>
</tr>
<tr>
<td>VSD</td>
<td>Pulmonic stenosis</td>
<td>Ebstein’s anomaly</td>
</tr>
<tr>
<td>PDA</td>
<td></td>
<td>Truncus arteriosus</td>
</tr>
<tr>
<td>Atrioventricular septal defect (endocardial cushion defect)</td>
<td></td>
<td>Total anomalous pulmonary venous drainage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tricuspid atresia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoplastic left heart syndrome</td>
</tr>
</tbody>
</table>

**Characteristic CXR Findings in CHD**
- Boot-shaped heart: tetralogy of Fallot, tricuspid atresia
- Egg-shaped heart: transposition of great arteries
- “Snowman” heart: total anomalous pulmonary venous return

**Figure 2. Common congenital heart diseases**

- **Moderate-to-Large VSD**
  - Size of VSD is inversely related to intensity of murmur
• history: delayed growth, decreased exercise tolerance, recurrent URTIs or “asthma” episodes
• physical exam: holosystolic murmur at LLSB, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur

• investigations
  • ECG: LVH, LAH, RVH
  • CXR: increased pulmonary vasculature, cardiomegaly, CHF
  • Echo: diagnostic

• management: treatment of CHF and surgical closure by 1 yr old

Patent Ductus Arteriosus

• patent vessel between descending aorta and left pulmonary artery (normally, functional closure within first 15 h of life, anatomical closure within first days of life)

• epidemiology
  • 5–10% of all congenital heart defects
  • delayed closure of ductus is common in premature infants (1/3 of infants <1,750 g); this is different from PDA in term infants
  • natural history: spontaneous closure common in premature infants, less common in term infants

• clinical presentation
  • history: asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use, CHF
  • physical exam: tachycardia, bounding pulses, hyperactive precordium, wide pulse pressure, continuous “machinery” murmur best heard at left infraclavicular area

• investigations
  • ECG: may show left atrial enlargement, LVH, RVH
  • ECHO is diagnostic
  • CXR: normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery

• management
  • indomethacin (Indocid®): antagonizes prostaglandin E2, which maintains ductus arteriosus patency; only effective in premature infants
  • catheter or surgical closure if PDA causes respiratory compromise, FTT, or persists beyond 3rd mo of life

2. OBSTRUCTIVE LESIONS

• present with decreased urine output, pallor, cool extremities and poor pulses, shock, or sudden collapse

Coarctation of the Aorta

• definition: narrowing of aorta (almost always at the level of the ductus arteriosus)

• epidemiology: commonly associated with bicuspid aortic valve (50%); Turner syndrome (35%)

• clinical presentation
  • history: often asymptomatic
  • physical exam
    • blood pressure discrepancy between upper and lower extremities (increased suspicion/severity if >20 mmHg difference)
    • diminished or delayed femoral pulses relative to brachial (i.e. brachial-femoral delay)
    • possible systolic murmur with late peak at apex, left axilla, and left back
    • if severe, presents with shock in the neonatal period when the ductus arteriosus closes

• investigations: ECG shows RVH early in infancy, LVH later in childhood; Echo or MRI for diagnosis

• prognosis: can be complicated by HTN; if associated with other lesions (e.g. PDA, VSD) can lead to CHF

• management: give prostaglandins to keep ductus arteriosus patent for stabilization and perform surgical correction in neonates; for older infants and children balloon arterioplasty may be an alternative to surgical correction

Aortic Stenosis

• 4 types: valvar (75%), subvalvar (20%), supravalvar, and idiopathic hypertrophic subaortic stenosis (5%)

• clinical presentation
  • history: often asymptomatic, but may be associated with CHF, exertional chest pain, syncope, or sudden death
  • physical exam: SEM at RUSB with aortic ejection click at the apex (only for valvar stenosis)

• investigations: Echo for diagnosis

• management: valvar stenosis is usually treated with balloon valvuloplasty, patients with subvalvar or supravalvar stenosis require surgical repair; exercise restriction required

Pulmonary Stenosis

• 3 types: valvar (90%), subvalvar, or supravalvar

• definition of critical pulmonary stenosis: inadequate pulmonary blood flow, dependent on ductus for oxygenation, progressive hypoxia and cyanosis

• natural history: may be part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with syndromes (e.g. congenital rubella, Noonan syndrome)

• clinical presentation
  • history: spectrum from asymptomatic to CHF
  • physical exam: wide split S2 on expiration, SEM at LUSB, pulmonary ejection click (for valvar lesions)

• investigations
  • ECG findings: RVH
  • CXR: post-stenotic dilatation of the main pulmonary artery (due to high velocity jet past stenotic valve)
  • Echo: diagnostic

• management: surgical repair if critically ill or if symptomatic in older infants/children
Cyanotic Congenital Heart Disease

- Systemic venous return re-enters systemic circulation directly
- Most prominent feature is cyanosis (O2 sat <75%)
- Hypoxic test differentiates between cardiac and other causes of cyanosis
  - Obtain preductal, right radial ABG in room air, then repeat after the child inspires 100% O2
  - If PaO2 improves to greater than 150 mmHg, cyanosis less likely cardiac in origin
- Pre-ductal and post-ductal pulse oximetry
  - >5% difference suggests R to L shunt

1. RIGHT-TO-LEFT SHUNT LESIONS

Tetralogy of Fallot
- Epidemiology: 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy with peak incidence at 2-4 mo of age
- Pathophysiology
  - Embryological defect due to anterior and superior deviation of the outlet septum leading to: VSD, RVOTO (i.e. pulmonary stenosis ± subpulmonary valve stenosis), over-riding aorta, and RVH
  - Infants may initially have a L → R shunt (therefore no cyanosis); however, RVOTO is progressive, leading to increasing R → L shunting with hypoxemia and cyanosis
  - Degree of RVOTO determines the direction and degree of shunt and, therefore, the extent of clinical cyanosis and degree of RVH
- Clinical presentation
  - History: Hypoxic "tet" spells
    - During exertional states (crying, exercise) the increasing pulmonary vascular resistance and decrease in systemic resistance causes an increase in right-to-left shunting
  - Clinical features include paroxysms of rapid and deep breathing, irritability and crying, increasing cyanosis, decreased intensity of murmur (decreased flow across RVOTO)
  - If severe, can lead to decreased level of consciousness, seizures, death
- Physical exam
  - Single loud S2 due to severe pulmonary stenosis (i.e. RVOTO), SEM at LSB
- Investigations
  - ECG: RAD, RVH
  - CXR: Boot-shaped heart, decreased pulmonary vasculature, right aortic arch (in 20%)
  - Echo: Diagnostic
- Management of spells
  - O2, knee-chest position, fluid bolus, morphine sulfate, propranolol
  - Treatment: Surgical repair at 4-6 mo of age; earlier if marked cyanosis or "tet" spells

2. OTHER CYANOTIC CONGENITAL HEART DISEASES

Transposition of the Great Arteries (TGA)
- Epidemiology: 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonates
- Pathophysiology: Parallel pulmonary and systemic circulations
  - Systemic: Body → RA → RV → aorta → body
  - Pulmonary: Lungs → LA → LV → pulmonary artery → lungs
- Survival is dependent on mixing through PDA, ASD, or VSD
- Physical exam
  - Neonates: Ductus arteriosus closure causes rapidly progressive severe hypoxemia unresponsive to oxygen therapy, acidosis, and death
  - VSD present: Cyanosis is not prominent; CHF within first weeks of life
  - VSD absent: No murmur
- Investigations
  - ECG: RAD, RVH, or may be normal
  - CXR: Egg shaped heart with narrow mediastinum ("egg on a string")
  - Echo: Diagnostic
- Management
  - Symptomatic neonates: prostaglandin E1 infusion to keep ductus open until balloon atrial septostomy
  - Surgical repair: arterial switch performed in the first two weeks in those without a VSD while LV muscle is still strong

Total Anomalous Pulmonary Venous Return
- Epidemiology: 1-2% of CHD
- Pathophysiology
  - All pulmonary veins drain into right-sided circulation (systemic veins, RA)
  - No direct oxygenated pulmonary venous return to left atrium
  - Often associated with obstruction at connection sites
  - ASD must be present for oxygenated blood to shunt into the LA and systemic circulation
- Management: Surgical repair in all cases and required urgently for severe cyanosis
Truncus Arteriosus
- **pathophysiology**
  - single great vessel gives rise to the aorta, pulmonary and coronary arteries
  - truncal valve overlies a large VSD
  - potential for coronary ischemia with fall in pulmonary vascular resistance
- **management**: surgical repair within first 6 wk of life

Hypoplastic Left Heart Syndrome
- **epidemiology**: 1-3% of CHD; most common cause of death from CHD in first mo of life
- **pathophysiology**: LV hypoplasia may include atretic or stenotic mitral and/or aortic valve, small ascending aorta, and coarctation of the aorta with resultant systemic hypoperfusion
- systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
- **management**
  - intubate and correct metabolic acidosis
  - IV infusion of prostaglandin E1 to keep ductus open
  - surgical palliation (overall survival 50% to late childhood) or heart transplant

# Congestive Heart Failure
- see Cardiology and Cardiac Surgery, C34

## Etiology
- CHD
- cardiomyopathy (primary or secondary)
- high output circulatory states (e.g. anemia, AVMs, cor pulmonale, hyperthyroidism)
- non-cardiac (e.g. sepsis, renal failure)
- pressure overload (e.g. aortic stenosis/co-arctation, pulmonary stenosis, HTN)
- volume overload (e.g. L to R shunt, valve insufficiency)

## History
- infant: weak cry, irritability, feeding difficulties, early fatigability, diaphoresis while sleeping or eating, respiratory distress, lethargy, FTT
- child: decreased exercise tolerance, fatigue, decreased appetite, respiratory distress, frequent URTIs or “asthma” episodes
- orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all uncommon in children

## Physical Findings
- 4 key features: tachycardia, tachypnea, cardiomegaly, hepatomegaly
- FTT
- alterations in peripheral pulses, four limb blood pressures (in some CHDs)
- dysmorphic features associated with congenital syndromes

## Investigations
- CXR: cardiomegaly, pulmonary venous congestion
- ECG: sinus tachycardia, signs of underlying cause (heart block, atrial enlargement, hypertrophy, ischemia/infarct)
- Echo: structural and functional assessment
- blood work: CBC, electrolytes, BUN, Cr, LFTs

## Management
- general: sit up, O₂, sodium and water restriction, increased caloric intake
- pharmacologic: diuretics, afterload reduction (e.g. ACEI), β-blockers; digoxin rarely used
- curative: correction of underlying cause

# Dysrhythmias
- see Cardiology and Cardiac Surgery, C16
- can be transient or permanent, congenital (structurally normal or abnormal), or acquired (toxin, infection, infarction)

## Sinus Arrhythmia
- phasic variations with respiration (present in almost all normal children)

## Sinus Tachycardia
- rate of impulses arising from sinus node is elevated (>150 bpm in infants, >100 bpm in older children)
- characterized by beat-to-beat heart rate variability with changes in activity, P waves present/normal, PR constant, QRS narrow
- etiology: HTN, fever, anxiety, sepsis, anemia/hypoxia, PE, drugs, etc.
- differentiate from SVT (see below) by slowing the sinus rate (vagal massage, β-blockers) to identify sinus P waves

Pediatric vs. Adult ECG
Pediatric ECG findings that may be normal:
- HR >100 bpm
- Shorter PR and QT intervals and QRS duration
- Inferior and lateral small Q waves
- RV la ger than LV in neonates, so normal to have:
  - RAD
  - Large precordial R waves
  - Upright T waves
  - Inverted T waves in the anterior precordial leads from early infancy to teen years
Premature Atrial Contractions
• may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitalis toxicity

Premature Ventricular Contractions
• common in adolescents
• benign if single, uniform, disappear with exercise, and no associated structural lesions
• if not benign, may degenerate into more severe dysrhythmias

Supraventricular Tachycardia
• abnormally rapid heart rhythm originating above the ventricles – most frequent sustained dysrhythmia in children
• no beat-to-beat HR variability, >220 bpm (infants) or >180 bpm (children), P waves absent/abnormal, PR indeterminable, QRS usually narrow
• pre-excitation syndromes (subset of SVT): WPW syndrome, congenital defect (see Cardiology and Cardiac Surgery, C21)

Complete Heart Block
• congenital heart block can be caused by maternal anti-Ro or anti-La (e.g. mother with SLE)
• often diagnosed in utero (may lead to development of fetal hydrops)
• clinical symptoms related to level of block (the lower the block, the slower the heart rate and greater the symptoms of inadequate cardiac output)
• symptomatic patients need a pacemaker

Heart Murmurs
• 50-80% of children have audible heart murmurs at some point in their childhood
• most childhood murmurs are functional (e.g. “innocent”) without associated structural abnormalities and have normal ECG and radiologic findings
• in general, murmurs can become audible or accentuated in high output states (e.g. fever, anemia)

Table 11. Differentiating Heart Murmurs

<table>
<thead>
<tr>
<th>Innocent</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Timing</td>
<td>SEM</td>
</tr>
<tr>
<td>Grade/Quality</td>
<td>&lt;3/6; soft/blowing/vibratory</td>
</tr>
<tr>
<td>Splitting</td>
<td>Physiologic S2</td>
</tr>
<tr>
<td>Extra Sounds/Clicks</td>
<td>None</td>
</tr>
<tr>
<td>Change of Position</td>
<td>Murmur varies</td>
</tr>
</tbody>
</table>

Table 12. Five Innocent Heart Murmurs

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
<th>Location</th>
<th>Description</th>
<th>Age</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Pulmonic Stenosis</td>
<td>Flow into pulmonary branch arteries from main, larger, artery</td>
<td>Left upper sternal border</td>
<td>Neonates, low-pitched, radiates to axilla and back</td>
<td>Neonates, usually disappears by 3-6 mo</td>
<td>PDA Pulmonary stenosis</td>
</tr>
<tr>
<td>Still’s Murmur</td>
<td>Flow across the pulmonic valve leaflets</td>
<td>Left lower sternal border</td>
<td>High-pitched, vibratory, LL SB or apex, SEM</td>
<td>3-6 yr</td>
<td>Subaortic stenosis Small VSD</td>
</tr>
<tr>
<td>Venous Hum</td>
<td>Altered flow in veins</td>
<td>Infraclavicular (R&gt;L)</td>
<td>Infraclavicular hum, continuous, R&gt;L</td>
<td>3-6 yr</td>
<td>PDA</td>
</tr>
<tr>
<td>Pulmonary Ejection</td>
<td>Flow through the pulmonic valve</td>
<td>Left upper sternal border</td>
<td>Soft, blowing, LUSB, SEM</td>
<td>8-14 yr</td>
<td>ASD Pulmonary stenosis</td>
</tr>
<tr>
<td>Supraclavicular Arterial Bruit</td>
<td>Turbulent flow in the carotid arteries</td>
<td>Supraclavicular</td>
<td>Low intensity, above clavicles</td>
<td>Any age</td>
<td>Aortic stenosis Bicuspid aortic valve</td>
</tr>
</tbody>
</table>

Infective Endocarditis
• see Infectious Diseases, ID16
Development

Approach to Global Developmental Delay

- a so known as Early Developmental Impairment

Definition
- performance significantly below average in two or more domains of development (gross motor, fine motor, speech/language, cognitive, social/personal, activities of daily living) in a child <5 yr of age
- predict a diagnosis of intellectual disability in the future

Epidemiology
- 5-10% of children have neurodevelopmental delay
- careful evaluation can reveal a cause in 50-70% of cases

Etiology
- CNS abnormalities (meningitis/encephalitis, brain malformation, trauma, etc.)
- sensory deficits (hearing, vision)
- environmental (psychosocial neglect, lead exposure, antenatal drug or alcohol exposure, etc.)
- genetic/chromosomal disorders (DS, Fragile X, etc.)
- metabolic disorders (inborn errors of metabolism, hypothyroidism, iron deficiency, etc.)
- obstetrical (prematurity, HIE, TORCH infections, etc.)
- sleep disorders
- seizures

Clinical Presentation
- history
  ■ prenatal - intrauterine exposures (infections, alcohol), prenatal diagnosis,
  ■ obstetrical – complications, APGAR, infections, seizures, screening
  ■ pediatric - detailed developmental milestones: rate of acquisition, regression of skills
  ■ associated problems: feeding, seizures, behaviour, sleep
  ■ ototoxic antibiotics, frequently ear infections
  ■ family history, consanguinity
  ■ social history
- physical exam
  ■ micro/macrocephaly, dysmorphic features head-to-toe, hepatosplenomegaly, height and weight,
  detailed neurological examination
- investigations (guided by history and physical examination)
  ■ neurodevelopmental assessment, neuroimaging, vision and hearing test, EEG, sleep study
  ■ OT, PT, and/or SLP assessments
  ■ psychosocial evaluation
  ■ blood work (lead, CBC, ferritin, TSH)
  ■ metabolic screening (glucose, electrolytes, lactate, ammonia, liver function, pyruvate, albumin,
  triglycerides, uric acid, amino acids, urine organic acids, acylcarnitines, creatine phosphokinase)
  ■ neurologic – EEG or head CT
  ■ genetics consultation (microarray, Fragile X testing, testing for inborn errors of metabolism)

Management
- dependent on specific area of delay
- therapy services (e.g. speech and language therapy for language delay, OT and/or PT for motor delay),
  early intervention services (e.g. infant development services, Ontario Early Years Centres)

Intellectual Disability

Definition
- state of functioning that begins in childhood and is characterized by limitations in both intelligence and
  adaptive skills
- historically defined as an IQ <70
- often preceded by diagnosis of global developmental delay

Epidemiology
- 1% of general population; M:F = 1.5:1

Clinical Presentation
- history
  ■ earlier age of onset correlates with greater severity of ID
  ■ well below average general intellectual functioning
  ■ significant deficits in adaptive functioning in at least 2 of: communication, self-care, home-living,
  social skills, self-direction, academic skills, work, leisure, health, safety
- physical exam
  ■ check growth, dysmorphic features, complete physical exam

<table>
<thead>
<tr>
<th>Severity</th>
<th>% Cases</th>
<th>IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>85</td>
<td>50-70</td>
</tr>
<tr>
<td>Moderate</td>
<td>10</td>
<td>35-49</td>
</tr>
<tr>
<td>Severe</td>
<td>3-4</td>
<td>20-34</td>
</tr>
<tr>
<td>Profound</td>
<td>1-2</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>
• investigations
  ■ standard zed psychology assessment (includes IQ test and measure of adaptive functioning)
  ■ vision, hearing, and neurologic assessment
  ■ genetic and metabolic testing as indicated

Management
• main objective: enhance adaptive functioning level
• requires an interprofessional team with strong case coordination
• emphasize community-based treatment and early intervention
• individual/family therapy, behaviour management services, therapy services (e.g. OT, SLP), medications
  for associated conditions
• education: life skills, vocational training, communication skills, family education
• psychosocial support for individual and family; respite care

Prognosis
• higher rates of sensory deficits, motor impairment, behavioural/emotional disorders, seizures,
  psychiatric illness

**Language Delay**

Definition
• no universally accepted definition, but often identified around 18 mo of age with enhanced well baby visit
• if formally tested, at least one standard deviation below mean of age on standardized testing
• can be expressive (ability to produce or use language), receptive (ability to understand language), or both

Epidemiology
• M>F
• ~10-15% of 2 yr old children have a language delay, but only 4-5% remain delayed after 3 yr of age
• ~6-8% of school-aged children have specific language impairment (many of whom were not identified
  before school entry)

Etiology
• intellectual disability
• developmental disorders - cerebral palsy, Autism Spectrum Disorder
  ■ constitutional language delay
  ■ genetic/metabolic: DS, Fragile X syndrome, Williams syndrome, hypothyroidism, PKU, etc.
  ■ mechanical problems: cleft palate, cranial nerve palsy, hearing impairment
  ■ medical condition: seizure disorder (includes acquired epileptic aphasia), CP, TORCH infection, iron
    deficiency, lead poisoning, etc.
  ■ psychosocial: neglect or abuse
  ■ selective mutism
  ■ language specific learning disorder
  ■ isolated language delay

Clinical Presentation
• history
  ■ concerns about hearing, delay in language development or regression in previously normal language
  development
  ■ delayed language milestones, presence of red flags, regression (see Table 5 Developmental Milestones)
  ■ must determine if language delay is expressive, receptive, or mixed
  ■ determine differences in behaviour at home, school, other social environments
  ■ risk factors: family history of speech and language delay, male, prematurity, low birth weight, hearing loss
• physical exam
  ■ guided by history; look for abnormal growth, dysmorphisms unusual social interactions (lack of eye
    contact not pointing)
  ■ include full exam of the external/internal ear (e.g. TM scarring), oral pharynx (e.g. cleft palate), and
    neurologic system (including tone)
• investigations
  ■ use of language specific screens in primary care setting: The Early Language Milestone
  ■ CAT/CLAMS, MCHAT, etc.
  ■ developmental evaluation
  ■ referred to an audiologist if hearing loss is suspected
  ■ CBC (to rule out anemia), venous blood lead levels, genetic/metabolic workup as indicated

Management
• specific to etiology
• often interdisciplinary and requires appropriate referrals: early intervention services, special education
  services, SLP, OHNS and dental professionals, general support services
• prevention: parents can read aloud to their child, engage in dialogic reading, avoid baby talk, narrate
  daily activities, etc.

Prognosis
• depends on etiology – best prognosis for developmental speech delay
• if language delay persists beyond 5 yr old, more likely to have difficulties in adulthood
• persistent language delay is associated with poor academic performance, behavioural problems, social
  isolation
Specific Learning Disorder

Definition
- specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
- a significant discrepancy between a child's intellectual ability and their academic performance
- types: reading (dyslexia), writing, mathematics (dyscalculia)

Epidemiology
- prevalence: 10%
- high incidence of psychiatric comorbidity: anxiety, dysthymia, conduct disorder, major depressive disorder, oppositional defiant disorder, ADHD

Etiology
- pathogenesis is unknown, likely genetic factors involved
- learning disabilities may be associated with a number of conditions:
  - genetic/metabolic: Turner syndrome, Klinefelter syndrome
  - perinatal: prematurity, low birth weight, birth trauma/hypoxia
  - postnatal: CNS damage, hypoxia, environmental toxins, FAS, psychosocial deprivation (understimulation), malnutrition
- poor visual acuity is NOT a cause

Risk Factors
- positive family history, prematurity, other developmental and mental health conditions, neurologic disorders (e.g. seizure disorders, neurofibromatosis), history of CNS infection/irradiation/traumatic injury

Clinical Presentation
- history and physical exam
  - school difficulties (academic achievement, behaviour, attention, social interaction, over-reliance on teacher)
  - development of negative self-concept → reluctance to participate even in areas of strength
  - social issues: overt hostility towards parents/teachers; difficulties making friends, bullying, and anxiety
  - look for dysmorphism, complete physical exam
- investigations
  - psychoeducational assessment
  - individual scores on achievement tests in reading, mathematics, or written expression (WISC III WRAT) >2 SD below that expected for age, education, and IQ
  - evaluate child's attention, memory, expressive language, coordination skills

Management
- provide quality instruction for specific learning disability
- support student by modifying the curriculum and/or providing accommodations (e.g. scribe for writing, extra time for tests, photocopied notes, etc.)
- consider grade retention in certain students (no guidelines exist, very rare in Ontario)
- specialized education placements that can provide educational remediation

Prognosis
- limited information available about persistence of learning disabilities over time
- low self-esteem, poor social skills, 40% school drop-out rate

Fetal Alcohol Spectrum Disorder

Definition
- term describing the range of effects of prenatal exposure to alcohol, including physical, mental behavioural, and learning disabilities
- abstinence from alcohol during pregnancy is recommended
- spectrum includes: FAS, partial FAS, ARBD (alcohol related brain damage) and ARND (alcohol related neurodevelopmental disorder)

Epidemiology
- prevalence of FAS and FASD is 0.1% and 1.0%, respectively
- most common preventable cause of intellectual disability

Pathogenesis
- specific mechanism of FASD is unknown, but hypotheses include nutritional deficits, toxic effects of acetaldehyde, alteration of placental transport, abnormal protein synthesis, and altered cerebral neurotransmission
Diagnosis
- often misdiagnosed or missed entirely
- diagnosis of FAS, ARBD, and ARND all require evidence of maternal drinking during pregnancy
- criteria for diagnosis of FAS
  - growth deficiency: low birth weight and/or decelerating weight over time not due to nutrition
  - characteristic pattern of facial anomalies: short palpebral fissures (<2SD below mean), flattened philtrum, thin upper lip (having all 3 features is highly specific for alcohol exposure, don't need maternal history to confirm)
  - CNS dysfunction (need ≥3): motor skills; neuroanatomy/neuropsychology; cognition; language; academic achievement; memory; attention; executive function (impulse control and hyperactivity); affect regulation; adaptive behaviour, social skills or social communication OR microcephaly in infant and young children
- criteria for diagnosis of ARBD
  - congenital anomalies, including malformations and dysplasias of the cardiac, skeletal, renal, ocular, and auditory systems
- criteria for diagnosis of ARND
  - CNS dysfunction (similar to FAS)
  - complex pattern of behavioural or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone

Management
- early diagnosis is essential to prevent secondary disabilities
- no cure, but individuals with FASD and their families should be linked to community resources and services to improve outcome

Prognosis
- secondary disabilities include unemployment, mental health problems, difficulties with the law, inappropriate sexual behaviour, disrupted school experience, peer problems

Attention Deficit Hyperactivity Disorder
- see Psychiatry, Neurodevelopmental Disorders, PS38

Autism Spectrum Disorder
- see Psychiatry, Neurodevelopmental Disorders, PS37

Motor Delay
- see Cerebral Palsy, P83 and Medical Genetics, Duchenne Muscular Dystrophy, MG7

Endocrinology

Diabetes Insipidus
- see Endocrinology, E18 and Nephrology, NP11

Syndrome of Inappropriate Antidiuretic Hormone
- see Endocrinology, E18 and Nephrology, NP10

Diabetes Mellitus

DIABETES MELLITUS TYPE 1
- see Endocrinology, Disorders of Glucose Regulation, E6

Epidemiology
- most common form of DM in children, M=F
- variable prevalence internationally, affects ~1-4,000 children in Canada
- can present at any age, but bimodal peaks at 5-7 yr old and at puberty

Clinical Presentation
- can present as polyuria (often manifested as nocturia or secondary enuresis), polydipsia, weight loss (lack of insulin leading to a catabolic state), polyphagia, DKA (~20%) (see Endocrinology, E11)
Management

- patients and families are best managed with a family-centred pediatric multidisciplinary team able to provide education, ongoing care, and psychosocial support surrounding survival skills, meal plans, and insulin injections as a cornerstone of treatment
- diet with consistent levels of carbohydrates, avoiding foods with high glycemic index is advised
- exercise recommended, extensive activity involving legs (walking, cycling, running) may cause prolonged hypoglycemia
- administer influenza immunization yearly to avoid complications to management
- blood glucose monitoring is especially important in children as they are more susceptible to hypoglycemia
- administer glucagon or dextrose for severe hypoglycemia
- if DKA present: ABCs, 100% O2, admit, monitors, correct fluid losses, conduct ECG (assess abnormal T waves), administer insulin and restore glucose gradually (first SC and then IV if no improvement), correct electrolyte disturbances, identify/treat precipitating event, avoid complications (i.e. cerebral edema)
- low threshold to investigate (CT/MRI) and treat DKA, as cerebral edema is a major concern
- signs of neurological deterioration – headache, bradycardia, irritability, decrease LOC, incontinence, specific neurological signs)
- administer mannitol for cerebral edema
- frequent BG, fluid and electrolyte monitoring
- see Endocrinology, E11

screen for micro- and macrovascular complications (regular ophthalmology assessments, BP, microalbuminuria), concurrent autoimmune diseases (thyroiditis, celiac disease, etc.), and mental health issues (depression, eating disorders), hypertension, dyslipidemia

Prognosis

- no cure currently
- short-term complications
  - hypoglycemia
  - due to missed/delayed meals, excess insulin or exercise, illness
  - can lead to seizures and/or coma
  - reversed with PO/IV glucose or IM glucagon
  - hyperglycemia
  - due to intercurrent illness, diet-to-insulin mismatch
  - risk of end-organ damage
  - DKA: due to missed insulin doses, infection; most common cause of death
- long-term complications
  - microvascular: retinopathy, nephropathy, neuropathy
  - macrovascular: metabolic syndrome, CVD, CAD, PVD
  - increased risk of other autoimmune diseases
  - hypertension, dyslipidemia

DIABETES MELLITUS TYPE 2

- see Family Medicine, FM22, and Endocrinology, E7
- impaired glucose metabolism due to increased peripheral insulin resistance
- rare before 10 yr of age, but more common in older children/adolescents
- prevalence is rising mainly due to the increased incidence of childhood obesity
- risk factors: obesity, positive family history, female gender, PCOS, hyperglycemia exposure in utero, certain ethnic groups
- risk reduced with breastfeeding
- clinical presentation may be similar to that of type 1 DM, though most children are asymptomatic
- may present in DKA or hyperglycemic hyperosmotic nonketotic state
- investigation – fasting plasma glucose recommended, oral glucose tolerance test for very obese children with multiple risk factors
- management
  - insulin used for severe metabolic decompensation at diagnosis (DKA, A1C > 9%), can wean off
  - initiate lifestyle modification program, including diet, weight loss, physical activity (moderate-to-vigorous activity for at least 60 min/d; screen time less than 2 h/d)
  - glycemic target: HbA1c ≤7%
  - if glycemic targets not achieved within 3-6 mo from diagnosis with lifestyle intervention alone, either metformin (first line), glimepiride, or insulin should be initiated
  - metformin can be initiated at diagnosis if HbA1c >7%
  - monitor HbA1c every 3 mo
  - advise patient to monitor finger-stick blood glucose levels if on medication with risk of hypoglycemia, are changing medication regimen, have not met treatment goals, or have intercurrent illness
  - screening – same as T1D plus annual screening for PCOS and NAFLD
- prognosis: includes microvascular and macrovascular complications similar to type 1 DM

Growth (see FTT)

APPROACH TO SHORT STATURE

Definition

- short stature: height <3rd percentile
- poor growth evidenced by growth deceleration (height crosses major percentile lines, growth velocity <25th percentile)
Epidemiology
• ~2.5% of the population by definition

Etiology
• see sidebar

Clinical Presentation
• history and physical exam
  ■ plot on growth curve (special growth charts available for Turner syndrome, achondroplasia, DS)
  ■ assess for dysmorphic features, disproportionate short stature
  ■ risk factors for GH deficiency: previous head trauma, history of intracranial bleed or infection, head surgery or irradiation, positive family history, breech delivery
  ■ decreased growth velocity may be more worrisome than actual height
• investigations
  ■ calculate mid-parental height: children are usually in a percentile between their parents’ height (mid-parental height = (mother + father’s height in cm ± 12.5cm)/2)
  ■ AP x-ray of left hand and wrist for bone age
  ■ GH testing
  ■ remaining investigations guided by history and physical (e.g. TSH, sweat chloride, etc.)

Management
• depends on severity of problem as perceived by parents/child
• no treatment for non-pathological short stature, except for idiopathic short stature
• GH therapy for GH deficiency: if administered at an early age, can help patients achieve adult height requirements
  ■ GH shown to be deficient by 2 different stimulation tests (with argining, glucagon, insulin)
  ■ growth velocity <3rd percentile or height <3rd percentile
  ■ bone age x-rays show unfused epiphyses/delayed bone age
• support and management of resultant self-image issues, social anxiety, etc.

Figure 7. Approach to the child with short stature

TALL STATURE
• height greater than two SD above the mean for a given age, sex, and race

Etiology
• constitutional/familial
  • endocrine: Beckwith-Wiedemann syndrome, hyperthyroidism, hypophyseal gigantism, precocious puberty
  • genetic: homocystinuria, Klinefelter syndrome, Marfan syndrome, Sotos syndrome

Hypercalcemia/Hypocalcemia/Rickets
• see Endocrinology, E37, E39, E42
Hyperthyroidism and Hypothyroidism

- may be congenital or acquired (for acquired causes, see Endocrinology, E22)

CONGENITAL HYPERTHYROIDISM
- also known as neonatal Graves’ disease

**Epidemiology**
- ~1:25,000 neonates, M=F

**Etiology**
- may be classified as permanent or transient congenital hypothyroidism (CH)
  - subcategorize into primary (85% dysgenesis, 15% thyroid gland disorder), secondary/central (pituitary/hypothalamic issue), or peripheral CH (deficits in thyroid hormone transport, metabolism or action)
  - permanent CH requires lifelong treatment, transient CH recovers to normal thyroid after neonatal period
  - causes of transient hypothyroidism: maternal - antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications; neonatal – neonatal iodine deficiency/excess, congenital liver hemangiomas, certain gene mutations

**Clinical Presentation**
- history and physical exam
  - usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  - prolonged jaundice, feeding difficulty, lethargy, constipation, umbilical hernia, macroglossia, large fontanelles, puffy face, swollen eyes
  - examine for congenital malformations (especially cardiac) and dysmorphic features
  - most commonly presents as a positive newborn screen result
- investigations
  - screen all infants for primary CH, repeat screening at 2 wk for infants at high risk: preterm, (very)-low birth weight, infants in NICU, specimen collection <24 h of life, multiple births
  - diagnosis through newborn screening of TSH (most sensitive for primary CH) or free T4; abnormal results should be confirmed with serum levels from venipuncture
    - ↑ TSH, ↓ free T4 in primary CH
    - ↓ TSH, ↑ free T4 in secondary CH
  - primary CH (optional) - radioisotope scanning/ultrasound of thyroid for severity, serum thyroglobulin, maternal antithyroid antibodies, urinary iodine
  - secondary CH: MRI, gene analysis, eye exam for optic nerve hypoplasia (assess pituitary)

**Management**
- thyroxine replacement, hormone normalization should be done within 2 wk to avoid cognitive impairment

**Prognosis**
- excellent outcome if treatment started within 1-2 mo of birth
- if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or disability (mild to profound), intellectual impairment, poor growth, hearing loss

CONGENITAL HYPOTHYROIDISM

**Epidemiology**
- incidence: 1:4,000 1:20,000 newborn births; F:M = 2:1
- one of the most common preventable causes of intellectual disability

**Etiology**
- may be classified as permanent primary, central, or transient hypothyroidism
- ~85% of primary cases are sporadic (mostly thyroid dysgenesis), remaining 15% hereditary (mostly inborn errors of thyroid synthesis)
- causes of transient hypothyroidism: maternal antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications

**Clinical Presentation**
- history and physical exam
  - usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  - prolonged jaundice, constipation, sluggish, hoarse cry, lethargy, poor feeding, macroglossia, coarse facial features, large fontanelles, umbilical hernia
- investigations
  - diagnosis through newborn screening of TSH or free T4; abnormal results should be confirmed with serum levels from venipuncture

**Management**
- thyroxine replacement
Prognosis
• excellent outcome if treatment started within 1-2 mo of birth
• if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or disability (mild to profound)

Sexual Development

AMBIGUOUS GENITALIA

Definition
• newborn or child whose gender is difficult to assign based on the appearance of genitalia
• subtype of DSD: a condition in which development of chromosomal, gonadal, or anatomic sex is atypical
• subtypes: 46,XX DSD, 46,XY DSD, ovotesticular DSD (true hermaphrodite)

Epidemiology
• incidence of genital abnormalities at birth is as high as 1:300
• prevalence of complex anomalies with true sexual ambiguity much lower at ~1:5,000

Etiology
• 46,XY DSD
  ■ inborn error of testosterone biosynthesis or Leydig cell hypoplasia
  ■ 5-α-reductase deficiency, androgen receptor deficiency or insensitivity
  ■ LH/hCG unresponsiveness
• 46,XX DSD
  ■ virilizing CAH (most common)
  ■ maternal source: virilizing ovarian or adrenal tumours, untreated maternal CAH, placental aromatase deficiency
• ovotesticular DSD
  ■ both ovarian follicles and seminiferous tubules in the same patient with a 46 XX karyotype
  ■ mixed gonadal dysgenesis

Risk Factors
• parental consanguinity, positive family history of ambiguous genitalia, early childhood illness/death, or primary amenorrhea, maternal medications during pregnancy (e.g. androgens, progesterones, danazol, phenytoin, aminoglutethimide, endocrine disruptors)

Clinical Presentation
• history
  ■ thorough obstetrical history, including prenatal screens and maternal medications
  ■ family history: autosomal recessive pattern may suggest CAH, X-linked recessive pattern may suggest androgen insensitivity syndrome
• physical exam
  ■ male pseudohermaphrodite (XY): small phallus, hypospadias, undescended testicles
  ■ female pseudohermaphrodite (XX): clitoral hypertrophy, labioscrotal fusion
  ■ look for concurrent midline defects, dysmorphic features, and congenital abnormalities
• investigations
  ■ karyotype and genetic workup as indicated
  ■ blood work: electrolytes and renin (evidence of salt-wasting in CAH); 17-OH-progesterone, androgens, FSH, and LH
  ■ imaging: abdominal U/S to look for uterus, testicles, ovaries

Management
• avoid announcement of probable sex or use of personal pronouns until all tests are complete
• continuous psychosocial support for parents and child during development
• elective surgical reconstruction of genitalia is sometimes possible

CONGENITAL ADRENAL HYPERPLASIA

Definition
• autosomal recessive disorder characterized by the partial or total defect of various synthetic enzymes required for cortisol and aldosterone production in the adrenal cortex
  ■ adrenal cortex normally produces balanced levels of aldosterone, cortisol and androgens

Epidemiology
• occurs in ~1:15,000 live births
• most common cause of ambiguous genitalia in genotypically normal females (46XX)

Etiology
• for biosynthetic pathways of adrenal cortex, see Endocrinology, E29
  ■ 21-OH responsible for ~95% of CAH cases
  ■ results in ↓ cortisol and aldosterone production with shunting toward ↑↑ androgens
  ■ cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
  ■ rarer causes include deficiencies in 11-OH, cholesterol desmolase, 17-OH, and 3-HSD
Clinical Presentation
- depends on which enzyme in cortisol synthesis pathway is defective
- presentation of 21-OH deficiency can be divided into
  - classic deficiency with salt wasting: inadequate aldosterone resulting in FTT, hyperkalemia, hyponatremia, hypoglycemia, acidosis (majority of classic CAH types)
  - classic deficiency without salt wasting: simple virilization with adequate aldosterone levels
    - females typically present with amenorrhea, precocious puberty, polycystic ovaries, hirsutism
    - males typically asymptomatic at birth, may show hyperpigmentation (from overproduction of melanocyte stimulating hormone), penile enlargement, rapid growth and accelerated skeletal maturation; present with signs of virilization later in life
  - non-classic CAH – mild androgen excess, sometimes asymptomatic, virilization present later in life, rarely associated with Addisonian crises
- 21-OH deficiency screening is part of many newborn screening programs across North America
- high serum levels of 17-OH progesterone in random blood sample diagnostic for 21-OH deficiency
  - assess plasma ACTH serum electrolytes, plasma glucose, plasma aldosterone, plasma renin activity, blood gas
  - ultrasound – look for enlarged adrenal gland and presence of uterus

Management
- correct any abnormalities in fluids, electrolytes, or serum glucose
- provide glucocorticoids (e.g. hydrocortisone)/mineralocorticoids (fludrocortisone) as necessary to reduce ACTH levels, extra glucocorticoids in times of stress
- psychosocial support

Prognosis
- complications if untreated include virilization, acne, salt wasting, hypotension

NORMAL PUBERTAL DEVELOPMENT

Physiology
- puberty occurs with the maturation of the HPG axis
  - ↑ pulsatile release of GnRH → ↑ release of LH and FSH → maturation of gonads, release of sex steroids
  - secondary sexual characteristics
  - adrenal production of androgens also required

Females
- onset: age 8-13 yr old (may start as early as 7 yr in girls of African descent)
- usual sequence
  1. thelarche: breast budding
  2. pubarche: axillary hair, body odour, mild acne
  3. growth spurt
  4. menarche: mean age 12.5 yr; indicates that growth spurt is almost complete; menses may be irregular in duration and length of cycle
- early puberty is common and often constitutional, late puberty is rare (rule out organic causes)

Males
- onset: age 9-14 yr old
- usual sequence
  1. testicular enlargement
  2. penile enlargement
  3. pubarche: axillary and facial hair, body odour, mild acne
  4. growth spurt: occurs later in boys
- early puberty is uncommon (rule out organic causes), late puberty is common and often constitutional
- gynecomastia (transient development of breast tissue) is a common self-limited condition seen in 50% of males during puberty (but any discharge from nipple or fixed mass should be investigated)

Tanner Staging
- scale used in pediatrics that defines physical measurements of development based on external primary and secondary sex characteristics
**Precocious Puberty**

**Definition**
- Development of secondary sexual characteristics 2-2.5 SD before population mean
- <8 yr old for females, <9 yr old for males

**Epidemiology**
- 1/10,000; F>M

**Etiology**
- Usually idiopathic in females (90%), more suggestive of pathology in males (50%)
- Central (GnRH dependent)
  - Hypergonadotropic hypergonadism; hormone levels as in normal puberty
  - Premature activation of the HPG axis
  - Differential diagnosis: idiopathic or constitutional (most common in females), CNS disturbances
    (tumours, hamartomas, post-meningitis, increased ICP, radiotherapy), NF, primary severe hypothyroidism
- Peripheral (GnRH independent)
  - Hypogonadotropic hypergonadism
  - Differential diagnosis: adrenal disorders (CAH, adrenal neoplasm), testicular/ovarian tumour,
    gonadotropin/hCG secreting tumour (hepatoblastoma, intracranial teratoma, germinoma),
    exogenous steroid administration, McCune-Albright syndrome, aromatase excess syndrome, rarely
    hypothyroidism (Van Wyk-Grumbach syndrome), primary severe hypothyroidism

**Clinical Presentation**
- History
  - Symptoms of puberty, family history of precocious puberty, medical illness
- Physical exam
  - Growth velocity
    - Prepubertal: 4 to 6 cm/yr
    - Growth spurt: boys 8-10 cm/yr, girls 6-8 cm/yr
  - Complete physical exam, including Tanner staging and neurological assessment
- Investigations
  - Initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free
    T4, DHEA-S, 17-OH-progesterone)
  - Secondary tests: MRI head, pelvic U/S, β-hCG, GnRH, and/or ACTH stimulation test

**Management**
- Indications for medical intervention to delay progression of puberty: rapid advancement of puberty,
  early age, risk of compromise of final adult height, psychological
- Central causes: goals are to preserve height and alleviate psychosocial stress; GnRH agonists
  (e.g. leuprolide) most effective
- Peripheral causes: goal is to limit effects of elevated sex steroids; treat underlying cause; medications that
  decrease the production of a specific sex steroid or block its effects (e.g. ketoconazole, spironolactone,
  tamoxifen, anastrozole), surgical intervention

---

*Figure 8. Tanner staging*

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilla elevation only</td>
<td>Breast and papilla elevated as small mound, enlargement of areola</td>
<td>Enlargement of breast and areola, no contour separation</td>
<td>Areola and papilla form secondary mound</td>
<td>Mature, nipple projects, no secondary mound</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Male Genital</th>
<th>FEMALE GENITAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hair, prepubertal</td>
<td>No hair, prepubertal</td>
</tr>
<tr>
<td>Small amount of long, straight or curled, slightly pigmented hair along labia majora</td>
<td>Small amount of long, straight or curled, slightly pigmented hair along labia majora</td>
</tr>
<tr>
<td>Darker, coarser, curly hair distributed sparsely over pubis</td>
<td>Darker, coarser, curly hair distributed sparsely over pubis</td>
</tr>
<tr>
<td>Adult type hair, no extension to medial thighs</td>
<td>Mature distribution with spread to medial thighs</td>
</tr>
</tbody>
</table>

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*A child with proven central precocious puberty should receive an MRI of the brain.*
DELAYED PUBERTY

Definition
- failure to develop secondary sex characteristics by 2-2.5 SD beyond the population mean
  - for males: lack of testicular enlargement by 14 yr old
  - for females: lack of breast development by 13 yr old OR absence of menarche by 16 yr old or within 5 yr of pubertal onset

Epidemiology
- M>F

Etiology
- usually constitutional delay in males, more suggestive of pathology in females
  - central causes
    - constitutional delay in activation of HPG axis (most common)
    - hypogonadotropic hypogonadism
  - peripheral causes
    - hypergonadotropic hypogonadism (e.g. primary gonadal failure, gonadal damage, Turner syndrome, hormone deficiency, androgen insensitivity syndrome, etc.)

Clinical Presentation
- history: weight loss, short stature, family history of puberty onset, medical illness, high performance athletes (females)
  - physical exam: growth velocity (minimum 4 cm/yr), Tanner staging, neurological exam, complete physical exam
  - investigations
    - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, T3, ACTH, PRL), CBC, electrolytes, BUN, Cr, LFTs, liver enzymes, ESR, CRP, urinalysis
    - secondary tests: MRI head, pelvic U/S, karyotype, IBD panel, celiac disease panel, LH levels following GnRH agonist

Management
- identify and treat underlying cause
- hormonal replacement: cyclic estradiol and progesterone for females, testosterone for males

Gastroenterology

Vomiting

History
- characteristic of emesis (e.g. projectile, bilious, bloody)
- pattern of emesis (e.g. association with feeds, cyclic, morning)
- associated symptoms (e.g. anorexia, diarrhea, etc.)
- red flags: bilious or bloody emesis, projectile vomit, abdominal distension and tenderness, high fever, signs of dehydration
- note that vomiting without diarrhea is most likely not gastroenteritis.
  - post tussive vomiting is also common with coughing fits in children

Physical Findings
- vital signs to determine clinical status and hydration state

Investigations
- CBC, electrolytes, BUN, Cr, amylase, lipase, glucose done routinely
- in sick child, add: ESR, venous blood gases, C&S (blood, stool), imaging

Table 13. Common Differential Diagnosis, Associated Findings, and Diagnostic Approach Based on Age

<table>
<thead>
<tr>
<th>Cause</th>
<th>Suggestive Findings</th>
<th>Diagnostic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEONATES – NON-BILIOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheoesophageal Fistula</td>
<td>Vomiting, excessive secretions soon after birth (e.g. drooling, choking, respiratory distress), inability to feed, inability to advance NG tube</td>
<td>Inability to advance NG tube, CXR, upper GI series with water-soluble contrast</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>Projectile vomiting immediately after feeding, dehydrated, palpable “olive” in RUQ, decreased stools, hunger</td>
<td>US of pylorus, upper GI study (if US not diagnostic) Electrolytes, ABG (hypokalemic, hypochloremic metabolic acidosis)</td>
</tr>
<tr>
<td>GERD</td>
<td>Fussiness after feeds, spit ups, arching of back, poor weight gain</td>
<td>Empiric trial of acid suppression, pH monitoring study, upper GI study, endoscopy</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Fever, lethargy, tachycardia, tachypnea, widening pulse pressure</td>
<td>CBC, cultures (blood, urine, CSF), CXR</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>Poor feeding, FTT, jaundice, hepatosplenomegaly, cardiomyopathy, dysmorphism, developmental delay</td>
<td>Electrolytes, ABG (hyponatremic, hyperkalemic metabolic acidosis), lactate, ammonia, LFTs, BUN, Cr, serum glucose, bilirubin, PT/PTT, CBC</td>
</tr>
</tbody>
</table>
Table 13. Common Differential Diagnosis, Associated Findings, and Diagnostic Approach Based on Age (continued)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Suggestive Findings</th>
<th>Diagnostic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEONATES – BI IOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal obstruction – malrotation with volvulus, meconium ileus</td>
<td>Bilious emesis, abdominal distension, pain, bloody stool, shock</td>
<td>AXR, upper GI series, contrast enema</td>
</tr>
<tr>
<td>Duodenal atresia/stenosis</td>
<td>Bilious emesis, abdominal distension often seen in DS, jaundice, polyhydramnios during pregnancy, hypokalemic hypochloremic metabolic alkalosis.</td>
<td>AXR, upper GI series (‘double bubble’ sign)</td>
</tr>
<tr>
<td>Hirschsprung’s disease</td>
<td>Bilious emesis, abdominal distension, pain, failure to pass stool</td>
<td>AXR, upper GI series, contrast enema, rectal biopsy</td>
</tr>
<tr>
<td>CHILDREN AND ADOLESCENTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute viral gastroenteritis</td>
<td>Diarrhea, fever, sick contact, recent travel</td>
<td>CBC, stool culture</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Periumbilical discomfort that later localizes to RLQ, fever, anorexia</td>
<td>Abdominal U/S</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Colicky progressive abdominal pain, drawing of legs up to chest, lethargy, bloody “red currant jelly” stool (Triad)</td>
<td>Abdominal U/S</td>
</tr>
<tr>
<td>Non-GI infection (e.g. meningitis)</td>
<td>Fever, localized findings depending on cause</td>
<td>Cultures (CSF, blood, urine), brain imaging, CXR</td>
</tr>
<tr>
<td>Increased ICP</td>
<td>Nocturnal waking, progressive recurrent headache worse with Valsalva, nuchal rigidity</td>
<td>Brain CT without contrast, Therapeutic LP in idiopathic intracranial HTN</td>
</tr>
<tr>
<td>Toxic ingestion</td>
<td>Finding possibly varying by substance–toxicidrome oft n a history of ingestion</td>
<td>Qualitative and sometimes quantitative levels (urine, blood)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Amenorrhea, morning sickness, bloating, breast tenderness</td>
<td>Urine β-hCG</td>
</tr>
<tr>
<td>Cyclic vomiting</td>
<td>At least 3 self-limited episodes of vomiting lasting 12 h, 7 d between episodes, no organic cause of vomiting</td>
<td>Diagnosis of exclusion</td>
</tr>
</tbody>
</table>

Management
- rehydration (see Fluids and Electrolytes, P69)
- treat underlying cause
  - antiemetic drugs can be used in children >2 years with severe vomiting is severe: promethazine, prochlorperazine, metoclopramide, ondansetron

**Gastroesophageal Reflux**

**Epidemiology**
- extremely common in infancy (up to 50%) but rarely causes GERD (GER disease)

**Clinical Presentation**
- vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<30 mL)
  - when to suspect gastroesophageal reflux disease (GERD), defined as when GER causes troublesome symptoms/complications
    - infant: poor weight gain, irritability, sleep disturbance, respiratory symptoms (coughing, choking, wheezing)
    - older child/adolescent: abdominal pain/heart burn, dysphagia, asthma, recurrent pneumonia/upper respiratory infections, recurrent otitis media, upper airway symptoms (chronic cough, hoarseness), dental erosions

**Investigations**
- thriving baby requires no investigation
- GERD can be a clinical diagnosis but diagnostic investigations may include
  - upper GI tract radiography – assesses anatomy and motility disorder
  - esophageal pH – quantify GER
  - upper endoscopy and esophageal biopsy – rule out other conditions that mimic GERD symptoms, assess GERD-related esophageal injury
  - warning signs of associated disorders requiring further investigations: bilious vomiting, GI tract bleeding, consistently forceful vomiting, fever, lethargy, hepatosplenomegaly, buging fontanelle, micro/macrocephaly, seizures, abdominal tenderness/distension, suspected genetic, metabolic syndrome or chronic disease

**Management**
- conservative (infant): thickened feeds, frequent and smaller feeds, elevation of head, changing formula to hydroyzled protein or amino acid based formula
- breastfeeding infants – mothers exclude milk and egg in diet
- older children/adolescent – same as adult management (see Gastroenterology, G6)
- medical
  - short-term parenteral feeding to enhance weight gain
  - ranitidine, PPI: decreases gastric acidity, decreases esophageal irritation
  - domperidone, metoclopramide: improves gastric emptying and GI motility; safety concerns and limited efficacy, should be reserved for children with gastroparesis contributing to GERD
- surgical: indicated for failure of medical therapy (Nissen fundopl cation)

**Complications**
- esophagitis, strictures, Barrett's esophagus, FTT, aspiration, oral feeding aversion
Tracheoesophageal Fistula
• see General Surgery, GS64

Pyloric Stenosis
• see General Surgery, GS62

Duodenal Atresia
• see General Surgery, GS63

Malrotation of the Intestine
• see General Surgery, GS63

Diarrhea
• definition of diarrhea varies with diet and age (stool normalcy difficult to define in children)
  infants → increase in stool frequency to twice as often per day; older children → 3+ loose or watery
  stools/d
  • duration: acute; <2 wk; chronic: >2 wk

Pathophysiology
• osmotic: due to non-absorbable solutes in GI tract (e.g. lactose intolerance)
• secretory: increased secretion of Cl– ions and water in intestinal lumen (e.g. bacterial toxin)
• malabsorption: less time for absorption due to increased motility or less villi to absorb (e.g. short bowel
  syndrome)

History
• frequency, duration, quality of diarrhea
• associated symptoms (e.g. fever, abdominal pain, hematochezia, etc.)
• recent antibiotic use or recent travel
• elements of diet

Physical Findings
• vital signs to determine clinical status and hydration state

Investigations
• acute diarrhea
  • stool for C&S, O&P, electron microscopy for viruses, C. difficile toxin, microscopy (leukocytes
    suggestive of invading pathogen), blood and urine cultures, blood work
  • chronic diarrhea
  • serial heights, weights, growth percentiles
  • if child growing well and thriving, workup is limited (stool cultures as above, stool reducing substances)
  • red flags: poor growth, chronic rash, other serious infections, hospitalizations for dehydration
  • require full workup (as per below)
  • stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, C. difficile toxin,
    3 d fecal fat, α-1-antitrypsin clearance, fecal elastase
  • urinalysis, urine culture
  • CBC, differential, ESR/CRP, smear, electrolytes, total protein, albumin, carotene, Ca2+, PO43–, Mg2+, Fe,
    ferritin, folate, fat-soluble vitamins, PT, INR
  • sweat chloride, celiac screen, thyroid function tests, urine VMA and HVA, HIV test, lead levels
  • CXR, upper GI series and follow-through
  • specialized tests: endoscopy, small bowel biopsy

Diarrhea is defined as an increase in
frequency and/or decreased consistency of
stools compared to normal

Normal stool volume
Infants: 5-10 g/kg/d
Children: 200 g/d

Diarrhea Red Flags
Bloody stool, fever, petechiae or purpura,
signs of severe dehydration, weight loss/FTT

Common Antibiotics that Can Lead to C.
difficle Infection
• Fluoroquinolones
• Clindamycin
• Penicillins (broad spectrum)
• Cephalosporins (broad spectrum)
Differential Diagnosis

Table 14. Differential Diagnosis of Diarrhea

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td></td>
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<tr>
<td>Rotavirus</td>
<td></td>
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<tr>
<td>Norwalk</td>
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<tr>
<td>Enteric adenovirus</td>
<td></td>
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<tr>
<td>Bacterial</td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td></td>
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<tr>
<td>Campylobacter</td>
<td></td>
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<tr>
<td>Shigella</td>
<td></td>
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<tr>
<td>Pathogenic E. coli</td>
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<tr>
<td>Yersinia</td>
<td></td>
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<tr>
<td>C. difficile</td>
<td></td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
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<tr>
<td>Giardia lamblia</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td></td>
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<tr>
<td>Antibiotic-induced</td>
<td></td>
</tr>
<tr>
<td>Non-specific: associated with systemic infection</td>
<td></td>
</tr>
<tr>
<td>Hirschsprung’s disease</td>
<td></td>
</tr>
<tr>
<td>Toxic ingestion</td>
<td></td>
</tr>
<tr>
<td>Primary disaccharidase deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td></td>
</tr>
<tr>
<td>0 – 3 mo</td>
<td>3 mo – 3 yr</td>
</tr>
<tr>
<td>No FTT</td>
<td>GI infection</td>
</tr>
<tr>
<td>FTT</td>
<td>Celiac disease</td>
</tr>
</tbody>
</table>

Gastroenteritis

**History**
- non-specific: diarrhea, vomiting, fever, anorexia, headache, myalgias, abdominal cramps
- bacterial and parasitic agents more common in older children (2-4 yr)
- recent infectious contacts: symptoms usually begin 24-48 h after exposure

**Physical Exam**
- febrile
- dehydrated: must assess extent (see Approach to Infant/Child with Dehydration, P69)

**Investigations**
- not usually necessary in young children
- stool analysis: leukocytes/erythrocytes suggests bacterial or parasitic etiology; pH <6 and presence of reducing substances suggests viral etiology

**Complications**
- viral gastroenteritis usually self-limiting (lasts 3-7 d in most cases)
- adverse effects related to hypovolemia, shock, tissue acidosis, and rapid onset and over-correction of electrolyte imbalances
- death in severe dehydration (rare in developed countries)

Table 15. Gastroenteritis

<table>
<thead>
<tr>
<th>Viral Infection</th>
<th>Bacterial Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Most common cause of gastroenteritis</td>
</tr>
<tr>
<td>Commonly: rotaviruses (most common), enteric adenovirus, norovirus (typically older children)</td>
<td>Salmonella, Campylobacter, Shigella, pathogenic E. coli, Yersinia, C. difficile</td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Associated with URTIs</td>
</tr>
<tr>
<td>Resolves in 3-7 d</td>
<td>Severe abdominal pain</td>
</tr>
<tr>
<td>Slight fever, malaise, vomiting, vague abdominal pain</td>
<td>High fever</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Day care, young age, sick contacts, immunocompromised</td>
</tr>
<tr>
<td>Bacterial infection: travel, poorly cooked meat, poorly refrigerated foods, antibiotics</td>
<td></td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Prevention and treatment of dehydration most important (see Dehydration, P69)</td>
</tr>
<tr>
<td>Early refeeding advisable, with age-appropriate diet upon completion of rehydration</td>
<td></td>
</tr>
<tr>
<td>On-demand for suspected gastroenteritis with mild to moderate dehydration or failed ORT and significant vomiting</td>
<td></td>
</tr>
<tr>
<td>Antibiotic or antiparasitic therapy when indicated, antidiarrheal medications not indicated</td>
<td></td>
</tr>
<tr>
<td>Notify Public Health authorities if appropriate</td>
<td></td>
</tr>
<tr>
<td>Promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission</td>
<td></td>
</tr>
<tr>
<td>Rotavirus vaccine</td>
<td></td>
</tr>
</tbody>
</table>
Toddler’s Diarrhea

Epidemiology
• most common cause of chronic diarrhea during infancy
• onset between 6-36 mo of age, ceases spontaneously between 2-4 yr

Clinical Presentation
• diagnosis of exclusion in thriving child
• 4-6 bowel movements per day
• diet history (e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption)
• stool may contain undigested food particles
• excoriated diaper rash

Management
• reassurance that it is self-limiting
• 4Fs (adequate Fibre, normal Fluid intake, 35-40% Fat, discourage excess Fruit juice)

Lactase Deficiency (Lactose Intolerance)

Clinical Presentation
• chronic, watery diarrhea and abdominal pain, bloating associated with dairy intake
• primary lactose intolerance: crampy abdominal pain with loose stool (older children, usually of East Asian and African descent)
• secondary lactose intolerance: older infant, persistent diarrhea (decreased lactase production post viral/bacterial infection, celiac disease, or IBD)

Diagnosis
• trial of lactose-free diet
• watery stool, acid pH, positive reducing sugars
• positive breath hydrogen test if >6 yr

Management
• lactose-free diet, soy formula
• lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

Irritable Bowel Syndrome

• see Gastroenterology, G23

Celiac Disease

• see Gastroenterology, G18
• in children: presents at any age, usually 6-24 mo with the introduction of gluten in the diet
• FTT with poor appetite, irritability, apathy, rickets, wasted muscles, flat buttocks rarely distended abdomen
• GI symptoms: anorexia, N/V, edema, anemia, abdominal pain
• non-GI manifestations: iron-deficiency anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty, behavioural changes
• associated with other autoimmune disorders (e.g. Type 1 diabetes MS, autoimmune hepatitis)

Milk Allergy (MA) & Cow’s Milk Protein Allergy

Pathophysiology
milk allergy (MA) is IgE mediated whereas cow’s milk protein allergy (i.e. food protein induced proctocolitis of infancy (FPIPI) is non-IgE mediated and more common

Clinical Presentation
• MA reactions occur within hours of exposure and are present on the skin (urticular, pruritus), upper and lower resp tract symptoms (wheeze, cough)
• FPIPI occurs between 2-8 of infancy, presents with:
  • proctocolitis: mild diarrhea, small amounts of bloody stools (common presentation in young infant)
  • enterocolitis: vomiting, diarrhea, anemia, hematochezia, constipation
  • enteropathy: chronic diarrhea, hypoalbuminemia
• up to 50% of children intolerant to cow’s milk may be intolerant to soy protein as well

Investigation
• food challenge (gold standard), skin prick test, serum measurement of allergen-specific IgE, patch testing
Management
• MA: stop exposure
• FPIPI: stop, reintroduce milk at 6-8 mo, vast majority (>90%) will outgrow intolerance by 1 yr
• casein hydrolysate formula (dairy-free e.g. Nutramigen®, Pregestimil®) or mother may sequentially remove cow's milk protein, all bovine protein, soy protein, legumes (7 d washout) and continue breastfeeding (with adequate calcium and vit D intake)

Inflammatory Bowel Disease
• see Gastroenterology, G19

Cystic Fibrosis
• see Respirology, P84

Constipation
• decreased stool frequency (<3 stools/wk) and/or stool fluidity (hard, pellet-like)

FUNCTIONAL CONSTIPATION
• 99% of cases of constipation
• Rome III criteria; ≥2 of the following
  ■ ≤2 defecations in the toilet/wk
  ■ ≥1 episode of fecal incontinence/wk
  ■ history of retentive posturing or excessive volitional stool retention
  ■ history of painful or hard bowel movements
  ■ large fecal mass in rectum
  ■ history of large diameter stools that may obstruct toilet

Pathophysiology
• lack of fibre in diet or change in diet, poor fluid intake, behavioural
  ■ infants: often occurs when introducing cow's milk after breast milk due to high fat and solute content, lower water content
  ■ toddlers/older children: can occur during toilet training or due to pain on defecation, leading to withholding of stool
  ■ two crucial time periods: toilet training and starting school

Management
• education: explanation of mechanism of functional constipation for parents/older children
• clean out: PEG 3350 flakes (1-1.5 g/kg/d, max 100 g/d), picosalax, PEGlyte®
• maintenance: adequate fluid intake (if <6 mo, 150 mL/kg/d), adequate dietary fibre (fruit, vegetables, whole grains), stool softening (PEG 3350, mineral oil), appropriate toilet training technique (dedicated time for defecation: 3-10 min, 1-2 x/d)
• children should be treated for at least 6 mo, and should not be weaned from maintenance therapy until they are having regular bowel movements without difficulty
• regular follow-up with ongoing support and encouragement is essential

Complications
• pain retention cycle: anal fissures + pain from withholding passing stool, chronic dilatation ± overflow incontinence

HIRSCHSPRUNG’S DISEASE (Congenital Aganglionic Megacolon)
• see General Surgery, GS64

OTHER ORGANIC DISORDERS CAUSING CONSTIPATION
• endocrine: hypothyroidism, DM, hypercalcemia
• neurologic: spinal cord abnormalities/trauma, NF
• anatomic: bowel obstruction, anus (imperforate, atresia, stenosis, anteriorly displaced)
• drugs: lead, chemotherapy, opioids
• others
Abdominal Pain

ACUTE ABDOMINAL PAIN

History
description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
- associated symptoms: N/V, diarrhea, fever

Physical Exam
- abdominal exam, rectal exam, rash

Investigations
- CBC, differential, urinalysis to rule out UTI

Table 16. Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Hepatobiliary Tract</th>
<th>Genitourinary</th>
<th>Hematologic</th>
<th>Metabolic</th>
<th>Drug and Toxins</th>
<th>Pulmonary</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td>Hepatitis Cholecystitis</td>
<td>UTI</td>
<td>Sickle cell crisis</td>
<td>Diabetic ketoacidosis</td>
<td>Erythromycin</td>
<td>Pneumonia</td>
<td>Functional pain</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Cholelithiasis</td>
<td>Urinary calculi</td>
<td>Henoch-Schönlein purpura</td>
<td>ketoacidosis</td>
<td>salicylate</td>
<td>Diaphragramic pleurisy</td>
<td>Infantile colic</td>
</tr>
<tr>
<td>Meenteric adenitis</td>
<td>Splenic rupture</td>
<td>Dysmenorrhea</td>
<td>Hemolytic uremic syndrome</td>
<td>Hypoglycemia</td>
<td>es</td>
<td>Angioneurotic edema</td>
<td>Pharyngitis</td>
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<tr>
<td>Constipation</td>
<td>Pancreatitis</td>
<td>Meckel’s diverticulum</td>
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<td>ileus</td>
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<tr>
<td>Abdominal trauma</td>
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<tr>
<td>Intestinal obstruction</td>
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<tr>
<td>(incarcerated hernia, intussusception, volvulus)</td>
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<tr>
<td>peritonitis</td>
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<td>Peptic ulcer</td>
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<tr>
<td>Meckel’s diverticulum</td>
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<tr>
<td>IBS</td>
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<tr>
<td>Food poisoning</td>
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<td></td>
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<tr>
<td>Lactose intolerance</td>
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</tbody>
</table>

APPENDICITIS
- see General Surgery, GS27
- most common cause of acute abdomen after 5 yr of age
- clinical features: low grade fever, abdominal pain, anorexia, N/V (after onset of pain), peritoneal signs (generalized peritonitis is a common presentation in infants/young children)
- treatment: surgical
- complications: perforation (common in young children), abscess

INTUSSUSCESSION
- telescoping of segment of bowel into distal segment causing ischemia and necrosis

Epidemiology
- 90% idiopathic, children with CF or GJ tube at significantly increased risk; M:F = 3:1
- 50% between 3-12 mo, 75% before 2 yr of age

Pathophysiology
- usual site: ileocecal junction; jejunum in children with GJ tubes
- lead point of telescoping segment may be swollen Peyer’s patches, Meckel’s diverticulum, polyp, malignancy, HSF structural abnormalities

Clinical Presentation
- “classic triad” (<25% patients) - abdominal pain, palpable mass, red currant jelly stools
  - often preceded by URTI
- sudden onset of recurrent, paroxysmal, severe periumbilical pain with pain-free intervals
- later vomiting (may be bilious) and rectal bleeding (late finding)
- shock and dehydration; lethargy may be only presenting symptom

Diagnosis
- U/S, air enema

Management
- air enema can be therapeutic (reduces intussusception in 75% of cases), reduction under hydrostatic pressure, surgery rarely needed
- recurrence rate 10-15%, need to consider pathologic lead point
**Chronic Abdominal Pain**

**Epidemiology**
- prevalence: 10% of school children (peak at 8-10 yr), F>M

**Etiology**
- organic (<10%)
  - gastrointestinal
  - constipation (cause vs. effect), infectious
  - IBD, esophagitis, peptic ulcer disease, lactose intolerance
  - anatomic anomalies, masses
  - pancreatic, hepatobiliary
  - celiac disease
  - genitourinary causes: recurrent UTI, nephrolithiasis, chronic PID, Mittelschmerz
  - neoplastic
- functional abdominal pain (90%): can be diagnosed when there are no alarming signs or symptoms, physical exam is normal, and stool sample tests are negative for occult blood; no further testing is required, unless high suspicion for organic cause
  - alarming symptoms include involuntary weight loss, deceleration of linear growth, GI blood loss, significant vomiting, chronic severe diarrhea, persistent upper or right lower quadrant pain, unexplained fever, family history of IBD
  - can be further subclassified into functional dyspepsia (pain in upper abdomen), irritable bowel syndrome (alternating bowel movements), abdominal migraine (paroxysmal abdominal pain, associated with anorexia, nausea, vomiting, pallor), functional abdominal pain syndrome

**Clinical Presentation**
- clustering episodes of vague, crampy periumbilical/epigastric pain, vivid pain description
- seldom awakens child from sleep, less common on weekends
- aggravated by exercise, alleviated by rest
- psychological factors related to onset and/or maintenance of pain, school avoidance
- psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
- diagnosis of exclusion

**Investigations**
- fecal occult blood and others based on clinical suspicion (CBC, ESR, urinalysis, etc.)

**Management**
- continue to attend school
- manage any emotional or family problems, counselling, CBT
- trial of high fibre diet, trial of lactose-free diet
  - medication should be for symptom relief – acid reduction therapy for dyspepsia, antispasmodic agents, smooth muscle relaxants for pain, nonstimulating laxatives or antidiarrheals for altered bowel pattern
- possible role for amitriptyline
- reassurance

**Prognosis**
- pain resolves in 30-50% of children within 2-6 wk of diagnosis
- 30-50% of children with functional abdominal pain have functional pain as adults (e.g. IBS)

**Abdominal Mass**

**Table 17. Differential Diagnosis for Abdominal Mass**

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal (note: 50% of abdominal masses in newborn are renal in origin)</td>
<td>Hydrourephrosis</td>
<td>Nephroblastoma (Wilms’ tumour)</td>
</tr>
<tr>
<td></td>
<td>Polycystic kidney disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hamartoma</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Ovarian cysts</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Hepatomegaly/splenomegaly</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Other</td>
<td>Pyloric stenosis</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td></td>
<td>Abdominal hernia</td>
<td>Retropertioneal sarcoma</td>
</tr>
<tr>
<td></td>
<td>Teratoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fecal impaction</td>
<td></td>
</tr>
</tbody>
</table>

**Upper Gastrointestinal Bleeding**
- see Gastroenterology, G25
Lower Gastrointestinal Bleeding

- see Gastroenterology, G27

Etiology
- acute
  - infectious (bacterial, parasitic)
  - antibiotic-induced (C. difficile)
  - NEC in preterm infants
  - anatomic
  - malrotation/volvulus, intussusception
  - Meckel's diverticulitis
  - anal fissures, hemorrhoids
  - vascular/hematologic
  - HSP
  - HUS
  - coagulopathy

- chronic
  - anal fissures (most common)
  - colitis
  - IBD
  - allergic (milk protein)
  - structural
  - polyps (most are hamartomas)
  - neoplasms (rare)
  - coagulopathy

Physical Exam
- hemodynamic status, evidence of FTT, fever
- anal and rectal exam: tags, fissures, anal fistulas, polyps, foreign body, blood per rectum
- stool appearance
- NG aspirate
- lower GI bleed may present as melena (if it involves the small bowel) or hematochezia

Investigations
- stool cultures (C&S, C. difficile toxin)
- urinalysis and microscopy
- CBC, smear, differential, ESR, CRP, electrolytes, urea, Cr, INR, PTT, albumin iron studies, amoeba titers
- radiologic investigations (including abdominal x-ray to rule out obstruction)
- Meckel's radionuclide scan

Management
- acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
- once stable, endoscopy and/or surgery as indicated

Genetics, Dysmorphisms, and Metabolism

- see Medical Genetics

Hematology

Approach to Anemia

![Figure 9. Approach to anemia](image-url)
Physiologic Anemia

- high Hb (>170 g/L) and reticulocyte count at birth is caused by a hypoxic environment in utero
- after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 wk of life, there is virtually no erythropoiesis due to new O2-rich environment), and increasing blood volume secondary to growth
- lowest levels about 100 g/L at 8-12 wk age (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
- usually no treatment required

Iron Deficiency Anemia

- most common cause of childhood anemia
- full term infants exhaust iron reserves by 6 mo of age
- premature infants have lower reserves, therefore exhausted by 2-3 mo of age
- common diagnosis between 6 mo-3 yr and 11-17 yr due to periods of rapid growth and increased iron requirements; adolescents also have poor diet and menstrual losses

Etiology
- children at risk (premature, LBW, low SES, etc.)
- dietary risk factors: whole cow milk in first year of life
- age > 6 mo: <2 servings/d of iron-fortified cereal, red meat, or legumes
- age < 12 mo: use of low-iron formula (<10 mg/L), primary diet of cow, goat, or soy milk
- age 1-5 yr: >16-20 oz/d of non-fortified milk
- blood loss
  - iatrogenic: repeated blood sampling (especially in hospitalized neonates)
  - allergic: cow’s milk protein-induced colitis

Clinical Manifestation
- usually asymptomatic until marked anemia. Symptoms may include: pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur, angular cheilitis, koilonychia (spoon nails)

Investigations
- CBC: low Hb, MCV, and MCH, reticulocyte count normal or high (absolute number low)
- Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
  - ratio < 13 suggests thalassemia
  - ratio > 13 suggests iron deficiency
- blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikilocytosis
- iron studies: low ferritin, other (low iron, high total iron binding capacity, high transferrin, low transferrin saturation)
- initial therapy: trial of iron

Prevention
- breastfed term infants: begin iron supplementation (1 mg/kg/d) at 4-6 mo, continuing until able to eat ≥2 feeds/d of iron-rich foods
- non-breastfed (<50% of diet) term infants: give iron-fortified formula from birth
- premature infants: give iron supplements from 1 mo through to 1 yr of age
- no cow’s milk until 9-12 mo, early introduction of red meat and iron-rich vegetables: total daily iron should be 11 mg (age 6-12 mo), 7 mg (age 1-3 yr)
- universal screening of Hb levels recommended at 9 mo

Management
- encourage diverse, balanced diet, limit homogenized milk to 16-20 oz/d
- oral iron therapy: 4-6 mg/kg/d elemental iron, divided bid to tid, for 3 mo
  - increased reticulocyte count in 2-3 d (peaks day 5-7)
  - increased hemoglobin in 4-30 d
  - repletion of iron stores in 1-3 mo
  - repeat hemoglobin levels after 1 mo of treatment
- poor response to oral iron therapy: non-adherence, medication intolerance, ongoing blood loss, IBD, celiac disease, incorrect diagnosis

Complications
- can cause irreversible effects on development if untreated (behavioural and intellectual deficiencies)
- angular cheilitis, glossitis, koilonychia (spoon nails)
**Vitamin K Deficiency**

**Etiology**
- Hemorrhagic disease of the newborn due to relative deficiencies of vitamin K-dependent coagulation factors
  - Generalized bleeding: GI/intracranial hemorrhage
  - IM injection at birth, can also be given orally (3 doses: at birth, 2-4 wk, 6-8 wk) but infants at higher risk of HDNB
  - Reason for administration at birth:
    - Human milk contains small amounts of vitamin K, and infants require ingestion of large volumes of human milk to promote GI bacterial colonization
    - Until few days after birth, susceptible to vitamin K deficiency

**Anemia of Chronic Disease**
- See Hematology, H13

**Sickle Cell Disease**
- See Hematology, H20

**Thalassemia**
- See Hematology, H18

**Hereditary Spherocytosis**
- See Hematology, H22

**Glucose-6-Phosphate Dehydrogenase Deficiency**
- See Hematology, H23

**Bleeding Disorders**
- See Hematology, H27

### Table 18. Evaluation of Abnormal Bruising/Bleeding

<table>
<thead>
<tr>
<th></th>
<th>PFA</th>
<th>PT</th>
<th>PTT</th>
<th>VIII:C</th>
<th>vWF</th>
<th>Platelets</th>
<th>Fibrinogen</th>
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<tr>
<td>Hemophilia A</td>
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<tr>
<td>von Willebrand Disease</td>
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<td>N</td>
<td>N or ↑</td>
<td>↓</td>
<td>N or ↓</td>
<td>N</td>
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<tr>
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<td>↑</td>
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<tr>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>N</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; PFA = platelet function assay; VIII:C = Factor VIII coagulant activity; vWF = von Willebrand Factor

**Immune Thrombocytopenic Purpura**

**Epidemiology**
- Most common cause of thrombocytopenia in childhood
- Peak age: 2-6 yr, M=F
- Incidence 5:100,000 children per year

**Etiology**
- Caused by autoantibodies that bind to platelet membranes → Fc-receptor mediated splenic uptake → destruction of platelets
Clinical Presentation
- 50% present 1-3 wk after viral illness (e.g. URTI, chicken pox)
- sudden onset of petechiae, purpura, epistaxis in an otherwise well child
- clinically significant bleed in only 3% (severe bleed more likely with platelet count <10) with <0.5% risk of intracranial bleed
- no lymphadenopathy, no hepatosplenomegaly
- labs: thrombocytopenia with normal RBC, WBC
- bone marrow aspirate only if atypical presentation (≥1 cell line abnormal, hepatosplenomegaly)
- differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), autoimmune (SLE, ALPS)

Management
- observation vs. pharmacologic intervention highly debated; spontaneous recovery in >70% of cases within 3 mo
- treatment with IVIg or prednisone if mucosal or internal bleeding, platelets <10, or at risk of significant bleeding (surgery, dental procedure, concomitant vasculitis or coagulopathy)
- life-threatening bleed: additional platelet transfusion ± emergency splenectomy
- persistent (>3-12 mo) or chronic (>12 mo): re-evaluate; treat if symptoms persist
- supportive: avoid contact sports and ASA/NSAIDs

Hemophilia
- see Hematology, H31

von Willebrand’s Disease
- see Hematology, H30

Oncology
- cancer is the second most common cause of death after injuries in children >1 yr of age
- cause is rarely known, but increased risk for children with: chromosomal syndromes (e.g. Trisomy 21), cancer predisposition syndromes (e.g. Li-Fraumeni syndrome), prior malignancies, neurocutaneous syndromes, immunodeficiency syndromes, family history, exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (30%) followed by brain tumours (25%), and lymphomas (15%)
- some malignancies are more prevalent in certain age groups
  - newborns: neuroblastoma, Wilms’ tumour, retinoblastoma
  - infancy and childhood: leukemia, neuroblastoma, CNS tumours, Wilms’ tumour, retinoblastoma
  - adolescence: lymphoma, gonadal tumours, germ cell tumours, bone tumours
- unique treatment considerations in pediatrics because radiation, chemotherapy, and surgery can impact growth and development, endocrine function, and fertility
- good prognosis: treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers (>80%)

Lymphadenopathy

Clinical Presentations
- features of malignant lymphadenopathy: firm, discrete, non tender, enlarging, immobile ± suspicious mass/imaging findings ± constitutional symptoms
- fluctuance, warmth, or tenderness are more suggestive of benign nodes (infection)

Differential Diagnosis
- infection
  - viral: URTI, EBV, CMV, adenovirus, HIV
  - bacterial: S. aureus, GAS, anaerobes, Mycobacterium (e.g. TB), cat scratch disease (Bartonella)
  - other: fungal, protozoan, Rickettsia
- autoimmune: rheumatoid arthritis, SLE, serum sickness
- malignancy: lymphoma, leukemia, metastatic solid tumours
- storage diseases: Niemann-Pick, Gaucher’s
- other: sarcoidosis, Kawasaki disease, histiocytoses

The American Society of Hematology 2011 Evidence-Based Practice Guideline for Immune Thrombocytopenia
Blood 2011;117(16):4190-207
Recommendations
- Bone marrow examination is unnecessary in children and adolescents with the typical features of ITP.
- Bone marrow examination is not necessary in children who fail IVIg therapy (grade 1B).
- Children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) may be managed without observation alone regardless of platelet count.
- For pediatric patients requiring treatment, a single dose of IV (0.8-1 g/kg) or a short course of corticosteroids may be useful as first-line treatment.
- IVIg can be used if a more rapid increase in the platelet count is desired.
- Anti-D therapy is not advised in children with a hematoglobin concentration that is decreased due to bleeding, or with evidence of autoimmune hemolytic anemia.

Suggestions
- Bone marrow examination is also not necessary in similar patients prior to initiation of treatment with corticosteroids or before splenectomy.
- Testing for antinuclear antibodies is not necessary in the evaluation of children and adolescents with suspected ITP.
- A single dose of anti-D can be used as first-line treatment in Rh-positive, nonsplenectomized children requiring treatment.
Investigations

- generalized lymphadenopathy
  - CBC and differential, blood culture
  - uric acid, LDH
  - ANA, RF, ESR
  - EBV/CMV/HIV serology
  - toxoplasma titre
  - fungal serology
  - CXR
  - TB tests
  - biopsy

- regional lymphadenopathy
  - period of observation if asymptomatic
  - trial of oral antibiotics
  - ultrasound
  - biopsy (especially if persistent >6 wk and/or constitutional symptoms)

Leukemia

- see Hematology, H37

Epidemiology

- mean age of diagnosis 2-5 yr but can occur at any age
- heterogeneous group of diseases
  - ALL (80%)
  - AML (15%)
  - CML (<5%)
- children with DS are 15x more likely to develop leukemia

Clinical Presentation

- infiltration of leukemic cells into bone marrow results in bone pain and bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in lymphadenopathy, hepatosplenomegaly, CNS manifestations, testicular disease
- fever, fatigue, weight loss, bruising, and easy bleeding
- hyperleukocytosis (total WBC >100 x 10⁹/L) is a medical emergency
  - presents clinically with respiratory or neurological distress caused by hyperviscosity of blood and leukostasis
  - risk of ICH, pulmonary leukostasis syndrome, tumour lysis syndrome
- management: fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes)

Management

- fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes)
- combination chemotherapy using non-cross resistant chemotherapy agents, allogeneic stem cell transplantation for high-grade or recurrent disease
- supportive care and management of treatment complications
  - febrile neutropenia: see Infectious Diseases, ID45
  - tumour lysis syndrome: see Hematology, H52

Prognosis

- 80-90% 5 yr event-free survival for ALL, 50-60% 5-yr survival for AML
- patients are stratified into standard risk and high risk based on WBC and age; other prognostic factors include presence of CNS/testicular disease, immunophenotype, cytogenetics, and initial response to therapy (most important prognostic variable)

Lymphoma

- see Hematology, H45

Epidemiology

- Hodgkin lymphoma: incidence is bimodal, peaks at ages 15-34 and >50 yr old
- non-Hodgkin lymphoma: incidence peaks at 7-11 yr

Clinical Presentation

- Hodgkin lymphoma
  - most common presentation is persistent, painless, firm, cervical or supraclavicular lymphadenopathy
  - can present as persistent cough or dyspnea (secondary to mediastinal mass) or less commonly as splenomegaly, axillary, or inguinal lymphadenopathy
  - constitutional symptoms in 30% of children
  - lymph nodes become sequentially involved as disease spreads

- Back pain in children must always be investigated!
  - Unlike adults, back pain in children often points to a pathological process
• non-Hodgkin lymphoma
  ■ generally categorized into lymphoblastic, large cell, and Burkitt's/Burkitt's-like lymphoma
  ■ rapidly growing tumour with distant metastases (unlike adult non-Hodgkin lymphoma)
  ■ signs and symptoms related to disease site: most commonly abdomen, chest (mediastinal mass), head and neck region

Management
• Hodgkin lymphoma
  ■ combination chemotherapy and radiation
  ■ aimed at limiting cumulative doses of anthracyclines (toxic to heart) and alkylators (risk of second malignancy, infertility) and limiting dose and field of radiation
  ■ increasing role for use of PET scanning to assess early disease response and plan therapy
• non-Hodgkin lymphoma
  ■ combination chemotherapy
  ■ no added benefit of radiation in pediatric protocols

Prognosis
• Hodgkin lymphoma: >90% 5 yr survival
• non-Hodgkin lymphoma: 75-90% 5 yr survival

Brain Tumours
• see Neurosurgery, NS11

Wilms’ Tumour (Nephroblastoma)

Epidemiology
• usually diagnosed between 2-5 yr; M=F
  ■ most common primary renal neoplasm of childhood
  ■ 5-10% of cases both kidneys are affected (simultaneously or in sequence)

Differential Diagnosis
• hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma

Clinical Presentation
• 80% present with asymptomatic, unilateral abdominal mass
• may also present with HTN, gross hematuria, abdominal pain, vomiting
• may have pulmonary metastases at time of diagnosis (respiratory symptoms)

Associated Congenital Abnormalities
• WAGR syndrome (Wilms’ tumour, Aniridia, Genital anomalies, mental Retardation) with 11p13 deletion
• Beckwith-Wiedemann syndrome:
  ■ characterized by enlargement of body organs (especially tongue), hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
  ■ also at increased risk for developing hepatoblastoma, and less commonly adrenocortical tumours, nephroblastomas, and rhabdomyosarcomas
• Denys-Drash syndrome characterized by gonadal dysgenesis and nephropathy leading to renal failure

Management
• staging ± nephrectomy
• chemotherapy, radiation for higher stages

Prognosis
• 90% long-term survival

Neuroblastoma

Epidemiology
• most common cancer occurring in first year of life
• neural crest cell tumour arising from sympathetic tissues (neuroblasts)

Clinical Presentation
• can originate from any site in sympathetic nervous system, presenting as mass in neck, chest, or abdomen (most common site is adrenal gland)
• signs and symptoms of disease vary with location of tumour
  ■ thoracic: dyspnea, Horner's syndrome
  ■ abdomen: palpable mass
  ■ spinal cord compression
metastases are common at presentation (>50% present with advanced stage disease):
- usually to bone or bone marrow (presents as bone pain, limp)
- can also present with peri-orbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, "blueberry muffin" skin nodules
- paraneoplastic: HTN, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from vasoactive intestinal peptide secretion), opsomyoclonus

Management
- depends on prognostic factors and may include combination of: surgery, radiation, chemotherapy, autologous stem cell transplantation, immunotherapy

Prognosis
- prognosis is often poor due to late detection
- good prognostic factors
  - "age and stage" are important determinants of better outcome: <18 mo, stage I, II, IV-S disease ("S" designates a "Special" classification only pertaining to infants)
  - primary site: posterior mediastinum and neck
  - low serum ferritin
  - more differentiated histology
  - tumour cell markers: aneuploidy, absent MYCN oncogene amplification

Bone Tumours

Cancer Predisposition Syndromes
- suspected in cases of multiple primary neoplasms, especially early onset for cancer type and/or family history consistent with known cancer predisposition syndrome (critical to obtain family history and refer if syndrome suspected)
- cancer predisposition syndromes with pediatric onset include Li-Fraumeni syndrome (soft tissue sarcomas, osteosarcoma, CNS tumours and adrenal cortical carcinoma), hereditary retinoblastoma and Fanconi anemia (leukemias)

Infectious Diseases

Fever

Definition
- fever: a practical definition is >38°C/100.4°F oral or rectal
- fever without a source/focus: acute febrile illness (typically <10 d duration) with no cause of fever even after careful history and physical
- fever of unknown orIGIN: daily or intermittent fevers for at least 2 consecutive wk of uncertain cause after careful history and physical, and initial laboratory assessment

Etiology
- infectious: anatomic approach (CNS, ears, upper and lower respiratory tract, GI, GU, skin, soft tissue, bones and joints, etc.)
- inflammatory: mainly autoimmune (Kawasaki disease, JIA, IBD, SLE, etc.)
- malignancy: childhood cancers (leukemia, lymphoma, neuroblastoma, etc.)
- miscellaneous: dehydration, drugs and toxins, post-immunization, familial dysautonomia, factitious disorder, etc.

Diagnosis
- history: duration, height and pattern of fever, associated symptoms, exposures, constitutional symptoms, recent antipyretic use, ethnic or genetic background, day care, sick contacts, travel, tick bites, age of child
- physical exam: toxic vs. non-toxic, vitals, growth, complete exams of the skin, HEENT, chest, abdomen, lymph nodes, genitalia
- investigations: guided by history, physical exam, and clinical suspicion

Evaluation of Neonates and Infants with Fever
- several protocols exist that attempt to identify neonates and young infants at low risk of serious bacterial infection (e.g. Rochester Criteria)
- such protocols are not as sensitive in the 1-28 d age group; therefore, febrile neonates should be considered high risk regardless of clinical presentation and laboratory findings
Management
- admit to hospital if appropriate
- treat the source if known
- replace fluid losses (e.g. from vomiting, diarrhea, etc.); maintenance fluid needs are higher in febrile child
- reassure parents that most fevers are benign and self-limited
- antipyretics (acetaminophen and/or ibuprofen) are not necessary in most cases, but can be given if child is uncomfortable

Acute Otitis Media

All of:
1. presence of middle ear effusion
2. presence of middle ear inflammation
3. acute onset of symptoms of middle ear effusion and inflammation

Epidemiology
- 60-70% of children have at least 1 episode of AOM before 3 yr of age
- 18 mo-6 yr most common age group
  - 22% of children in this age range will develop AOM in the first wk of a viral URI
  - one third of children have had ≥3 episodes by age 3; peak incidence January to April

Etiology
- S. pneumoniae: 32% of cases (decreasing since the introduction of PCV7 and PCV 13)
  - H. influenzae (non-typeable): >50% of refractory AOM
- M. catarrhalis: 14% of cases – less virulent
- GAS
- viral – more likely to spontaneously resolve
- less common - anaerobes (newborns) , Gram-negative enterics (infants)

Predisposing Factors
- Eustachian tube dysfunction/obstruction
- swelling of tubal mucosa: URTI, allergic rhinitis, chronic rhinosinusitis
- obstruction/infiltration of Eustachian tube ostium: adenoid hypertrophy (not due to obstruction but by maintaining a source of infection), barotrauma (sudden changes in air pressure)
- inadequate tensor palatini function: cleft palate (even aft. r repair)
- abnormal Eustachian tube: genetic syndromes such as DS, Crouzon, Apert
- disruption of action of cilia of Eustachian tube: Kartagener’s syndrome, CF
- immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, CF

Rochester Criteria – Developed to Identify Infants <60 d of Age with Fever at Low Risk of Serious Bacterial Infection

<table>
<thead>
<tr>
<th>Clinically</th>
<th>Well</th>
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<tr>
<td>WBC Count</td>
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<tr>
<td>Bands</td>
<td>&lt;1.5 x 10^9/L</td>
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<tr>
<td>Urinalysis</td>
<td>&lt;10 WBC/HPF</td>
</tr>
<tr>
<td>Stool</td>
<td>&lt;5 WBC/HPF</td>
</tr>
</tbody>
</table>

Past Health
- Born ≥37 wk
- Home with/before mom
- No hospitalizations
- No prior antibiotic use
- No prior treatment for unexplained hyperbilirubinemia
- No chronic disease
- Low risk (Rochester) criteria
  - Consider observation
  - Partial SWU2+Abx
  - without antibiotics
  - May consider empiric antibiotic5
  - Admit, Full SWU1, empiric antibiotic5

Clinical Assessment of AOM in Pediatrics

Purpose: To summarize the evidence on AOM diagnosis, treatment and the association of the heptavalent pneumococcal conjugate vaccine (PCV7) use with AOM microbiology.

Methods: Systematic review of diagnostic studies with a criterion standard, observational studies, and RCTs comparing AOM microbiology with and without PCV7, and RCTs assessing antibiotic treatment.

Results: 135 studies were included. Otoscopic findings of tympanic membrane bulging (positive likelihood ratio (PLR) 5.1 (2.2-11.9)) were associated with accurate diagnosis. Prevalence of S. pneumoniae decreased while that of H. influenzae increased pre vs. post-PCV7. Clinical success was higher with immediate ampicillin or amoxicillin versus placebo (73% vs. 60%; pooled rate difference 12%, 95% CI 5-18%; NNT 9, 95% CI 6-20). The risk of rash or diarrhea was increased by 3 to 5%. Some evidence suggested greater success with immediate versus delayed antibiotics. No significant differences were seen in terms of comparative effectiveness of antibiotics.

Conclusion: Otoscopic findings are critical to accurate AOM diagnosis. Antibiotics are somewhat effective than no treatment despite a higher accuracy of antibiotics. Prevalence of S. pneumoniae decreased while that of H. influenzae increased pre vs. post-PCV7. Clinical success was higher with immediate ampicillin or amoxicillin versus placebo (73% vs. 60%; pooled rate difference 12%, 95% CI 5-18%; NNT 9, 95% CI 6-20). The risk of rash or diarrhea was increased by 3 to 5%. Some evidence suggested greater success with immediate versus delayed antibiotics. No significant differences were seen in terms of comparative effectiveness of antibiotics.
Risk Factors

- prolonged bottle feeding, while laying down and/or shorter duration of breast feeding
- pacifier use
- second hand smoke
- crowded living conditions (day care/group child care facilities) or sick contacts
- family history of otitis media
- orofacial abnormalities
- immunodeficiency
- ethnicity – First Nations and Inuit
  - for recurrent AOM: lower levels of secretory IgA or persistent biofilms in the middle ear

Pathogenesis

- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features

- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers: ear-tugging (this alone is not a good indicator of pathology), hearing loss, balance disturbances (rare), irritable, poor sleeping, vomiting and diarrhea, anorexia
- otoscopy of TM: hyperemia, bulging, pus may be seen behind TM, loss of landmarks (e.g. handle and long process of malleus not visible)

Diagnosis

- most important criteria for AOM is a bulging TM (all children with bulging TM had AOM and only 8% of children with non-bulging TM had AOM) – Reference: Shaikh N, Hoberman A, Rockette HE, Kurs-Lasky M 2012

Management

- 1st line
  - amoxicillin 75-90 mg/kg/d divided into two doses: safe, effective, and inexpensive. Use high doses to overcome MIC for penicillin binding proteins (method of resistance)
  - if penicillin allergic: macrolide (clarithromycin, azithromycin – high resistance), trimethoprim-sulphamethoxazole (Bactrim®)
- 2nd line
  - amoxicillin-clavulanic acid (Clavulin®)
  - cephalosporins: cefuroxime axetil (Ceftin®), ceftriaxone (Rocephin®), cefaclor (Ceclor®), cefixime (Suprax®)
  - AOM deemed unresponsive if clinical signs/symptoms and otoscopic findings persist beyond 48 h of antibiotic treatment
  - use second line treatment for otitis-conjunctivitis syndrome (AOM with bacterial conjunctivitis) because *H. influenzae* and *M. catarrhalis* are more likely pathogens which are Beta lactamase producing, so Amoxicil is ineffective
  - symptomatic therapy: antipyretics/analgesics (e.g. acetaminophen), deconges ants (may relieve nasal congestion but does not treat AOM)
  - prevention: parent education about risk factors, pneumocooccal and influenza vaccines, surgery (e.g. tympanostomy tubes)
  - choice of surgery for recurrent AOM depends on whether local factors (Eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinusitis) are responsible

Complications

- extracranial: hearing loss and speech delay (secondary to persistent middle ear effusion), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
- intracranial: meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis

Recommendations

- Management of AOM should include an assessment of pain; if pain is present, the clinician should recommend treatment to reduce pain.
- Prescribe antibiotic therapy for AOM (bilateral or unilateral) in children 6 mo and older with severe signs or symptoms (i.e. moderate or severe otalgia or otalgia for at least 48 h or temperature 39°C [102.2°F] or higher).
- For bilateral or unilateral AOM in children 6 mo through 23 mo of age without severe signs or symptoms (i.e. mild otalgia for less than 48 h and temperature less than 39°C [102.2°F]) either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver(s). With observation ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48-72 h of onset of symptoms.
- Do NOT prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM.
- Recommend annual influenza vaccine and pneumococcal conjugate vaccine to all children according to vaccination schedule.
**Otitis Media with Effusion**

**Definition**
- presence of fluid in the middle ear without signs or symptoms of ear infection

**Epidemiology**
- most common cause of pediatric hearing loss
- not exclusively a pediatric disease
- follows AOM frequently in children
- middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10%

**Risk Factors**
- same as AOM

**Clinical Features**
- conductive hearing loss ± tinnitus
- fullness – blocked ear
- ± pain, low grade fever
- otoscopy of TM
  - discoloration – amber or dull grey
  - meniscus fluid level behind TM
  - air bubbles
  - retraction pockets/TM atelectasis
  - flat tympanogram
- most reliable finding with pneumatic otoscopy is immobility

**Treatment**
- expectant: 90% resolve by 3 mo
- document hearing loss with audiogram (see Otolaryngology Figure 16B and Figure 17B, OT10-11)
- no statistical proof that antihistamines, decongestants, antibiotics clear disease faster
- surgery: myringotomy ± ventilation tubes ± adenoidectomy (if enlarged or on insertion of second set of tubes after first set falls out)
- ventilation tubes to equalize pressure and drain ear

**Complications of OME**
- hearing loss, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma especially when retraction pockets involve pars flaccida
- retraction of tympanic membrane, atelectasis, ossicular fixation

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**Gastroenteritis**
- see Gastroenterology, P34

**HIV Infection**
- see Infectious Diseases, ID27
### Table 19. Common Infectious Pediatric Exanthems

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen(s)</th>
<th>Incubation Period</th>
<th>Communicability</th>
<th>Mode of Transmission</th>
<th>Rash</th>
<th>Associated Features</th>
<th>Management</th>
<th>Outcomes and Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema Infectiosum (i.e. Fifth Disease/Slapped Cheek)</td>
<td>Parvovirus B19</td>
<td>4-14 d</td>
<td>Low risk of transmission once symptomatic</td>
<td>Respiratory secretions or infected blood</td>
<td>Appearance: uniform, erythematous maculopapular ‘lacy’ rash</td>
<td>Initial 7-10 d of flu-like illness and fever</td>
<td>Supportive</td>
<td>Rash fades over days to week, but may reappear months later with sunlight, exercice Aplastic crisis</td>
</tr>
<tr>
<td>Gianotti-Crosti Syndrome (i.e. Papular Acrodermatitis)</td>
<td>EBV and Hep B (majority)</td>
<td>Variable</td>
<td>None</td>
<td>—</td>
<td>Appearance: asymptomatic symmetric papules</td>
<td>Viral prodrome</td>
<td>Supportive</td>
<td>Resolves in 3-12 wk</td>
</tr>
<tr>
<td>Hand, Foot, and Mouth Disease</td>
<td>Coxsackie group A</td>
<td>3-5 d</td>
<td>Likely 1-7 d after symptoms but may be up to months</td>
<td>Direct and indirect contact with infected bodily fluids, fecal-oral</td>
<td>Appearance: vesicles and pustules on an erythematous base</td>
<td>Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue)</td>
<td>Supportive</td>
<td>Mainly dehydration</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>HSV 1, 2</td>
<td>1-26 d</td>
<td>Direct contact, often through saliva for HSV-1 and sexual contact for HSV-2</td>
<td>Grouped vesicles on an erythematous base</td>
<td>Enanthem: vesicles/erosions in the ANTERIOR oral cavity (buccal mucosa, tongue)</td>
<td>Mainly supportive Consider oral or topical antivirals</td>
<td>Mainly supportive</td>
<td>Local: secondary skin infections, keratitis, gingivostomatitis CNS: encephalitis Disseminated hepatitis DIC Eczema herpeticum</td>
</tr>
<tr>
<td>Kawasaki Disease</td>
<td>See P87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>Morbillivirus</td>
<td>8-13 d</td>
<td>4 d before and after rash</td>
<td>Airborne</td>
<td>Appearance: erythematous maculopapular</td>
<td>Prodrome of cough, coryza, conjunctivitis (3 Cs)</td>
<td>Infected: supportive Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure Respiratory isolation, report to Public Health Prevention: MMR vaccine</td>
<td>Secondary bacterial infections: AOM, sinusitis, pneumonia Encephalitis Rare: myocarditis, pericarditis, thrombocytopenia, Stevens-Johnson syndrome, GN, subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Disease</td>
<td>Pathogen(s)</td>
<td>Incubation Period</td>
<td>Communicability</td>
<td>Mode of Transmission</td>
<td>Rash</td>
<td>Associated Features</td>
<td>Management</td>
<td>Outcomes and Complications</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>Non-Specific Enteroviral Exanthems</strong></td>
<td>Enteroviruses</td>
<td>Variable</td>
<td>Variable</td>
<td>Direct and indirect contact with infected bodily fluids</td>
<td>Polymorphous rash (macules, papules, vesicles, petechiae, urticaria)</td>
<td>Systemic involvement is rare, but possible</td>
<td>Supportive</td>
<td>Diagnosis confirmed using viral cultures (NP and rectal swabs)</td>
</tr>
<tr>
<td><strong>Roseola</strong></td>
<td>HHV 6</td>
<td>5-15 d</td>
<td>Unknown</td>
<td>—</td>
<td>Appearance: blanching, pink, maculopapular</td>
<td>High grade fever</td>
<td>Supporting</td>
<td>CNS: febrile seizures (10-25%), aseptic meningitis, Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Rubella</strong></td>
<td>Rubivirus</td>
<td>14-21 d</td>
<td>7 d before and after eruptions</td>
<td>Droplet</td>
<td>Appearance: pink, maculopapular</td>
<td>Prodrome of low grade fever and occipital/retroauricular nodes</td>
<td>Infected: supportive</td>
<td>Prevention: MMR vaccine, Report to Public Health, Exceptional prognosis with acquired disease, Arthritis may last days to weeks, Encephalitis, Irreversible defects in congenitally infected patients (i.e. congenital rubella syndrome)</td>
</tr>
<tr>
<td><strong>Scarlet Fever</strong></td>
<td>See P53</td>
<td>0-21 d</td>
<td>1-2 d pre-eruptions and 5 d post-eruption</td>
<td>Mainly airborne, but also through direct contact with vesicle fluid</td>
<td>Appearance: groups of skin lesions, polymorpheric, from macules to papules to vesicles to crusts</td>
<td>Significant pruritis</td>
<td>Supporting</td>
<td>Avoid salicylates (due to risk of Reye syndrome), Consider antivirals, Respiratory and contact isolation, report to Public Health, Prevention: varicella vaccine, Skin: bacterial suprainfection, necrotizing fasciitis, CNS: acute encephalitis and cerebellar ataxia, Systemic: hepatitis, DIC</td>
</tr>
<tr>
<td><strong>Varicella</strong></td>
<td>Varicella zoster virus</td>
<td>0-21 d</td>
<td>1-2 d pre-eruptions and 5 d post-eruption</td>
<td>Mainly airborne, but also through direct contact with vesicle fluid</td>
<td>Appearance: groups of skin lesions, polymorpheric, from macules to papules to vesicles to crusts</td>
<td>Significant pruritis</td>
<td>Supporting</td>
<td>Prevention: varicella vaccine, Skin: bacterial suprainfection, necrotizing fasciitis, CNS: acute encephalitis and cerebellar ataxia, Systemic: hepatitis, DIC, Congenital varicella syndrome if intrapartum infection</td>
</tr>
</tbody>
</table>
**Infectious Mononucleosis**

**Definition**
- Systemic viral infection caused by EBV with multivisceral involvement; often called "the great imitator"

**Epidemiology**
- Peak incidence between 15-19 yr old
- ~50% of children in developed countries have a primary EBV infection by 5 yr old, but <10% of children develop clinical infection

**Etiology**
- EBV: a member of herpesviridae
- Transmission is mainly through infected saliva ("kissing disease") and sexual activity (less commonly); incubation period of 1-2 mo

**Risk Factors**
- Infectious contacts, sexually active, multiple sexual partners in the past

**History**
- Prodrome: 2-3 d of malaise, anorexia
- Infants and young children: often asymptomatic or mild disease
- Older children and adolescents: malaise, fatigue, fever, sore throat, abdominal pain (often LUQ), headache, myalgia

**Physical Exam**
- Classic triad: febrile, generalized non-tender lymphadenopathy, pharyngitis/tonsillitis (exudative)
- ± hepatosplenomegaly
- ± periocular edema, ± rash (urticarial, maculopapular, or petechial) – more common after inappropriate treatment with β-lactam antibiotics
- Any “-itis” (including arthritis, hepatitis, nephritis, myocarditis, encephalitis, etc.)

**Investigations**
- Heterophil antibody test (Monospot® test)
  - 85% sensitive in adults and older children, but only 50% sensitive if <4 yr of age
  - False positive results with HIV, SLE, lymphoma, rubella, parvovirus
- EBV titres
- CBC and differential, blood smear: reactive lymphocytes, lymphocytosis, Downey cells ± anemia ± thrombocytopenia
- Throat culture to rule out streptococcal pharyngitis

**Management**
- Supportive: adequate rest, hydration, saline gargles, and analgesics for sore throat
- Splenic enlargement is often not clinically apparent so all patients should avoid contact sports for 6-8 wk
- If airway obstruction secondary to nodal and/or tonsillar enlargement is present (especially younger children), admit for steroid therapy
- Acyclovir does NOT reduce duration of symptoms or result in earlier return to school/work

**Prognosis**
- Most acute symptoms resolve in 1-2 wk, though fatigue may last for months
- Short-term complications: splenic rupture, Guillain-Barré syndrome

**Infectious Pharyngitis/Tonsillitis**

**Definition**
- Inflammation of the pharynx, especially the tonsils if present, causing a sore throat

**Etiology**
- Viral (~80%): adenoviruses, enteroviruses, coxsackie, upper respiratory tract viruses, EBV, CMV
- Bacterial (~20%): mainly GAS, M. pneumoniae (older children), N. gonorrhoeae (sexually active), C. diphtheriae (unvaccinated), Fusobacterium necrophorum (anaerobe causing Lemierre syndrome)
- Fungal: Candida

**Epidemiology**
- Season: GAS pharyngitis more common in late winter or early spring; viral all year long
- Age: GAS pharyngitis peak incidence at 5-12 yr of age and uncommon <3 yr; viral pharyngitis affects all ages

**History**
- GAS: sore throat (may be severe), fever, malaise, headache, abdominal pain, N/V, absence of other URTI symptoms
- Viral: sore throat (often mild), conjunctivitis, cough, rhinorrhea, hoarseness, diarrhea, flu-like symptoms (fever, malaise, myalgia)
Physical Exam
- GAS: febrile, pharyngeal/tonsillar erythema and exudates, enlarged (>1 cm) and tender anterior cervical lymph nodes, palatal petechiae, strawberry tongue, scarlatiniform rash
- viral: afebrile, mild tonsillar exudates, minor and non-tender adenopathy, viral exanthems

Investigations
- no single sign or symptom reliably identifies GAS as the causative organism in children with sore throat
- scores are used to predict if throat culture will be positive (e.g. McIsaac Criteria)
  - these score systems have not been found to be sensitive or specific enough to diagnose GAS in children and adolescents with sore throat
- suspected diagnosis of GAS pharyngitis should be confirmed with a rapid streptococcal antigen test and a follow-up throat culture if the rapid test is negative

Management
- antibiotics (for GAS/S. pyogenes)
  - penicillin V or amoxicillin or erythromycin (if penicillin allergy) x 10 d
  - can prevent rheumatic fever if given within 9 d of symptoms; does NOT alter risk of post-streptococcal GN
- supportive: hydration and acetaminophen for discomfort due to pain and/or fever
- follow-up: if uncomplicated course, no follow-up or post antibiotic throat cultures needed
- prophylaxis: consider tonsillectomy for proven, recurrent streptococcal tonsillitis

Complications
- preventable with antibiotics: AOM, sinusitis, cervical adenitis, mastoiditis, retropharyngeal/peritonsillar abscess, sepsis
- immune-mediated complications: scarlet fever, acute rheumatic fever, post-streptococcal GN, reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (i.e. PANDAS)

SCARLET FEVER
- diffuse erythematous eruption
- delayed-type hypersensitivity reaction to pyrogenic exotoxin produced by GAS
- acute onset of fever, sore throat, strawberry tongue
- 24-48 h after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa; Pastia's lines may be accentuated in flexural areas
- within 24 h, sandpaper rash becomes generalized with perioral sparing, non-pruritic, non-painful, blanchable
- rash fades after 3-4 d, may be followed by desquamation
- treatment is penicillin, amoxicillin, or erythromycin x 10 d

RHEUMATIC FEVER
- inflammatory disease due to antibody cross-reactivity following GAS infection
- affects ~1:10,000 children in developed world; much more prevalent in developing nations; peak incidence at 5-15 yr of age
- mainly a clinical diagnosis based on Jones Criteria (revised)
  - requires 2 major OR 1 major and 2 minor PLUS evidence of preceding strep infection (history of scarlet fever, GAS pharyngitis culture, positive rapid Ag detection test, ASOTs)
- treatment: penicillin or erythromycin for acute course x 10 d, prednisone if severe carditis
- secondary prophylaxis with daily penicillin or erythromycin
- complications
  - acute: myocardiitis, conduction system aberrations (sinus tachycardia, atrial fibrillation), valvulitis (acute MR), pericarditis
  - chronic: valvular heart disease (mitral and/or aortic insufficiency/stenosis), infectious endocarditis ± thromboembolic phenomenon
  - onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever

POST-STREPTOCOCCAL GLOMERULONEPHRITIS
- most common in children aged 4-8 yr old; M>F
- antigen-antibody mediated complement activation with diffuse, proliferative GN
- occurs 1-3 wk following initial GAS infection (skin or throat)
- clinical presentation varies from asymptomatic, microscopic and macroscopic hematuria (cola-coloured urine) to all features of nephritic syndrome (see Nephritic Syndrome, P72)
- diagnosis is confirmed with elevated serum antibody titres against streptococcal antigens (ASOT, anti-DNase B), low serum complement (C3)
- management
  - symptomatic: fluid and sodium restrictions; loop diuretics for HTN and edema
  - in severe cases, may require dialysis if renal function significantly impaired
  - treat with penicillin or erythromycin if evidence of persistent GAS infection
- 95% of children recover completely within 1-2 wk; 5-10% have persistent hematuria
Meningitis

Definition
• inflammation of the meninges surrounding the brain and spinal cord

Epidemiology
• peak age: 6-12 mo; 90% of cases occur in children <5 yr old

Etiology
• viral: enteroviruses, HSV
• bacterial: age-related variation in specific pathogens
• fungal and parasitic meningitis also possible
• most often due to hematogenous spread or direct extension from a contiguous site

Risk Factors
• unvaccinated
• immunocompromise: asplenia, DM, HIV, prematurity
• recent or current infections: AOM, sinusitis, orbital cellulitis
• neuroanatomical: congenital defects, dermal sinus, neurosurgery, cochlear implants, recent head trauma
• exposures: day care centres, household contact, recent travel

History
• signs and symptoms variable and dependent on age, duration of illness, and host response to infection
• infants: fever, lethargy, irritability, poor feeding, vomiting, diarrhea, respiratory distress, seizures
• children: fever, headache, photophobia, N/V, confusion, back/neck pain/stiffness, lethargy, irritability

Physical Exam
• infants: toxic, hypothermia, bulging anterior fontanelle, respiratory distress, apnea, petechial/purpuric rash, jaundice
• children: toxic, LOC, nuchal rigidity, Kernig’s and Brudzinski’s signs, focal neurologic findings, petechial/purpuric rash

Investigations
• blood work: CBC, electrolytes, Cr, BUN, glucose, C&S
• LP required for definitive diagnosis
  • Gram stain, bacterial C&S, WBC count and differential, RBC count, glucose, protein concentration
  • acid-fast stain if suspect TB
  • PCR for specific bacteria if available (helpful if already treated with antibiotics)
  • urinalysis and urine C&S in infants, Gram stain and culture of petechial/purpuric lesions
  • HSV and enterovirus PCR if suspected

Table 20. CSF Findings of Meningitis

<table>
<thead>
<tr>
<th>Component</th>
<th>Normal Child</th>
<th>Normal Newborn</th>
<th>Bacterial Meningitis</th>
<th>Viral Meningitis</th>
<th>Herpes Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (µL)</td>
<td>0-6</td>
<td>0-30</td>
<td>&gt;1,000 (cloudy, xanthochromic)</td>
<td>100-500*</td>
<td>10-1,000</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>0</td>
<td>2-3</td>
<td>&gt;50</td>
<td>&lt;40</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>2.2-4.4</td>
<td>1.8-6.7</td>
<td>&lt;1.66</td>
<td>&gt;1.66</td>
<td>&gt;1.66</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>0.2-0.3</td>
<td>0.19-1.49</td>
<td>&gt;1.0</td>
<td>0.50-1.0</td>
<td>&gt;0.75</td>
</tr>
<tr>
<td>RBC (µL)</td>
<td>0-2</td>
<td>0-2</td>
<td>0-10</td>
<td>0-2</td>
<td>10-50</td>
</tr>
</tbody>
</table>


Management
• supportive care
  • preservation of adequate cerebral perfusion by maintaining normal BP and managing ICP
  • close monitoring of fluids, electrolytes, glucose, acid-base disturbances, coagulopathies
• bacterial meningitis
  • if suspected or cannot be excluded, commence empiric antibiotic therapy while awaiting cultures or if LP contraindicated or delayed
  • isolation with appropriate infection control procedures until 24 h after culture-sensitive antibiotic therapy
  • fluid restrict if any concern for SIADH
  • hearing test
• report to Public Health; prophylactic antibiotics for close contacts of Hib and N. meningitidis meningitis
### Table 21. Antibiotic Management of Bacterial Meningitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Main Pathogens</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 28 d</td>
<td>GBS, E. coli, Listeria Other: Gram-negative bacilli</td>
<td>Ampicillin + cefotaxime</td>
</tr>
<tr>
<td>28 to 90 d</td>
<td>Overlap of neonatal pathogens and those seen in older children</td>
<td>Cefotaxime + Vancomycin (+ Ampicillin if immunocompromised)</td>
</tr>
<tr>
<td>&gt;90 d</td>
<td>S. pneumoniae, N. meningitidis</td>
<td>Ceftriaxone ± vancomycin If Penicillin allergic: Vancomycin + Rifampin</td>
</tr>
</tbody>
</table>

- **viral meningitis**
  - mainly supportive (except for HSV)
  - acyclovir for HSV meningitis
  - report to Public Health
- prophylaxis: appropriate vaccinations significantly decrease incidence of bacterial meningitis (see *Routine Immunization*, P4)

### Complications
- mortality: neonate 15-20%, children 4-8%; pneumococcus > meningococcus > Hib
- acute: SIADH, subdural effusion/empyema, brain abscess disseminated infection (osteomyelitis, septic arthritis, abscess), shock/DIC
- chronic: hearing loss, neuromotor/cognitive delay, learning disabilities, neurological deficit, seizure disorder, hydrocephalus

### Mumps

#### Definition
- acute, self-limited viral infection that is most commonly characterized by adenitis and swelling of the parotid glands

#### Epidemiology
- incidence in Ontario has declined since introduction of two-dose MMR vaccination schedule
- average of 25 reported cases per yr
- majority of reported cases in children between 5-10 yr of age

#### Etiology
- mumps virus (RNA virus of the genus Rubulavirus in the Paramyxoviridae family)
- transmission via respiratory droplets, direct contact fomites
- incubation period: 14-25 d
- infectivity period: 7 d pre-parotitis to 5 d post-parotitis
- upper respiratory tract lymph nodes salivary glands, gonads, pancreas, meninges, kidney, heart, thyroid

#### History
- non-specific prodome of fever, headache, malaise, myalgias (especially neck pain)
- usually followed within 48 h by parotid swelling secondary to parotitis (bilateral, preauricular, ear pushed up and out)
- parotid gland is tender and pain worsened with spicy or sour foods
- one third of infections do not cause clinically apparent salivary gland swelling and may simply present as an URTI

#### Investigations
- clinical diagnosis, but may be confirmed with IgM positive serology within 4 wk of acute infection
- may also use PCR or viral cultures from oral secretions, urine, blood, and CSF
- blood work: CBC (leukopenia with relative lymphocytosis), serum amylase (elevated)

#### Management
- mainly supportive: analgesics, antipyretics warm or cold packs to parotid may be soothing
- admit to hospital if serious complications (meningitis, pancreatitis)
- droplet precautions recommended until 5 d after onset of parotid swelling
- prophylaxis: routine vaccination (see *Routine Immunization*, P4)

#### Complications
- common: aseptic meningitis, orchitis/oophoritis
- less common: encephalitis, pancreatitis, thyroiditis, myocardiitis, arthritis, GN, ocular complications, hearing impairment
Pertussis

**Definition**
- prolonged respiratory illness characterized by paroxysmal coughing and inspiratory “whoop”

**Epidemiology**
- ∼10 million children <1 yr old affected worldwide, causes up to 400,000 deaths/yr
- greatest incidence among children <1 yr (not fully immunized) and adolescents (waning immunity)

**Etiology**
- *Bordetella pertussis*: Gram negative pleomorphic rod
- highly contagious; transmitted via respiratory droplets released during intense coughing
- incubation period: 6-20 d; most contagious during catarrhal phase but may remain contagious for weeks after

**History**
- prodromal catarrhal stage
  - lasts 1-7 d; URTI symptoms (coryza, mild cough, sneezing) with NO or LOW-GRADE fever
- paroxysmal stage
  - lasts 4-6 wk; characterized by paroxysms of cough (“100 day cough”), sometimes followed by inspiratory whoop (“whooping cough”)
  - infants <6 mo may present with post-tussive apnea, whoop is often absent
  - onset of attacks precipitated by yawning, sneezing, eating, physical exertion
  - ± post-tussive emesis, may become cyanotic before whoop
  - vomiting after whooping episodes
- convalescent stage
  - lasts 1-2 wk; characterized by occasional paroxysms of cough, but decreased frequency and severity
  - non-infectious but cough may last up to 6 mo

**Investigations**
- NP specimen using aspirate or NP swab
  - gold standard: culture using special media (Regan-Lowe agar)
  - PCR to detect pertussis antigens
- blood work: CBC (lymphocytosis) and serology (antibodies against *B. pertussis*)

**Management**
- admit if paroxysms of cough are associated with cyanosis and/or apnea and give O₂
- supportive care
  - antimicrobial therapy indicated if *B. pertussis* isolated, or symptoms present for <21 d
    - use macrolide antibiotics (azithromycin, erythromycin, or clarithromycin)
- droplet isolation until 5 d of treatment and report to Public Health
- prophylaxis
  - macrolide antibiotics for all household contacts
  - prevention with vaccination in infants and children (Pentacel®), and booster in adolescents (Adacel®) *(see Routine Immunization, P4)*

**Complications**
- pressure-related from paroxysms: subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
- respiratory: sinusitis, pneumonia, aspiration, atelectasis, pneumomediastinum, pneumothorax, alveolar rupture
- neurological: seizures (~3%), encephalopathy, ICH
- mortality: ~0.3%; highest risk in infants <6 mo old

Pneumonia
- see Respirology, P80

Periorbital (Preseptal) and Orbital Cellulitis
- see Ophthalmology, OP9

Sexually Transmitted Infections
- see Family Medicine, FM42 and Gynecology, GY27
Sinusitis

- see Family Medicine, FM43
- complication of ≤10% of URTIs in children
- clinical diagnosis
- diagnostic imaging is NOT required to confirm diagnosis in children
  - routine CT not recommended, but consider if suspect complications of sinusitis, persistent/ recurrent disease, need for surgery
- antibiotic therapy for all children (although nearly half resolve spontaneously within 4 wk)
- complications: preseptal/orbital (preseptal/orbital cellulitis, orbital abscess, osteomyelitis, etc.), intracranial (meningitis, abscess, etc.), Pott's Puffy tumour

Urinary Tract Infection

Definition
- infection of the urinary bladder (cystitis) and/or kidneys (pyelonephritis)

Epidemiology
- overall prevalence in infants and young children presenting with fever is 7%
- <4-6 wk old: more common in boys
- >1 yr old: females have two- to four-fold higher prevalence

Etiology
- majority (>95%) have a single cause (~70% E. coli)
- Gram-negative bacilli: E. coli, Klebsiella, Proteus, Enterobacter, Pseudomonas
- Gram-positive cocci: S. saprophyticus, Enterococcus

Risk Factors
- non-modifiable: female gender, Caucasian, previous UTIs, family history
- modifiable: urinary tract abnormalities (VUR, neurogenic bladder, obstructive uropathy, posterior urethral valve), dysfunctional voiding, repeated bladder catheterization, uncircumcised males, labial adhesions, sexually active, constipation, toilet training

History
- infants and young child: often just fever or non-specific symptoms (poor feeding, irritability, FTT, jaundice, f <28 d old, vomiting)
- older child: fever, urinary symptoms (dysuria, urgency, frequency, incontinence, hematuria), abdominal, and/or flank pain

Physical Exam
- infants and young child: toxic vs. non-toxic, febrile, FTT, jaundice; look for external genitalia abnormalities (phimosis, labial adhesions) and lower back signs of occult myelodysplasia (e.g. hair tufts), which may be associated with neurogenic bladder
- older child: febrile, suprapubic and/or CVA tenderness, abdominal mass (enlarged bladder or kidney); may present with short stature, FTT, or HTN secondary to renal scarring from previously unrecognized or recurrent UTIs

Investigations
- sterile urine specimen
  - clean catch, catheterization, suprapubic aspiration or ‘Tap and Rub’ technique
  - urinalysis (leukocyte esterase, nitrites, erythrocytes, hemoglobin), microscopy (bacteria and leukocytes, erythrocytes), C&S
- diagnosis established if urinalysis suggests infection AND if ≥50,000 colony-forming units per mL of a uropathogen cultured

Management
- admit if: <2 mo old, urosepsis, persistent vomiting, inability to tolerate oral medication, moderate-severe dehydration, immunocompromised complex urologic pathology, inadequate follow-up, failure to respond to outpatient treatment
- supportive care: maintenance of hydration and adequate pain control
- antibiotics
  - base on local antimicrobial susceptibility patterns
  - commence broad empiric therapy until results of urine C&S known, and then tailor as appropriate
  - neonates: IV ampicillin and gentamicin
  - infants and older children: oral antibiotics (based on local E. coli sensitivity) if outpatient; IV ampicillin and gentamicin if inpatient
  - duration 7-10 d
- imaging
  - renal and bladder U/S for all febrile infants (<2 yr) with UTIs looking for anatomical abnormalities, hydromephrosis, abscess
  - VCUG not recommended after 1st febrile UTI unless U/S reveals hydronephrosis, obstructive uropathies or other signs suggestive of high-grade VUR

Features Suggestive of Pyelonephritis
- High-grade fever
- Flank or high abdominal pain
- CVA tenderness on palpation

Bagged urine specimen not useful for ruling in UTI (high false positive rate >85%), but useful for ruling out UTI (high sensitivity)
- follow-up: outpatients to return in 24-48 h if no clinical response and seek prompt medical evaluation for future febrile illnesses
- prophylaxis: generally not recommended unless higher grades of VUR

**Complications**
- long-term morbidity: focal renal scarring develops in 8% of patients; long-term significance unknown

### Neonatology

#### Gestational Age and Size

**Definitions**
- classification by GA
  - preterm: <37 wk
  - near-term: 35-37 wk
  - term: 37-42 wk
  - post-term: >42 wk
- classification by birth weight
  - SGA: 2 SD < mean weight for GA or <10th percentile
  - AGA: within 2 SD of mean weight for GA
  - LGA: 2 SD > mean weight for GA or >90th percentile

**Table 22. Abnormalities of Gestational Age and Size**

<table>
<thead>
<tr>
<th>Features</th>
<th>Causes</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Term Infants</td>
<td>Spontaneous: cause unknown</td>
<td>RDS, apnea of prematurity, chronic lung disease, bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>&lt;37 wk</td>
<td>Maternal disease: HTN, DM, cardiac and renal disorders</td>
<td>Feeding difficulties, NEC</td>
</tr>
<tr>
<td></td>
<td>Fetal conditions: multiple pregnancy, congenital abnormalities, macrosomia, red blood cell immunization, fetal infection</td>
<td>Hypocalcemia, hypoglycemia, hypothermia</td>
</tr>
<tr>
<td></td>
<td>Pregnancy issues: placental insufficiency, placenta previa, uterine malformations, previous preterm birth, infection, placental abruption</td>
<td>Anemia, jaundice</td>
</tr>
<tr>
<td></td>
<td>Behavioural and psychological contributors: smoking, EtOH, drug use, psychosocial stressors</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td></td>
<td>Sociodemographic factors: age, socioeconomic conditions</td>
<td>ICH/IVH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDA</td>
</tr>
<tr>
<td>Post-Term Infants</td>
<td>Most cases unknown</td>
<td>Increased risk of stillbirth or neonatal death</td>
</tr>
<tr>
<td>&gt;42 wk</td>
<td>Increased in first pregnancies</td>
<td>Increased birthweight</td>
</tr>
<tr>
<td></td>
<td>Previous post-term birth</td>
<td>Fetal “postmaturity syndrome”: impaired growth due to placental dysfunction</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
<td>Meconium aspiration</td>
</tr>
<tr>
<td>SGA Infants</td>
<td>Extrinsic causes: placental insufficiency, poor nutrition, HTN, multiple pregnancies, drugs, EtOH, smoking</td>
<td>Perinatal hypoxia</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td></td>
<td>Hypoglycemia, hypocalemia, hypothermia, hyperviscosity (polycythemia), jaundice, hypomobility</td>
</tr>
<tr>
<td>Asymmetric (head-sparing): late onset, growth arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetric: early onset, faster growth</td>
<td>Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic</td>
<td>PDA</td>
</tr>
<tr>
<td>LGA Infants</td>
<td>Maternal DM</td>
<td>Birth trauma, perinatal depression (meconium aspiration)</td>
</tr>
<tr>
<td>&gt;90th percentile</td>
<td>Racial or familial factors</td>
<td>RDS, TTN</td>
</tr>
<tr>
<td></td>
<td>Increasing parity</td>
<td>Jaundice, polycythemia</td>
</tr>
<tr>
<td></td>
<td>Previous LGA infant, high BMI, large pregnancy weight gain</td>
<td>Hypoglycemia, hypocalemia</td>
</tr>
<tr>
<td></td>
<td>Certain syndromes</td>
<td></td>
</tr>
</tbody>
</table>

**Routine Neonatal Care**

1. erythromycin ointment: applied to both eyes for prophylaxis of ophthalmia neonatorum (of questionable efficacy)
2. vitamin K IM: prophylaxis against HDNB
3. newborn screening tests in Ontario
   - in Ontario, newborn screening tests for metabolic disorders (amino acid disorders, organic acid disorders, fatty acid oxidation defects, biotinidase deficiency, galactosemia)
   - blood disorders (SCD, other hemoglobinopathies)
   - endocrine disorders (CAH, congenital hypothyroidism)
   - others (CF, severe combined immunodeficiency)
   - congenital hearing loss
4. if mother Rh negative: send cord blood for blood group and direct antiglobulin test
5. if mother hepatitis B surface antigen positive: HBIG and start hepatitis B vaccine series
Neonatal Resuscitation

- assess Apgar score at 1 and 5 min
- if <7 at 5 min then reassess q5min, until >7
- do not wait to assign Apgar score before initiating resuscitation

Table 23. Apgar Score

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>Absent</td>
<td>&lt;100/min</td>
<td>&gt;100/min</td>
</tr>
<tr>
<td>Respiratory Effort</td>
<td>Absent</td>
<td>Slow, irregular</td>
<td>Good, crying</td>
</tr>
<tr>
<td>Irritability</td>
<td>No response</td>
<td>Grimace</td>
<td>Cough/cry</td>
</tr>
<tr>
<td>Tone</td>
<td>Limp</td>
<td>Some flexion of extremities</td>
<td>Active motion</td>
</tr>
<tr>
<td>Colour</td>
<td>Blue, pale</td>
<td>Body pink, extremities blue (acrocyanosis)</td>
<td>Completely pink</td>
</tr>
</tbody>
</table>

Initial Resuscitation

- anticipation: know maternal history, history of pregnancy, labour, and delivery
- steps to take for all infants
  - warm (radiant heater, warm blankets) and dry the newborn (remove wet blankets)
  - position and clear airway (“sniffing” position)
  - stimulate infant: rub lower back gently or flick soles of feet EXCEPT if meconium present (in which case tracheal suction first)
- assess breathing and heart rate

Table 24. Interventions Used in Neonatal Resuscitation

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>0.1-0.3 mL/kg/dose of 1:10,000 (0.01-0.03 mg/kg) IV 0.5-1 mL/kg/dose of 1:10,000 (0.05-0.1 mg/kg) endotracheally can be considered while awaiting IV access (IV preferred) Can be repeated q3-5 min pm</td>
<td>HR &lt;60 and not rising</td>
<td>Side effects: tachycardia, HTN, cardiac arrhythmias</td>
</tr>
<tr>
<td>Fluid Bolus (NS, whole blood, Ringer’s lactate)</td>
<td>10 mL/kg</td>
<td>Evidence of hypovolemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May need to be repeated</td>
<td>Avoid giving too rapidly as large volume rapid infusions can be associated with IVH</td>
</tr>
</tbody>
</table>

Approach to the Depressed Newborn

- a depressed newborn lacks one or more of the following characteristics of a normal newborn
  - pulse >100 bpm
  - cries when stimulated
  - actively moves all extremities
  - has a good strong cry
- approximately 10% of newborn babies require assistance with breathing after delivery

Table 25. Etiology of Respiratory Depression in the Newborn

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Problems</td>
<td>RDS/hyaline membrane disease, Pulmonary hypoplasia, CNS depression, MAS, Pneumonia, Pneumothorax, Pleural effusions, Congenital malformations</td>
</tr>
<tr>
<td>Anemia (severe)</td>
<td>Erythroblastosis fetalis, Secondary hydrops fetalis</td>
</tr>
<tr>
<td>Maternal Causes</td>
<td>Drugs/anesthesia (opiates, magnesium sulphate), DM, Maternal myasthenia gravis</td>
</tr>
<tr>
<td>Congenital Malformations/Birth Injury</td>
<td>Nuchal cord, perinatal depression, Bilateral phrenic nerve injury, Potter’s sequence</td>
</tr>
<tr>
<td>Shock</td>
<td>Antepartum hemorrhage</td>
</tr>
<tr>
<td>CHD</td>
<td>Transposition of the great arteries with intact ventricular septum</td>
</tr>
<tr>
<td>Other</td>
<td>Hypothermia, Hypoglycemia, Infection</td>
</tr>
</tbody>
</table>

Use of 100% Oxygen in Neonatal Resuscitation

Findings from animal and theoretical studies have suggested potential adverse effects with the administration of 100% oxygen. However, given available data is limited in general and only obtained from newborn samples, the 2015 neonatal resuscitation guidelines have provided the following recommendation: “Since an oxygen saturation of 100% may correspond to a PaO2 anywhere between ~80 and 500 mm Hg, in general it is appropriate to wean the FIO2 for a saturation of 100%, provided the oxyhemoglobin saturation can be maintained ≥94%.” (Class IIb, LOE C).

Targeted Preductal SpO2 After Birth

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>SpO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60-65%</td>
</tr>
<tr>
<td>2</td>
<td>65-70%</td>
</tr>
<tr>
<td>3</td>
<td>70-75%</td>
</tr>
<tr>
<td>4</td>
<td>75-80%</td>
</tr>
<tr>
<td>5</td>
<td>80-85%</td>
</tr>
<tr>
<td>10</td>
<td>85-95%</td>
</tr>
</tbody>
</table>

Corrective Actions for PPV in Neonatal Resuscitation

- MR SOPA
  - Mask readjustment
  - Reposition airway
  - Suction mouth and nose
  - Open mouth
  - Pressure increase
  - Alternative airway
Common Conditions of Neonates

Apnea

Definition
- “periodic breathing”: normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with pauses lasting 5-10 s
- “apnea”: absence of respiratory gas flow for >20 s (or less if associated with bradycardia or desaturation)
  - 3 types:
    - central: no chest wall movement, no signs of obstruction
    - obstructive: chest wall movement continues against obstructed upper airway, no airflow
    - mixed: combination of central and obstructive apnea

Differential Diagnosis
- in term infants, apnea requires full workup as it can be associated with sepsis
- other causes
  - CNS
  - apnea of prematurity (<34 wk): combination of CNS immaturity and obstructive apnea; resolves by 36 wk GA; diagnosis of exclusion
  - seizures
  - ICH
  - hypoxic injury
  - infectious: sepsis, meningitis, NEC
  - GI: GERD, aspiration with feeding
  - metabolic: hypoglycemia, hyponatremia, hypocalcemia, inborn error of metabolism
  - cardiovascular: anemia, hypovolemia, PDA, heart failure
  - medications: morphine

Management
- O2, ventilatory support, maintain normal blood gases
- tactile stimulation
- correct underlying cause
- medications: methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)

Bleeding Disorders in Neonates

Clinical Presentation
- oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), subgaleal hemorrhage and prolonged bleeding following circumcision

Etiology
- 4 major categories
  - increased platelet destruction: maternal ITP or SLE, infection/sepsis, DIC, neonatal alloimmune thrombocytopenia, autoimmune thrombocytopenia
  - decreased platelet production/function: pancytopenia, bone marrow replacement, Fanconi anemia, Trisomy 13 and 18
  - metabolic: congenital thyrotoxicosis, inborn error of metabolism
  - coagulation factor deficiencies (see Hematology, H31): hemophilia A/B, HDNB
NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

**Epidemiology**
- 1 per 4,000-5,000 live births

**Pathophysiology**
- platelet equivalent of Rh disease of the newborn
- occurs when mother is negative for HPA and fetus is positive
- development of maternal IgG antibodies against HPA antigens on fetal platelets

**Clinical Presentation**
- petechiae, purpura, thrombocytopenia in otherwise healthy neonate
- severe disease can lead to intracranial bleeding

**Diagnosis**
- maternal and paternal platelet typing and identification of platelet alloantibodies

**Treatment**
- IVIg to mother prenatally starts in second trimester ± steroids ± fetal platelet transfusions
- treat neonate with IVIg
- if transfusion required should be with washed maternal platelets or donor HPA negative platelets

AUTOIMMUNE THROMBOCYTOPENIA

**Pathophysiology**
- caused by antiplatelet antibodies from maternal ITP or SLE
- passive transfer of antibodies across placenta

**Clinical Presentation**
- similar presentation to neonatal alloimmune thrombocytopenia, but thrombocytopenia usually less severe

**Treatment**
- steroids to mother for 10-14 d prior to delivery or IVIg to mother before delivery
- treat neonate with IVIg (usually if platelets <60,000)
- transfusion of infant with maternal/donor platelets only in severe cases, as antibodies will destroy transfused platelets

HEMORRHAGIC DISEASE OF THE NEWBORN

**Pathophysiology**
- caused by vitamin K deficiency
- factors II, VII, IX, X are vitamin K-dependent, therefore both PT and PTT are abnormal

**Etiology and Clinical Presentation**
- neonates at risk of vitamin K deficiency if: vitamin K poorly transferred across the placenta; maternal use of antiepileptics; insufficient bacterial colonization of colon at birth to synthesize vitamin K; breastfed (vitamin K intake inadequate in breastfed infants)
- vitamin K poorly transferred across the placenta
- insufficient bacterial colonization of colon at birth to synthesize vitamin K
- vitamin K intake inadequate in breastfed infants
- maternal use of antiepileptics is an additional risk factor
- neonate may present with hematomas, ICH (causing apnea or seizures), internal bleeding, hematuria, bruising, prolonged bleeding (often from mucous membranes, umbilicus, circumcision, and venipunctures)

**Prevention**
- vitamin K IM administration at birth to all newborns

---

**Bronchopulmonary Dysplasia**

**Definition**
- also known as chronic lung disease
- clinically defined as O₂ requirement for >28 d plus persistent need for oxygen and/or ventilatory support at 36 wk corrected GA
- damage to developing lungs with prolonged intubation/ventilation, high levels O₂, infections

**Investigations**
- CXR findings may demonstrate decreased lung volumes areas of atelectasis, signs of inflammation, and hyperinflation
Treatment
- no good treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, but use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcomes

Prognosis
- chronic respiratory failure may lead to pulmonary HTN, poor growth, and right-sided heart failure
- patients with bronchopulmonary dysplasia may continue to have significant impairment and deterioration in lung function late into adolescence
- some lung abnormalities may persist into adulthood including airway obstruction, airway hyper-reactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcomes

Cyanosis

Management
- ABGs
  - elevated CO₂ suggests respiratory cause
  - hyperoxia test (to distinguish between cardiac and respiratory causes of cyanosis): get baseline PaO₂ in room air, then PaO₂ on 100% O₂ for 10-15 min
    - PaO₂ <150 mmHg: suggests cyanotic CHD or possible PPHN (see Cardiology, P16)
    - PaO₂ >150 mmHg: suggests cyanosis likely due to respiratory or non cardiac cause
  - CXR: look for respiratory abnormalities (pneumothorax, respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)

Diaphragmatic Hernia

Definition
- developmental defect of the diaphragm with herniation of abdominal organs into thorax
- associated with pulmonary hypoplasia and PPHN

Clinical Presentation
- respiratory distress, cyanosis
- scaphoid abdomen and barrel-shaped chest
- affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
- heart sounds shifted to contralateral side
- asymmetric chest movements, trachea deviated away from affected side
- may present outside of neonatal period
- often associated with other anomalies (cardiovascular, CNS, chromosomal abnormalities)
- CXR: bowel loops in thorax (usually left side), displaced mediastinum
Treatment
- immediate intubation required at birth: DO NOT bag mask ventilate because air will enter stomach and further compress lungs
- place large bore orogastric tube to decompress bowel
- initial stabilization and management of pulmonary hypoplasia and PPHN, hemodynamic support and surgery when stable

Hypoglycemia

Definition
- glucose <2.6 mmol/L

Etiology
- decreased carbohydrate stores: premature, SGA, RDS, maternal HTN
- endocrine: hormonal deficiencies (GH, cortisol, epinephrine), insulin excess (infant of diabetic mother, Beckwith-Wiedemann syndrome/islet cell hyperplasia), HPA axis suppression (panhypopituitarism)
- inborn errors of metabolism: fatty acid oxidation defects, galactosemia
- miscellaneous: sepsis, hypothermia, polycythemia

Clinical Findings
- signs often non-specific and subtle: lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

Management
- identify and monitor infants at risk (pre-feed blood glucose checks)
- begin oral feeds as soon as possible after birth and ensure regular feeds
- if significant and/or symptomatic hypoglycemia, provide glucose IV and titrate according to blood sugar levels
- if persistent hypoglycemia or no predisposing cause, send "critical blood work" during an episode of hypoglycemia: ABG, ammonia, β-hydroxybutyrate, cortisol, free fatty acids, GH, insulin, lactate, urine dipstick for ketones

Intraventricular Hemorrhage

Definition
- hemorrhage originating in the periventricular subependymal germinal matrix

Epidemiology
- incidence and severity inversely proportional to GA
- 50% of IVH occurs within 8 h of birth; 90% occurs by day 3

Risk Factors
- preterm infants, hemodynamic instability, RDS, coagulopathy

Clinical Presentation
- many infants with IVH are asymptomatic
- subtle signs: apnea, bradycardia, changes in tone or activity, altered LOC
- catastrophic presentation: bulging fontanelle, sudden drop in hematocrit, acidosis, seizures, hypotension

Classification
- Papile classification
- parenchymal hemorrhage may also occur in the absence of IVH
- routine head U/S screening of all preterm infants <32 wk or <1,500 g gestation throughout NICU stay
- consider MRI at term for extremely LBW infants

Management of Acute Hemorrhage
- supportive care to maintain blood volume and acid-base status
- avoid fluctuations in blood pressure and cerebral blood flow
- follow-up with serial imaging

Prognosis
- outcome depends on grade of IVH
- short-term sequelae for severe IVH: mortality, extension of bleed, posthemorrhagic hydrocephalus, posthemorrhagic infarction, cyst formation
- possible long-term major neurological sequelae: CP, cognitive deficits, motor deficits, visual and hearing impairment
- Grades I and II hemorrhages have a relatively favourable prognosis
- greatest morbidity and mortality is seen with Grade IV hemorrhage and posthemorrhagic hydrocephalus requiring ventriculoperitoneal shunt placement
Jaundice

Clinical Presentation
- jaundice is visible at serum bilirubin levels of 85-120 µmol/L; visual assessment is often misleading
- look at sclera, tip of nose in natural light
jaundice more severe/prolonged (due to increased retention of bilirubin in the circulation) with:
prematurity, acidosis, hypoalbuminemia, dehydration, hemolysis

Jaundice is very common – 60% of term newborns develop visible jaundice

Jaundice in the first 24 h of life and conjugated hyperbilirubinemia are always pathological

Jaundice must be investigated if:
- It occurs within 24 h of birth
- Conjugated hyperbilirubinemia is present
- Unconjugated bilirubin rises rapidly or is excessive for patient’s age and weight
- Persistent jaundice lasts beyond 1-2 wk of age

Figure 13. Approach to neonatal hyperbilirubinemia

PHYSIOLOGIC JAUNDICE

Epidemiology
- term infants: onset 3-4 d of life, resolution by 10 d of life
- premature infants: higher peak and longer duration

Pathophysiology
- increased hematocrit and decreased RBC lifespan
- immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
- increased enterohepatic circulation

Breastfeeding Jaundice
- common; due to a lack of milk production → dehydration → exaggerated physiologic jaundice

Breast Milk Jaundice
- 1 per 200 breastfed infants
- glucuronyl transferase inhibitor found in breast milk
- onset 7 d of life, peak at 2-3 wk of life, usually resolved by 6 wk

Table 26. Risk Factors for Jaundice

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Perinatal Factors</th>
<th>Neonatal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic group (e.g. Asian, native American)</td>
<td>Birth trauma (cephalohematoma, ecchymoses)</td>
<td>Difficulty establishing breastfeeding</td>
</tr>
<tr>
<td>Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility)</td>
<td>Prematurity</td>
<td>Infection (sepsis, hepatitis)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
<td>Genetic factors</td>
</tr>
<tr>
<td>Family history/previous child required phototherapy</td>
<td></td>
<td>Polycythemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPN</td>
</tr>
</tbody>
</table>
PATHOLOGIC JAUNDICE
• all cases of conjugated hyperbilirubinemia; some cases of unconjugated hyperbilirubinemia are pathologic

Investigations
• unconjugated hyperbilirubinemia
  • hemolytic workup: CBC, reticulocyte count, blood group (mother and infant), peripheral blood smear, Coombs test
  • if baby is unwell or has fever: septic workup (CBC and differential, blood and urine cultures ± LP, CXR)
  • other: G6PD screen (especially in males), TSH
• conjugated hyperbilirubinemia must be investigated without delay
  • consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic workup, galactosemia screen (erythrocyte galactose-1-phosphate uridyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat chloride
• predicting occurrence of severe hyperbilirubinemia (Refer to: http://www.cps.ca/documents/position/hyperbilirubinemia-newborn)
  • either TSB or TcB concentration be measured in all infants between 24 h and 72 h of life
  • if the infant does not require immediate treatment, results should be plotted on predictive nomogram to determine the risk of progression to severe hyperbilirubinemia

TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA
• to prevent kernicterus
  • breastfeeding does not usually need to be discontinued, ensure adequate feeds and hydration
  • lactation consultant support, mother to pump after feeds
  • treat underlying causes (e.g. sepsis)
    • insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
    • serum bilirubin should be monitored during and immediately after therapy (risk of rebound because photoisomerization reversible when phototherapy discontinued)
    • contraindicated in conjugated hyperbilirubinemia: results in “bronzed” baby
    • side effects: skin rash, diarrhea, eye damage (eye shield used routinely for prevention), dehydration
    • use published guidelines and nomogram for initiation of phototherapy
  • exchange transfusion
    • indications: high bilirubin levels as per published graphs based on age, weeks gestation
    • most commonly performed for hemolytic disease and G6PD deficiency
    • use of IVIg in case of severe hyperbilirubinemia (DAT+) becoming evidence-based practice

KERNICTERUS

Etiology
• unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin is deposited in the brain resulting in permanent damage (typically basal ganglia or brainstem)
• incidence increases as serum bilirubin levels increase above 340 µmol/L
• can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, acidosis, hypothermia, hypoglycemia, and prematurity

Clinical Presentation
• up to 15% of infants have no obvious neurologic symptoms
  • early stage: lethargy, hypotonia, poor feeding, emesis (bilirubin encephalopathy)
  • mid stage: hypertonia, high pitched cry, opisthotonic posturing (back arching), bulging fontanelle, seizures, pulmonary hemorrhage
  • late stage (first year and beyond)
    • hypotonia delayed motor skills, extrapyramidal abnormalities (choreoathetoid CP), gaze palsy, mitral regurgitation, sensorineural hearing loss

Prevention
• exchange transfusion, IVIg if indicated
**BILIARY ATRESIA**

**Definition**
- atresia of the extrahepatic bile ducts which leads to cholestasis and increased conjugated bilirubin after the first wk of life
- progressive obliterative cholangiopathy

**Epidemiology**
- incidence: 1:10,000-15,000 live births
- associated anomalies in 10-35% of cases: situs inversus, congenital heart defects, polysplenia

**Clinical Presentation**
- dark urine, pale stool, jaundice (persisting for >2 wk), abdominal distension, hepatomegaly

**Diagnosis**
- conjugated hyperbilirubinemia, abdominal U/S, operative cholangiogram
- HIDA scan (may be bypassed in favour of biopsy if timing of diagnosis is critical)
- liver biopsy

**Treatment**
- surgical drainage procedure
- hepatoporoenterostomy (Kasai procedure; most successful if <8 wk of age)
- two thirds will eventually require liver transplantation
- vitamins A, D, E, and K; diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

---

**Necrotizing Enterocolitis**

**Definition**
- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon

**Epidemiology**
- affects 1-5% of preterm newborns admitted to NICU

**Pathophysiology**
- postulated mechanism of bowel ischemia: mucosal damage and enteral feeding → bacterial growth → bowel necrosis/gangrene/perforation

**Risk Factors**
- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis

**Clinical Presentation**
- usually presents at 2-3 wk of age
- distended abdomen
- increased amount of gastric aspirate/vomitus with bile staining
- frank or occult blood in stool
- feeding intolerance
- diminished bowel sounds
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

**Investigations**
- AXR: pneumonitis intestinalis (intramural air is a hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, lactate, blood culture, electrolytes
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnea

**Treatment**
- NPO (7-10 d), vigorous IV fluid resuscitation, decompression with NG tube, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 d)
- serial AXRs detect early perforation (40% mortality in perforated NEC)
- peritoneal drain/surgery if perforation
- surgical resection of necrotic bowel and surgery for complications (e.g. perforation, strictures)

---

**Influence of Enteral Nutrition on Occurrences of Necrotizing Enterocolitis in Very-Low-Birth-Weight Infants**


**Study**: Case control study of very-low-birth-weight (VLBW) infants and occurrences of NEC within 30 d of life.


**Main Outcome**: NEC defined using stage ≥ 2 of modified Bell criteria.

**Results**: 55 infants developed NEC within 30 d of life (5.4%). Those with NEC had higher odds of having been fed breast milk <7 d (OR: 4.02), not having achieved full enteral feeding during the first mo (OR: 3.50), and having had parenteral feeding (OR: 2.70).

**Conclusions**: Occurrence of NEC can be reduced with breast milk feeding beyond 7 d and early full enteral feeding.
**Persistent Pulmonary Hypertension of the Newborn**

**Definition**
- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- classified as primary (absence of risk factors) or secondary

**Epidemiology**
- incidence 1.9/1,000 live births

**Clinical Presentation**
- usually presents within 12 h of birth with severe hypoxemia/cyanosis; may have only mild respiratory distress

**Pathophysiology**
- elevated pulmonary pressures cause R → L shunt through PDA, foramen ovale → decreased pulmonary blood flow → hypoxemia → further pulmonary vasoconstriction

**Risk Factors**
- secondary PPHN: asphyxia, MAS, RDS, sepsis, pneumonia, structural abnormalities (e.g., diaphragmatic hernia, pulmonary hypoplasia)
- more common in term or post-term infants

**Investigations**
- measure pre- and post-ductal oxygen levels
- hyperoxia test to exclude CHD
- ECG (RV strain)
- Echo reveals increased pulmonary arterial pressure and a R → L shunt across PDA and patent foramen ovale; also used to rule out other cardiac defects

**Treatment**
- maintain good oxygenation (SaO2 >95%) in at-risk infants
- O2 given early and tapered slowly, minimize stress and metabolic demands, maintain normal blood gases, circulatory support
- mechanical ventilation, high frequency oscillation in a sedated muscle-relaxed infant
- nitric oxide, surfactant
- extracorporeal membrane oxygenation used in some centres when other therapy fails

**Respiratory Distress in the Newborn**

**Clinical Presentation**
- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, subcostal/intercostal indrawing, nasal flaring
- duskyenes, central cyanosis
- decreased air entry, crackles on auscultation

**Differential Diagnosis of Respiratory Distress**
- pulmonary: RDS (Respiratory Distress Syndrome), TTN (Transient Tachypnea of the Newborn), MAS (Meconium Aspiration Syndrome), pleural effusion, pneumothorax, congenital lung malformations
- infectious: sepsis, pneumonia
- cardiac: CHD (cyanotic, acyanotic), PPHN
- hematologic: blood loss, polycythemia
- anatomic: TEF, congenital diaphragmatic hernia, mucous or meconium plug, upper airway obstruction (see Otalaryngology, OT41)
- metabolic: hypoglycemia, inborn errors of metabolism
- neurologic: CNS damage (trauma, hemorrhage), drug withdrawal syndromes

**Investigations**
- CXR, ABG (or venous blood gas from umbilical venous line)
- CBC, blood cultures, blood glucose
- ECG if indicated
### Table 28. Distinguishing Features of RDS, TTN, MAS

<table>
<thead>
<tr>
<th></th>
<th>RDS</th>
<th>TTN</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Surfactant deficiency → poor lung compliance due to high alveolar surface tension → atelectasis → ↓ surface area for gas exchange → hypoxia + acidosis → respiratory distress <em>“Hyaline membrane disease”</em></td>
<td>Delayed resorption of fetal lung fluid → accumulation of fluid in peribronchial lymphatics and vascular spaces → tachypnea <em>“Wet lung syndrome”</em></td>
<td>Meconium is sterile but causes airway obstruction, chemical inflammation, and surfactant inactivation leading to chemical pneumonitis</td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td>Preterm</td>
<td>Usually term and late preterm</td>
<td>Term and post-term</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Maternal DM, preterm delivery</td>
<td>Maternal DM, preterm delivery</td>
<td>Meconium-stained amniotic fluid</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>Male sex</td>
<td>Post term delivery</td>
</tr>
<tr>
<td></td>
<td>LBW</td>
<td>Macrosomia (&gt;4,500 g)</td>
<td>Post term delivery</td>
</tr>
<tr>
<td></td>
<td>Acidosis, sepsis</td>
<td>Elective Cesarean section or short labour</td>
<td>Post term delivery</td>
</tr>
<tr>
<td></td>
<td>Hypothyxia</td>
<td>Late preterm delivery</td>
<td>Post term delivery</td>
</tr>
<tr>
<td></td>
<td>Second born twin</td>
<td></td>
<td>Post term delivery</td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Respiratory distress within first few hours of life, worsens over next 24-72 h</td>
<td>Tachypnea within the first few hours of life ± retractions, grunting, nasal flaring</td>
<td>Respiratory distress within hours of birth</td>
</tr>
<tr>
<td></td>
<td>Hyoxia</td>
<td>Often NO hypoxia or cyanosis</td>
<td>Small airway obstruction, chemical pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
<td></td>
<td><em>tachypnea, barrel chest with audible crackles</em></td>
</tr>
<tr>
<td><strong>CXR Findings</strong></td>
<td>Homogenous infiltrates</td>
<td>Perihilar infiltrates <em>“Wet silhouette”</em>, fluid in fissures</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td></td>
<td>Air bronchograms</td>
<td></td>
<td>Patchy atelectasis</td>
</tr>
<tr>
<td></td>
<td>Decreased lung volumes</td>
<td></td>
<td>Patchy and coarse infiltrates</td>
</tr>
<tr>
<td></td>
<td>May resemble pneumonia (GBS)</td>
<td></td>
<td>10-20% have pneumothorax</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>Prenatal corticosteroids (e.g. Celestone® 12 mg q24h x 2 doses) if risk of preterm delivery &lt;34 wk</td>
<td>Where possible, avoidance of elective Cesarean delivery, particularly before 38 wk GA</td>
<td>If infant is depressed at birth, intubate and suction below vocal cords</td>
</tr>
<tr>
<td></td>
<td>Monitor lecithin:sphingomyelin (L/S) ratio with amniocentesis, L/S &gt;2:1 indicates lung maturity</td>
<td></td>
<td>Avoidance of factors associated with in utero passage of meconium (e.g. post term delivery)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Resuscitation</td>
<td>Supportive</td>
<td>Resuscitation</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>Oxygen if hypoxic</td>
<td>Oxygen</td>
</tr>
<tr>
<td></td>
<td>Ventilation</td>
<td>Ventilator support (e.g. CPAP)</td>
<td>Ventilatory support</td>
</tr>
<tr>
<td></td>
<td>Surfactant (decreases alveolar surface tension, improves lung compliance, and maintains functional residual capacity)</td>
<td>IV fluids and NG tube feeds if too tachypneic to feed orally</td>
<td>Surfactant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhaled nitric oxide</td>
<td>Extracorporeal membrane oxygenation for PPHN</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>In severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia</td>
<td>Hypoxemia</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercapnea</td>
<td>Hypercapnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acidosis</td>
<td>Acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPHN</td>
<td>PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumothorax</td>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemical pneumonitis</td>
<td>Chemical pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary surfactant inhibition</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Dependent on GA at birth and severity of underlying lung disease; long-term risks of chronic lung disease</td>
<td>Recovery usually expected in 24-72 h</td>
<td>Dependent on severity, mortality up to 20%</td>
</tr>
</tbody>
</table>

**PNEUMONIA**
- see Respirology, P75
- consider in infants with prolonged or premature rupture of membranes, maternal fever, or if mother is GBS positive
- suspect if infant exhibits respiratory distress, temperature instability, or WBC is low, elevated, or left-shifted
- symptoms may be non-specific
- CXR: hazy lung and/or distinct infiltrates (may be difficult to differentiate from RDS)

**Retinopathy of Prematurity**
- see Ophthalmology, OP38
Sepsis in the Neonate

Table 29. Sepsis Considerations in the Neonate

<table>
<thead>
<tr>
<th>Early Onset (&lt;72 h)</th>
<th>Late Onset (72 h – 28 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical transmission, 95% present within 24 h after birth</td>
<td>Acquired after birth</td>
</tr>
<tr>
<td>Risk factors: Maternal infection: UTI, GBS positive, previous child with GBS sepsis or meningitis</td>
<td>Most common in preterm infants in NICU (most commonly due to coagulase negative Staphylococcus)</td>
</tr>
<tr>
<td>Maternal fever/leukocytosis/chorioamnionitis</td>
<td>Other pathogens implicated include GBS, anaerobes, E. coli, Klebsiella</td>
</tr>
<tr>
<td>Prolonged rupture of membranes (&gt;18 h)</td>
<td></td>
</tr>
<tr>
<td>Preterm labour</td>
<td></td>
</tr>
<tr>
<td>Pathogens: GBS, E. coli, Listeria most common</td>
<td></td>
</tr>
<tr>
<td>Pneumonia more common with early onset sepsis</td>
<td></td>
</tr>
</tbody>
</table>

Signs of Sepsis
- no reliable absolute indicator of occult bacteremia in infants <3 mo, most specific result has been WBC <5
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distension, diarrhea
- hypotonia, seizures, lethargy
- jaundice, hepatomegaly, petechiae, purpura

Skin Conditions of the Neonate

Table 30. Common Neonatal Skin Conditions

<table>
<thead>
<tr>
<th>Neonatal Skin Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Response (Cutis Marmorata, Acrocyanosis)</td>
<td>Transient mottling when exposed to cold; usually normal, particularly if premature</td>
</tr>
<tr>
<td>Vernix Caseosa</td>
<td>Soft, creamy, white layer covering baby at birth</td>
</tr>
<tr>
<td>Congenital Dermal Melanocytosis ('Mongolian Spots')</td>
<td>Slate grey macules over lower back and buttocks (may look like bruises); common in dark skinned infants</td>
</tr>
<tr>
<td>Capillary Hemangioma</td>
<td>Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yr, 90% by 9 yr</td>
</tr>
<tr>
<td>Erythema Toxicum</td>
<td>Yellow-white papules/pustules surrounded by erythema, eosinophils within the lesions; common rash, resolves by 2 wk</td>
</tr>
<tr>
<td>Milia</td>
<td>Lesions 1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolving</td>
</tr>
<tr>
<td>Transient Pustular Melanosis</td>
<td>Brown macular base with pustules, seen more commonly in African American infants; may be present at birth</td>
</tr>
<tr>
<td>Nevus Simplex (Salmon Patch)</td>
<td>Transient macular vascular malformation of the eyelids and/or neck (&quot;Angel Kiss&quot; or &quot;Stork Bite&quot;); most lesions disappear by 1 yr of life</td>
</tr>
<tr>
<td>Neonatal Acne</td>
<td>Inflammatory papules and pustules mainly on face; self resolving usually within 4 mo</td>
</tr>
</tbody>
</table>

Fluids and Electrolytes

Approach to Infant/Child with Dehydration

Etiology
- decreased intake: poor oral intake during acute illness, breastfeeding difficulties, eating disorders
- increased losses: common sites include GI tract (diarrhea, vomiting, bleeding), skin/mucous membranes (fever, burns, hemorrhage, stomatitis), urine (osmotic diuresis [e.g. hyperglycemia, DKA], diuretic therapy, DI, post-obstructive/post ATN recovery diuresis), and respiratory tract (tachypnea, bronchiolitis, pneumonia)
Management

- If suspect dehydration based on history (acute illness, decreased number of wet diapers, lethargy, changes in mental status, increased thirst, etc.), you must:

1) Determine degree of extracellular volume contraction

| Table 31. Assessment of Degree of Extracellular Volume Contraction Based on Physical Exam |
|----------------------------------------|-----------------|-----------------|-----------------|
|                                       | Mild            | Moderate        | Severe          |
| Age                                   | <2 yr           | >2 yr           |                  |
| Pulse                                 | Normal, full    | Rapid           | Rapid, weak     |
| Blood Pressure                         | Normal          | Low to normal   | Decreased in shock (very late finding in pediatrics and very dangerous) |
| Urine Output                          | Decreased       | Markedly decreased | Anuria          |
| Oral Mucosa                           | Slightly dry    | Dry             | Parched         |
| Anterior Fontanelle                   | Normal          | Sunken          | Markedly sunken |
| Eyes                                   | Normal          | Sunken          | Markedly sunken |
| Skin Turgor                           | Normal          | Decreased       | Tenting         |
| Capillary Refill                      | Normal (< 3 s)  | Normal to increased | Increased (> 3 s) |

* Note that percentages refer to percent loss of pre-illness body weight

2) Determine the likely electrolyte disturbance

- Dependent on etiology of dehydration and type of fluid loss (isotonic vs. hypertonic vs. hypotonic)

<table>
<thead>
<tr>
<th>Table 32. Electrolyte Content of Various Bodily Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodily Fluid</td>
</tr>
<tr>
<td>Saliva</td>
</tr>
<tr>
<td>Gastric Juice</td>
</tr>
<tr>
<td>Pancreatic Juice</td>
</tr>
<tr>
<td>Bile</td>
</tr>
<tr>
<td>Small Bowel</td>
</tr>
<tr>
<td>Large Bowel</td>
</tr>
<tr>
<td>Sweat</td>
</tr>
</tbody>
</table>

- For moderate and severe dehydration, initial investigations should include urinalysis and blood work examining electrolyte (Na⁺, K⁺, Cl⁻), glucose, and acid-base (blood pH, pCO₂, HCO₃⁻ disturbances) and impaired renal function (creatinine, BUN)

3) Determine if the child requires PO or IV rehydration

- Dehydrated child must receive adequate fluid management, including replacement of ongoing losses and maintenance fluids

- ORT indication: mild to moderate dehydration caused by diarrhea
  - Advantages: ↓ cost, no IV needed, ↓ incidence of iatrogenic hyper/hyponatremia, parental involvement in therapy

- IV rehydration indications: indications for IV rehydration therapy: severe dehydration requiring close monitoring and frequent assessment of electrolytes, inability to tolerate ORT (e.g. vomiting, alteration in mental status, ileus, monosaccharide malabsorption, etc.), inability to provide ORT, failure of ORT in providing adequate rehydration (e.g. persistent diarrhea or vomiting)

4) Return the child to a normal volume and electrolyte status by replacing current deficits and ongoing losses

![Figure 6. Algorithm for deficit replacement and replacement of ongoing losses in the dehydrated child](image-url)
5) Provide the appropriate fluid and electrolyte maintenance daily requirements

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>100:50:20 Rule (24 h maintenance fluids)</th>
<th>4:2:1 Rule (hourly rate of maintenance fluids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 kg</td>
<td>100 cc/kg/d</td>
<td>4 cc/kg/h</td>
</tr>
<tr>
<td>11-20 kg</td>
<td>1000 cc + 50 cc/kg/d for every kg &gt; 10 kg</td>
<td>40 cc + 2 cc/kg/h for every kg &gt; 10 kg</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>1500 cc + 20 cc/kg/d for every kg &gt; 20 kg</td>
<td>60 cc + 1 cc/kg/h for every kg &gt; 20 kg</td>
</tr>
</tbody>
</table>

- in children, all maintenance fluids should have a dextrose component due to their higher risk of hypoglycemia, especially if they are NPO
- common IV fluid combinations used in pediatrics
  - newborn: D10W
  - first month of life: D5W/0.45 2 NS + KCl 20 mEq/L (only add KCl if voiding well)
  - children: D5W/NS + KCl 20 mEq/L or D5W/0.45 NS + KCl 20 mEq/L; NS bolus for dehydration
- most important thing to remember when correcting Na aberration due to fluid deficits
  - risk of cerebral edema with rapid rehydration with hypotonic or isotonic solutions (i.e. NS), therefore replace fluid slowly with close monitoring; aim to adjust (increase or decrease) plasma [Na+] by no more than 12 mmol/L/d
  - management depends on etiology, severity of symptoms, and timing (acute vs. chronic)

6) Continue to monitor fluid and electrolyte status
- accurate monitoring of daily fluid intake (PO and IV) and ongoing losses (urine output, diarrhea, emesis, drains)
- if child receiving >50% of maintenance fluids through IV, serum electrolyte values should be monitored daily and therapy adjusted accordingly
- avoid iatrogenic hyper/hyponatremia, keep the possibility of SIADH in mind

### Nephrology

#### Common Pediatric Renal Diseases

<table>
<thead>
<tr>
<th>Neonate</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flank Mass</td>
<td>Hydronephrosis, polycystic disease (autosomal dominant or recessive subtypes), tumor</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Renal vein thrombosis, asphyxia, malformation, trauma</td>
</tr>
<tr>
<td>Anuria/Oliguria</td>
<td>Bilateral renal agenesis, obstruction, asphyxia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child and Adolescent</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cola/Red-Coloured Urine</td>
<td>Acute GN (post-streptococcal, HSP, IgA nephropathy, etc.), hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis)</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>Urologic disease (nephrolithiasis, trauma, etc.), UTI, acute GN</td>
</tr>
<tr>
<td>Edema</td>
<td>Nephrotic syndrome, nephritis, acute/chronic renal failure, consider cardiac or liver disease</td>
</tr>
<tr>
<td>HTN</td>
<td>GN, renal failure, dysplasia (consider coarctation, drugs, endocrine causes)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>DM, central and nephrogenic DI, renal Fanconi’s syndrome (genetic/metabolic/acquired causes), hypercalcemia, polyuric renal failure (renal dysplasia)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Orthostatic, nephrotic syndrome (MCD, etc.), GN</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Dehydration, ATN, interstitial nephritis, acute or chronic kidney disease (i.e. renal failure)</td>
</tr>
<tr>
<td>Urgency</td>
<td>UTI, vulvovaginitis</td>
</tr>
</tbody>
</table>

### Hemolytic Uremic Syndrome

**Definition**
- simultaneous occurrence of the triad of 1) non-immune microangiopathic hemolytic anemia, 2) thrombocytopenia, and 3) acute renal injury

**Epidemiology**
- annual incidence of 1-2 per 100,000 in Canada
- most common cause of acute renal failure in children

**Etiology**
- diarrhea positive HUS: 90% of pediatric HUS from *E. coli* O157:H7, shiga toxin, or verotoxin
- diarrhea negative HUS: other bacteria, viruses, drugs, familial/genetic
Pathophysiology
- toxin binds, invades, and destroys colonic epithelial cells, causing bloody diarrhea
- toxin enters the systemic circulation, attaches to, and injures endothelial cells (especially in kidney), causing a release of endothelial products (e.g. von Willebrand factor, platelet aggregating factor)
- platelet/fibrin thrombi form in multiple organ systems (e.g. kidney, pancreas, brain, etc.) resulting in thrombocytopenia
- RBCs are forced through occluded vessels, resulting in fragmented RBCs (schistocytes) that are removed by the reticuloendothelial system (hemolytic anemia)

History and Physical Exam
- history: initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea; within 5-7 d begins to show signs of anemia, thrombocytopenia, and renal insufficiency
- physical exam: pallor, jaundice (hemolysis), edema, petechiae, HTN

Investigations
- CBC (anemia, thrombocytopenia), blood smear (schistocytes), electrolytes, renal function, urinalysis (microscopic hematuria), stool cultures, and verotoxin/shigella toxin assay

Management
- mainly supportive: nutrition, hydration, ventilation (if necessary), blood transfusion for symptomatic anemia
- monitor electrolytes and renal function: dialysis if electrolyte abnormality (hyperkalemia) cannot be corrected, fluid overload, or uremia
- steroids are not helpful
- antibiotics are contraindicated because death of bacteria leads to increased toxin release and worse clinical course

Prognosis
- <5% mortality, 5-25% long-term renal damage (HTN, proteinuria, decreased renal function)

Nephritic Syndrome

Definition
- acute or chronic syndrome affecting the kidney, characterized by glomerular injury and inflammation, and defined by hematuria (>5 RBCs per high-powered microscope field) and the presence of dysmorphic RBCs and RBC casts on urinalysis
- often accompanied by at least one of proteinuria (<50 mg/kg/d), edema, HTN, azotemia, and oliguria

Epidemiology
- highest incidence in children aged 5-15 yr old

Etiology
- humoral immune response to a variety of etiologic agents → immunoglobulin deposition → complement activation, leukocyte recruitment, release of growth factors/cytokines → glomerular inflammation and injury → porous podocytes → hematuria + RBC casts ± proteinuria
- HTN secondary to fluid retention and increased renin secretion by ischemic kidneys

Table 35. Major Causes of Nephritic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Decreased C3</th>
<th>Normal C3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong> (idiopathic)</td>
<td>Post-infectious GN (most common cause of acute GN in pediatrics)</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td></td>
<td>Membranoproliferative</td>
<td>Idiopathic rapidly progressive GN</td>
</tr>
<tr>
<td></td>
<td>Type I (50-80%)</td>
<td>Anti-GBM disease</td>
</tr>
<tr>
<td></td>
<td>Type II (&gt;80%)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong> (systemic disease)</td>
<td>SLE</td>
<td>HSP (very common)</td>
</tr>
<tr>
<td></td>
<td>Bacterial endocarditis</td>
<td>Polyaartitis nodosa</td>
</tr>
<tr>
<td></td>
<td>Abscess or shunt nephritis</td>
<td>Granulomatosis with polyangiitis</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinemia</td>
<td>Goodpasture’s syndrome</td>
</tr>
</tbody>
</table>

History and Physical Exam
- often asymptomatic; some overlap in clinical findings for nephritic and nephrotic syndrome
- gross hematuria, mild-moderate edema, oliguria, HTN
- signs and symptoms suggestive of underlying systemic causes (e.g. fever, arthralgias, rash, dyspnea, pulmonary hemorrhage)

Investigations
- urine
  - dipstick (hematuria, 0 to 2+ proteinuria) and microscopy (>5 RBCs per high-powered microscope field, acanthocytes, RBC casts)
  - first morning urine protein/creatinine ratio (<200 mg/mmol)
• blood work
  • impaired renal function (↑ Cr and BUN) resulting in ↓ pH and electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia)
  • mild anemia on CBC (secondary to hematuria)
  • hyponatremia (secondary to proteinuria)
  • appropriate investigations to determine etiology: C3/C4 levels, serologic testing for recent streptococcal infection (ASOT, anti-hyaluronidase, anti-streptokinase, anti-NAD, anti-DNAse B), ANA, anti-DNA antibodies, ANCA, serum IgA levels, anti-GBM antibodies
  • renal biopsy should be considered only in the presence of acute renal failure, no evidence of streptococcal infection, normal C3/C4

Management
• treat underlying cause
• symptomatic
  • renal insufficiency: supportive (dialysis if necessary), proper hydration
  • HTN: salt and fluid restriction (but not at expense of renal function) ACEI or ARBs for chronic persistent HTN (not acute cases because ACEI or ARBs may decrease GFR further)
  • edema: salt and fluid restriction, possibly diuretics (avoid if significant intravascular depletion)
  • corticosteroids if indicated: IgA nephropathy, lupus nephritis, etc.

Prognosis
• dependent on underlying etiology
• complications include HTN, heart failure, pulmonary edema, chronic kidney injury (requiring renal transplant)

Nephrotic Syndrome

Definition
• clinical syndrome affecting the kidney, characterized by significant proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia

Epidemiology
• highest incidence in children 2-6 yr old, M>F

Etiology
• primary (idiopathic): nephrotic syndrome in the absence of systemic disease (most common cause in pediatrics)
  • glomerular inflammation ABSENT on renal biopsy: MCD (85%), focal segmental glomerular sclerosis
  • glomerular inflammation PRESENT on renal biopsy: membranoproliferative GN, IgA nephropathy
• secondary: nephrotic syndrome associated with systemic disease or due to another process causing glomerular injury (<10% in pediatrics)
  • autoimmune: SLE, DM, rheumatoid arthritis
  • genetic: sickle cell disease, Alport syndrome
  • infections: hepatitis B/C, post-streptococcal, infective endocarditis, HUS, HIV
  • malignancies: leukemia, lymphoma
  • medications: captopril, penicillamine, NSAIDs, antiepileptics
  • vasculitides: HSP, granulomatosis with polyangiitis
• congenital: congenital nephropathy of the Finnish type, Denys-Drash syndrome, etc.

History and Physical Exam
• non-specific symptoms such as irritability, malaise, fatigue, anorexia, or diarrhea
  • edema
    • often first sign: detectable when fluid retention exceeds 3-5% of body weight
    • starts periocular and often pretibial → edematous areas are white, soft, and pitting
    • gravity dependent: periocular edema ↓ and pretibial edema ↑ over the day
    • anasarca may develop (i.e. marked periocular and peripheral edema, ascites, pleural effusions, scrotal/labial edema)
• decrease in effective circulating volume (e.g. tachycardia, HTN, oliguria, etc.)
• foamy urine is a possible sign of proteinuria
Investigations

- urine
  - urine dipstick (3 to 4+ proteinuria, microscopic hematuria) and microscopy (oval fat bodies, hyaline casts)
  - first morning urine protein/creatinine ratio (>200 mg/mmol)
- blood work
  - diagnostic: hypoalbuminemia (<25 g/L), hyperlipidemia/hypercholesterolemia (total cholesterol >5 mmol/L)
  - secondary: electrolytes (hypocalcemia, hyperkalemia, hyponatremia), renal function (↑ BUN and Cr), coagulation profile (4 PTT)
  - appropriate investigations to rule out secondary causes: CBC, blood smear, C3/C4, ANA, hepatitis B/C titres, ASOT, HIV serology, etc.
- consider renal biopsy if: HTN, gross hematuria, renal function, low serum C3/C4, no response to steroids after 4 wk of therapy, frequent relapses (>2 in 6 mo), presentation before first yr of life (high likelihood of congenital nephrotic syndrome), presentation ≥12 yr (rule out more serious renal pathology than MCD)

Management

- MCD: oral prednisone 2 mg/kg/d (or equivalent) for up to 12 wk → varicella status should be known before starting
- consider cytotoxic agents, immunomodulators, or high-dose pulse corticosteroid if steroid resistant
- symptomatic
  - edema: salt and fluid restriction, possibly diuretic (avoid if significant intravascular depletion); furosemide + albumin for anasarca
  - hyperlipidemia: generally resolves with remission; limit dietary fat intake; consider statin therapy if persistently nephrotic
  - hypoalbuminemia: IV albumin and furosemide not routinely given; consider if refractory edema
  - abnormal BP: control BP; fluid resuscitation if severe intravascular depletion; ACEI or ARBs for persistent HTN
  - diet: no added salt; monitor caloric intake and supplement with Ca2+ and Vit D if on corticosteroids
  - daily weights and BP to assess therapeutic progress
  - secondary infections: treat with appropriate antimicrobials; antibiotic prophylaxis not recommended; pneumococcal vaccine at diagnosis and varicella vaccine after remission; varicella Ig + acyclovir if exposed while on corticosteroids
  - secondary hypercoagulability: mobilize, avoid hemoconcentration due to hypovolemia, prompt sepsis treatment; heparin if thrombi occur

Prognosis

- generally good: 80% of children responsive to corticosteroids
- up to 2/3 experience relapse, often multiple times; sustained remission with normal kidney function usually by adolescence
- complications: ↑ risk of infections (spontaneous peritonitis, cellulitis, sepsis); hypercoagulability due to decreased intravascular volume and antithrombin III depletion (PE, renal vein thrombosis); intravascular volume depletion, leading to hypotension, shock, renal failure; side effects of drugs

Hypertension in Childhood

Definition

- HTN: sBP and/or dBP ≥95th percentile for sex, age, and height on ≥3 occasions
- pre-HTN: sBP and/or dBP ≥90th percentile but <95th percentile OR BP ≥120/80 irrespective of age, gender, and height

Table 36. 95th Percentile Blood Pressures (mmHg)

<table>
<thead>
<tr>
<th>Age (Yr)</th>
<th>Female 50th Percentile for Height</th>
<th>Female 75th Percentile for Height</th>
<th>Male 50th Percentile for Height</th>
<th>Male 75th Percentile for Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104/58</td>
<td>105/59</td>
<td>103/56</td>
<td>104/57</td>
</tr>
<tr>
<td>6</td>
<td>111/74</td>
<td>113/74</td>
<td>114/74</td>
<td>115/75</td>
</tr>
<tr>
<td>12</td>
<td>123/80</td>
<td>124/81</td>
<td>123/81</td>
<td>125/82</td>
</tr>
<tr>
<td>17</td>
<td>128/84</td>
<td>130/85</td>
<td>136/87</td>
<td>138/87</td>
</tr>
</tbody>
</table>


Epidemiology

- prevalence: 3-5% for HTN, 7-10% for pre-HTN; M>F
- increasing prevalence of pre-HTN over the last 25+ yr
Etiology
- primary HTN
  - diagnosis of exclusion
  - most common in older children (≥10 yr), especially if positive family history, overweight, and only mild HTN
  - responsible for ~90% of cases of HTN in adolescents, rarely in young children
- secondary HTN
  - identifiable cause of HTN (most likely etiology depends on age)
  - responsible for majority of childhood HTN
  - always consider white coat HTN for all ages

Table 37. Etiology of Secondary HTN by Age Group

<table>
<thead>
<tr>
<th>System</th>
<th>Neonates</th>
<th>1 mo-6 yr</th>
<th>7-12 yr</th>
<th>&gt;13 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine/Metabolic</td>
<td>CAH</td>
<td>Wilms' tumour (↑ renin) Neuroblastoma (↑ catecholamines)</td>
<td>Endocrinopathies*</td>
<td>Endocrinopathies*</td>
</tr>
<tr>
<td>Renal</td>
<td>Congenital renal disease</td>
<td>Renal parenchymal disease</td>
<td>Renal parenchymal disease</td>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td>Vascular</td>
<td>Coarctation of the aorta</td>
<td>Coarctation of the aorta RAS</td>
<td>Renovascular abnormalities</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Corticosteroids Cyclosporine and tacrolimus</td>
<td>Corticosteroids OCP Cyclosporine and tacrolimus</td>
<td>Corticosteroids OCP Cyclosporine and tacrolimus</td>
<td>Corticosteroids OCP Recreational drugs (amphetamines, cocaine, etc.)</td>
</tr>
</tbody>
</table>

*Note: may include hyperthyroidism, hyperparathyroidism, Gushing’s syndrome, primary hyperaldosteronism/Carr’s syndrome, pheochromocytoma

Risk Factors
- primary HTN: male gender, positive family history, obesity, obstructive sleep apnea, African American, prematurity/LBW
- secondary HTN: history of renal disease, abdominal trauma, family history of autoimmune diseases, umbilical artery catheterization

History
- often asymptomatic, but can include FTT, fatigue, epistaxis
- symptoms of hypertensive emergency
  - neurologic: headache, seizures, focal complaints, change in mental status, visual disturbances
  - cardiovascular: symptoms of MI or heart failure (chest pain, palpitations, cough, SOB)
- symptoms of secondary HTN: guided by etiology; ask about medications and recreational drugs (current and past)

Physical Exam
- BP measurement (make sure correct cuff size is used), plot on growth chart, BMI
- look for signs of hypertensive emergency (e.g. full neurologic exam, ophthalmoscopy, precordial exam, peripheral pulses, perfusion status)
- look for signs of secondary HTN

Investigations
- laboratory
  - urine dipstick for hematuria and/or proteinuria (renal disease), urine catecholamines (pheochromocytoma, neuroblastoma)
  - blood work: renal function tests (electrolytes, Cr, BUN), consider renin and aldosterone levels (RAS, Conn’s syndrome, Wilms’ tumour)
  - other specific hormones if indicated on history and physical
  - imaging: Echo (coarctation, heart function), abdominal U/S (RAS, abdominal mass), renal radionuclide imaging (renal scarring)

Management
- treat underlying cause
- non-pharmacologic: modify concurrent cardiovascular risk factors (weight reduction, exercise, salt restriction, smoking cessation)
- pharmacologic: gradual lowering of BP using thiazide diuretics; no antihypertensives have been formally studied in children; if hypertensive emergencies use hydralazine, labetalol, sodium nitroprusside
- management of end-organ damage (e.g. retinopathy, LVH)
- consider referral to specialist

Prognosis
- end-organ damage (similar to adults) including LVH, CHF cerebrovascular insults, renal disease, retinopathy
Neurology

Seizure Disorders

• see Neurology N18

Differential Diagnosis of Seizures in Children

• benign febrile seizure
• CNS: infection, tumour, HIE, trauma, hemorrhage
• metabolic: hypoglycemia, hypocalcemia, hyponatremia
• idiopathic epilepsy and epileptic syndromes
• others: neurocutaneous syndromes, AVM, drug ingestions/withdrawal
• seizure mimics

Investigations

• lab tests: CBC, electrolytes, calcium, magnesium, glucose
• toxicology screen if indicated
• EEG
• CT/MRI, if indicated (focal neurological deficit or has not returned to baseline several hours after seizure)
• consider LP if first-time non-febrile seizure (not indicated for determining recurrence risk of benign febrile seizures or to determine seizure type or epileptic syndrome)

CHILDHOOD EPILEPSY SYNDROMES

Infantile Spasms

• brief, repeated symmetric contractions of neck, trunk, extremities (flexion and extension) lasting 10-30 s
• occur in clusters; often associated with developmental delay; onset 4-8 mo
• 20% unknown etiology (usually good response to treatment); 80% due to metabolic or developmental abnormalities, encephalopathies, or are associated with neurocutaneous syndromes (usually poor response to treatment)
• can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hypsarrhythmia) or Lennox-Gastaut (see below)
• typical EEG hypsarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
• management: ACTH, vigabatrin, benzodiazepines

Lennox-Gastaut

• characterized by triad of 1) multiple seizure types, 2) diffuse cognitive dysfunction, and 3) slow generalized spike and slow wave EEG
• onset commonly 3-5 yr of age
• seen with underlying encephalopathy and brain malformations
• management: valproic acid, benzodiazepines, and ketogenic diet; however, response often poor

Juvenile Myoclonic Epilepsy (Janz Syndrome)

• myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
• adolescent onset (12-16 yr of age); autosomal dominant with variable penetrance
• typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
• management: lifelong treatment (valproic acid); excellent prognosis

Childhood Absence Epilepsy

• multiple daily absence seizures lasting <30 s without post-ictal state that may resolve spontaneously or become generalized in adolescence
• peak age of onset 6-7 yr, F>M, strong genetic predisposition
• typical EEG: 3 Hz spike and wave
• management: valproic acid or ethosuximide

Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes

• focal motor seizures involving tongue, mouth, face, upper extremity usually occurring in sleep-wake transition states; remains conscious, but aphasic post-ictally
• onset peaks at 5-10 yr of age; 16% of all non-febrile seizures; remits spontaneously in adolescence without sequelae
• typical EEG: repetitive spikes in centrotemporal area with normal background
• management: frequent seizures controlled by carbamazepine, no medication if infrequent seizures
General Approach to Treatment
- education for patient and parents including education and precautions in daily life (e.g. buddy system, showers instead of baths)
- medication
  - initiate: treatment with drug appropriate to seizure type; often if >2 unprovoked afebrile seizures within 6-12 mo
  - optimize: start with one drug and increase dosage until seizures controlled
  - if no effect, switch over to another before adding a second antiepileptic drug
- ketogenic diet (high fat diet): used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

Generalized and Partial Seizures
- see Neurology, N44

Febrile Seizures

Epidemiology
- most common cause of seizure in children (3-5% of children)
- M>F, age 6 mo-6 yr

Clinical Presentation
- often with associated illness or fever and family history
- no evidence of CNS infection/inflammation before or after seizure; no history of non-febrile seizures

Table 38. Comparison of Typical and Atypical Febrile Seizures

<table>
<thead>
<tr>
<th>Simple/Typical (70-80%)</th>
<th>Complex/Atypical (20-30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following:</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td>Duration &lt; 15 min (85% &lt; 5 min)</td>
<td>Duration &gt; 15 min</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>Focal onset or focal features during seizure</td>
</tr>
<tr>
<td>No recurrence in 24 h period</td>
<td>Recurrent seizures (&gt; 1 in 24 h period)</td>
</tr>
<tr>
<td>No neurological impairment or developmental delay before or after seizure</td>
<td>Previous neurological impairment or neurological deficit after seizure</td>
</tr>
</tbody>
</table>

Workup
- history: determine focus of fever, description of seizure, medications, trauma history, development, family history
- physical exam: LOC, signs of meningitis, neurological exam, head circumference, focus of infection
- septic workup including LP if suspecting meningitis (strongly consider if child <12 mo; consider if child is 12-18 mo; only if meningeal signs present if child >18 mo)
- if typical febrile seizure, investigations only for determining focus of fever
- EEG/CT/MRI brain not warranted unless atypical febrile seizure or abnormal neurologic findings

Management
- counsel and reassure patient and parents
  - febrile seizures do not cause brain damage
  - very small risk of developing epilepsy: 9% in child with multiple risk factors; 2% in child with typical febrile seizures compared to 1% in general population
  - 33% chance of recurrence (mostly within 1 yr of first seizure and in children <1 yr old)
  - antipyretics and fluids for comfort (though neither prevent seizure)
  - prophylaxis with antiepileptic drugs not recommended
  - if high risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home
- treat underlying cause of fever

Recurrent Headache
- see Neurology, N44

Differential Diagnosis
- primary headache: tension, migraine, cluster
- secondary headache: see Neurology, N44

General Assessment
- if unremarkable history and neurological and general physical exam is negative, most likely diagnosis is migraine or tension headache
- CT or MRI if history or physical reveals red flags
- inquire about level of disability, academic performance, after-school activities
Hypotonia

- decreased resistance to passive movements – “floppy baby”

Differential Diagnosis

central: chromosomal (DS, Prader-Willi, Fragile X syndrome), metabolic (hypoglycemia, kernicterus), perinatal problems (asphyxia, ICH), endocrine (hypothyroidism, hypopituitarism), systemic illness (TORCH infection, sepsis, dehydration), CNS malformations, dysmorphic syndromes

peripheral: motor neuron (spinal muscular atrophy, polio), peripheral nerve (Charcot-Marie-Tooth syndrome) neuromuscular junction (myasthenia gravis), muscle fibre (mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

History and Physical Exam

- proper assessment of tone requires accurate determination of GA
- differentiate between UMN and LMN lesion: spontaneous posture (spontaneous movement, movement against gravity, frog-leg position); muscle weakness; joint mobility (hyperextensibility); muscle bulk; presence of fasciculations
- postural maneuvers
  - traction response: pull to sit, look for flexion of arms to counteract traction and head lag
  - axillary suspension: suspend infant by holding at axilla and lifting; hypotonic babies will slip through grasp because of low shoulder girdle tone
  - ventral suspension: infant is prone and supported under the abdomen by one hand; infant should be able to hold up extremities; inverted “U” posturing demonstrates hypotonia
- dysmorphic features, cognitive ability, reflexes, strength

Investigations

- rule out systemic disorders (e.g. electrolytes, ABG, blood glucose, CK, and serum/urine investigations for multiple etiologies including mitochondrial causes)
- neuroimaging: MRI/MRA when indicated
- EMG, muscle biopsy/NCS
- chromosome analysis, genetic testing, metabolic testing, neuromuscular testing

Treatment

- depends on etiology: some treatments available for specific diagnosis
- counsel parents on prognosis and genetic implications
- refer patients for specialized care, refer for rehabilitation, OT, PT; assess feeding ability

Cerebral Palsy

Definition

- a symptom complex, not a disease
- non-progressive central motor impairment syndrome due to insult to or anomaly of the immature CNS
- incidence: 1.5–2.5/1,000 live births (industrialized nations)
- life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion

Etiology

- often obscure, no definite etiology identified in 1/3 of cases
- 10% related to intrapartum asphyxia; 10% due to postnatal insult (infections, asphyxia, prematurity with IVH and trauma)
- association with LBW babies

Clinical Presentation

- general signs: delay in motor milestones, developmental delay, learning disabilities, visual/hearing impairment, seizures, microcephaly, uncoordinated swallow (aspiration)

Table 39. Types of Cerebral Palsy

<table>
<thead>
<tr>
<th>Type</th>
<th>% of Total</th>
<th>Characteristics</th>
<th>Area of Brain Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic</td>
<td>70-80%</td>
<td>Truncal hypotonia in first yr, increased tone, increased reflexes, clonus</td>
<td>UMN of pyramidal tract, Diplegia associated with periventricular leukomalacia in premature babies, Quadriplegia associated with HIE (asphyxia), higher incidence of intellectual disability</td>
</tr>
<tr>
<td>Athetoid/</td>
<td>10-15%</td>
<td>Athetosis (involuntary writhing movements), chorea (involuntary jerky movements)</td>
<td>Basal ganglia (may be associated with kernicterus)</td>
</tr>
<tr>
<td>Dyskinetic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxic</td>
<td>&lt;5%</td>
<td>Poor coordination, poor balance (wide based gait), can have intention tremor</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Mixed</td>
<td>10-15%</td>
<td>More than one of the above motor patterns</td>
<td></td>
</tr>
</tbody>
</table>
Investigations
• may include metabolic screen, chromosome studies, serology, neuroimaging (MRI), EMG, EEG (if seizures), ophthalmology assessment, audiology assessment

Treatment
• maximize potential through multidisciplinary services such as primary care physician, OT, PT, SLP, school supports, etc.
• orthopedic management (e.g. dislocations, contractures, rhizotomy)
• management of symptoms: spasticity (baclofen, Botulinum toxin), constipation (stool softeners)

Neurocutaneous Syndromes
• characterized by tendency to form tumours of the CNS, PNS, viscera, and skin

NEUROFIBROMATOSIS TYPE I
• autosomal dominant but 50% are the result of new mutations
• also known as von Recklinghausen disease
• incidence 1:3,000, mutation in NF1 gene on 17q11.2 (codes for neurofibromin protein)
• learning disorders, abnormal speech development, and seizures are common
• diagnosis of NF-1 requires 2 or more of:
  ■ ≥6 café-au-lait spots (>5 mm if prepubertal, >1 5 cm if postpubertal)
  ■ ≥2 neurofibromas of any type or one plexiform neurofibroma
  ■ ≥2 Lisch nodules (hamartomas of the iris)
  ■ optic glioma
  ■ freckling in the axillary or inguinal region
  ■ a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
  ■ a first degree relative with confirmed NF-1

NEUROFIBROMATOSIS TYPE II
• autosomal dominant
• incidence 1:33,000
• characterized by predisposition to form intracranial, spinal tumours
• diagnosed when bilateral vestibular schwannomas are found, or a first degree relative with NF-2 and either unilateral vestibular schwannoma, or any two of the following: meningioma, glioma, schwannoma neurofibroma, posterior subcapsular lenticular opacities.
• treatment consists of monitoring for tumour development and surgery

Respirology
Approach to Dyspnea
• determine if patient is sick or not sick; ABCs
• history: onset, previous episodes, precipitating events, associated symptoms, past medical/family history of respiratory disease
• physical exam: vitals, SpO2, evidence of cyanosis, respiratory, cardiovascular
• investigations: CBC and differential, electrolytes, BUN, Cr, NP swab, ABG, CXR, ECG (based on clinical findings)

Figure 17. Approach to dyspnea in childhood
Upper Respiratory Tract Diseases

- see Otolaryngology, OT40
- diseases above the thoracic inlet characterized by inspiratory stridor, hoarseness, and suprasternal retractions
- differential diagnosis of stridor: croup, bacterial tracheitis, epiglottitis, foreign body aspiration, subglottic stenosis (congenital or iatrogenic), laryngomalacia/tracheomalacia (collapse of airway cartilage on inspiration)

Table 40. Common Upper Respiratory Tract Infections in Children

<table>
<thead>
<tr>
<th>Croup (Laryngotracheobronchitis)</th>
<th>Bacterial Tracheitis</th>
<th>Epiglottis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy</strong></td>
<td>Subglottic laryngitis</td>
<td>Subglottic tracheitis</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Common in children &lt;6 yr, with peak incidence between 7-36 mo</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Common in fall and early winter</td>
<td>All age groups</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Parainfluenza (75%)</td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td>Influenza A and B</td>
<td>H. influenzae</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>α-hemolytic strep</td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
<td>Pneumococcus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. catarrhalis</td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Common prodrome: rhinorrhea, pharyngitis, cough ± low-grade fever</td>
<td>Simiar symptoms as croup, but more rapid deterioration with high fever</td>
</tr>
<tr>
<td></td>
<td>Hoarse voice</td>
<td>Toxic appearance</td>
</tr>
<tr>
<td></td>
<td>Barking cough</td>
<td>Does not respond to croup treatments</td>
</tr>
<tr>
<td></td>
<td>Stridor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worse at night</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Clinical diagnosis</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td></td>
<td>CXR in atypical presentation: “steeple sign” from subglottic narrowing</td>
<td>Endoscopy: definitive diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Stridor at rest is an EMERGENCY</td>
<td>Usually requires intubation</td>
</tr>
<tr>
<td></td>
<td>No evidence for humidified O₂</td>
<td>IV antibiotics</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone: PO 1 dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Racemic epinephrine: nebulized, 1-3 doses, q1-2h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intubation if unresponsive to treatment</td>
<td></td>
</tr>
</tbody>
</table>

Lower Respiratory Tract Diseases

- obstruction of airways below thoracic inlet, produces more expiratory sounds
- classic symptom: wheezing

Differential Diagnosis of Wheezing

- common: asthma (recurrent wheezing episodes, identifiable triggers, typically over 6 yr), bronchiolitis (first episode of wheezing, usually under 1 yr), recurrent aspiration (often neurological impairment), pneumonia (fever, cough, malaise)
- uncommon: foreign body (acute unilateral wheezing and coughing), CF (prolonged wheezing, unresponsive to therapy), bronchopulmonary dysplasia (often develops after prolonged ventilation in the newborn)
- rare: CHF, mediastinal mass, bronchiolitis obliterans, tracheobronchial anomalies

Pneumonia

Etiology

- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

Clinical Presentation

- incidence is greatest in first year of life with viral causes being most common in children <5 yr
- fever, cough, tachypnea
- CXR: diffuse, streaky infiltrates bilaterally
- bacterial causes may present with cough, fever, chills, dyspnea, more dramatic CXR changes (e.g. lobar consolidation, pleural effusion)

Management

- supportive therapy: hydration, antipyretics, humidified O₂
Table 41. Common Causes and Treatment of Pneumonia at Different Ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Atypical Bacteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomates</td>
<td>GBS</td>
<td>CMV</td>
<td>Mycoplasma hominis</td>
<td>Ampicillin + gentamicin / tobramycin (add erythromycin if suspect Chlamydia)</td>
</tr>
<tr>
<td></td>
<td>E. coli</td>
<td>Herpes virus</td>
<td>Ureaplasma urealyticum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Listeria</td>
<td>Enterovirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 mo</td>
<td>S. aureus</td>
<td>CMV, RSV</td>
<td>Chlamydia trachomatis</td>
<td>Cefturoxime OR ampicillin ± erythromycin OR clarithromycin</td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. pneumoniae</td>
<td>Parainfluenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo-5 yr</td>
<td>S. pneumoniae</td>
<td>RSV</td>
<td>Mycoplasma pneumonia</td>
<td>Amoxicillin (if mild) OR ampicillin OR cefuroxime</td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>Adenovirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>S. pneumoniae</td>
<td>Influenza</td>
<td>Mycoplasma pneumonia</td>
<td>Erythromycin OR clarithromycin (1st line) OR ampicillin OR cefuroxime</td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td>Varicella</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>Adenovirus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bronchiolitis

Definition
LRTI, usually in children <2 yr, that has wheezing and signs of respiratory distress

Epidemiology
- the most common LRTI in infants, affects 50% of children in first 2 yr of life; peak incidence at 6 mo, winter or early spring
- increased incidence of asthma in later life

Etiology
- RSV (>50%), parainfluenza, influenza, rhinovirus, adenovirus, M. pneumoniae (rare)

Clinical Presentation
- prodrome of URTI with cough and/or rhinorrhea, possible fever
- feeding difficulties, irritability
- wheezing, crackles, respiratory distress, tachypnea, tachycardia, retractions, poor air entry; symptoms often peak at 3-4 d

Investigations
- CXR (only in severe disease, poor response to therapy, chronic episode): air trapping, peribronchial thickening, atelectasis, increased linear markings
- NP swab: direct detection of viral antigen (immunofluorescence)
- WBC can be normal

Treatment
- self-limiting disease with peak symptoms usually lasting 2-3 wk
- mild to moderate distress
  - supportive: PO or IV hydration, antipyretics for fever, regular or humidified high flow O2
  - severe distress
    - as above ± intubation and ventilation as needed
    - consider rebetol (Ribavirin®) in high risk groups: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodeficient
    - monthly RSV-Ig or palivizumab (monoclonal antibody against the F-glycoprotein of RSV) is protective against severe disease in high risk groups; case fatality rate <1%
- antibiotics have no therapeutic value unless there is secondary bacterial pneumonia
- indications for hospitalization
  - hypoxia: O2 saturation <92% on initial presentation
  - persistent resting tachypnea >60/min and retractions after several salbutamol masks
  - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
  - young infants <6 mo old (unless extremely mild)
  - significant feeding problems
  - social problem (e.g. inadequate care at home)

Children with bronchiolitis do not respond to ipratropium bromide (Atrovent®) or steroids
Asthma

Definition
- inflammatory disorder of the airways characterized by recurrent episodes of reversible small airway obstruction, resulting from airway hyperresponsiveness to endogenous and exogenous stimuli
- very common, presents most often in early childhood
- associated with other atopic diseases such as allergic rhinitis or atopic dermatitis

Clinical Presentation
- episodic bouts of wheezing, dyspnea, tachypnea, cough (usually at night/early morning, with activity, or cold exposure)
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze

Triggers
- URTI (viral or Mycoplasma), weather (cold exposure, humidity changes), allergens (pets), irritants (cigarette smoke) exercise, emotional stress, drugs (ASA, β-blockers)

Classification
- mild: occasional attacks of wheezing or coughing (<2/wk); symptoms respond quickly to inhaled bronchodilators; never needs systemic corticosteroids
- moderate: more frequent episodes with symptoms persisting and chronic cough; decreased exercise tolerance; sometimes needs systemic corticosteroids
- severe: daily and nocturnal symptoms; frequent ED visits and hospitalizations; usually needs systemic corticosteroids

Management
- acute
  - O₂ (keep O₂ saturation >94%) and fluids if dehydrated
  - β₂-agonists: salbutamol (Ventolin®) MDI + spacer (nebulized or IV in very severe episodes with impending respiratory failure), 3 puffs (<20 kg) or 10 puffs q20min for first h (>20 kg)
  - ipratropium bromide (Atrovent®) if severe: MDI + spacer, 3 puffs (<20 kg) or 6 puffs (>20 kg) q20min with salbutamol, or add to first 3 salbutamol masks (0.25 mg if <20 kg, 0.5mg if >20 kg)
  - steroids: prednisone (1-2 mg/kg x 5 d) or dexamethasone 0.5 mg/kg/d x 5 d or 0.6 mg/kg/d x 2 d; in severe disease, use IV steroids
  - continue to observe; can discharge patient if asymptomatic for 2-4 h after last dose
- chronic
  - education, emotional support, avoid allergens or irritants, develop an “action plan”
  - exercise program (e.g. swimming)
  - monitor respiratory function with peak flow meter (improves self-awareness of status)
  - PFTs for children >6 yr
  - reliever therapy: short acting β₂-agonists (e.g. salbutamol)
  - controller therapy (first line therapy for all children): low dose daily inhaled corticosteroids
  - second line therapy for children <12 yr: moderate dose of daily inhaled corticosteroids
  - second line therapy for children >12 yr: leukotriene receptor antagonist OR long acting β₂-agonist in conjunction with low dose inhaled corticosteroids; leukotriene receptor antagonist monotherapy may be considered an alternative second line therapy
  - severe asthma unresponsive to first and second line treatments: injection immunotherapy
  - aerochamber for children using daily inhaled corticosteroids
  - indications for hospitalization
    - ongoing need for supplemental O₂
    - persistently increased work of breathing
    - β₂-agonists are needed more often than q4h after 4 8 h of conventional treatment
    - patient deteriorates while on systemic steroids

Cystic Fibrosis

- see Respirology, R12

Etiology
- 1: per 3,000 live births, mostly Caucasians
- autosomal recessive, CFTR gene found on chromosome 7 (ΔF508 mutation in 70%, but >1,600 different mutations identified) resulting in a dysfunctional chloride channel on the apical membrane of cells
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction
**Clinical Presentation**
- neonatal: meconium ileus, prolonged jaundice, antenatal bowel perforation
- infancy: pancreatic insufficiency with steatorrhea and FTT (despite voracious appetite), anemia, hypoproteinemia, hyponatremia
- childhood: heat intolerance, wheezing or chronic cough, recurrent chest infections (S. aureus, P. aeruginosa, H. influenzae), hemoptysis, nasal polyps, distal intestinal obstruction syndrome, rectal prolapse, clubbing of fingers
- older patients: COPD, infertility (males), decreased fertility (female)

**Investigations**
- sweat chloride test x 2 (>60 mEq/L)
  - false positive tests: malnutrition, atopic dermatitis, hypothyroidism, hypoparathyroidism, GSD, adrenal insufficiency, G6PD, Klinefelter syndrome, technical issues, autonomic dysfunction, familial cholestasis syndrome
  - false negative tests: technical problem with test, malnutrition, skin edema, mineralocorticoids

**Management**
- nutritional counselling: high calorie diet, pancreatic enzyme replacements, fat soluble vitamin supplements
- management of chest disease: physiotherapy, postural drainage, exercise, bronchodilators, aerosolized DNAse and inhaled hypertonic saline, antibiotics (e.g. cefalosporin, cloxacillin, ciprofloxacin, inhaled tobramycin depending on sputum C&S), lung transplantation
- genetic counselling

**Complications**
- respiratory failure, pneumothorax (poor prognostic sign), cor pulmonale (late), pancreatic fibrosis with DM, gallstones, cirrhosis with portal HTN, infertility (male)
- early death (current median survival in Canada is 46.6 yr)

---

**Rheumatology**

**Evaluation of Limb Pain**

<table>
<thead>
<tr>
<th>Table 42. Differential Diagnosis of Limb Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>Transient synovitis</td>
</tr>
<tr>
<td>JIA</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
</tr>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>HSP</td>
</tr>
<tr>
<td>Anatomic/Orthopedic</td>
</tr>
<tr>
<td>Legg-Calvé-Perthes disease</td>
</tr>
<tr>
<td>Slipped capital femoral epiphysis</td>
</tr>
<tr>
<td>Osgood-Schlatter disease</td>
</tr>
<tr>
<td>Neoplastic</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Bone tumour</td>
</tr>
<tr>
<td>Hematologic</td>
</tr>
<tr>
<td>Hemophilia (hemarthrosis)</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>Pain Syndromes</td>
</tr>
<tr>
<td>Growing pains</td>
</tr>
<tr>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
</tr>
</tbody>
</table>

- must rule out infection, malignancy, and acute orthopedic conditions
History
- demographics (age, gender)
- pattern of onset and progression of symptoms (including acuity and chronicity)
- morning stiffness, limp/weight-bearing status, night pain
- joint involvement (type, distribution) ± spine (axial) involvement
- extra-articular manifestations and systemic symptoms
- functional status – activities of daily living
  family history (arthritis, IBD, psoriasis, spondyloarthropathies, uveitis, bleeding disorders, sickle cell anemia)
- past medical illness, intercurrent infection, travel, sick contact history, joint injury

Physical Exam
- growth parameters
- screening examination (pediatric gait, arms, legs, spine exam)
- joint exam: inspection/palpation (swelling, erythema, warmth, tenderness, deformity), ROM
- adjacent structures (bone, tendon, muscle, skin)
- leg length
- neurologic exam

Investigations
- basic: CBC and differential, blood smear, ESR, CRP, x ray
- as indicated: blood (ANA, RF, culture, viral/bacterial serology, CK, PTT, sickle cell screen, immunoglobulins, complement), urinalysis, synovial fluid (cell count, Gram stain, culture), TB skin test, imaging, bone marrow aspiration, slit lamp exam

Growing Pains

Epidemiology
- age 2-12 yr, M=F

Clinical Presentation
- diagnosis of exclusion
- intermittent, non-articular pain in childhood with normal physical exam findings
- pain at night, often bilateral and limited to the calf, shin, or thigh; typically short-lived
- relieved by heat, massage, mild analgesics
- child is well, asymptomatic during the day, no functional limitation
- possible family history of growing pains

Management
- lab investigations not necessary if typical presentation; reassurance and supportive management

Transient Synovitis of the Hip

Epidemiology
- age 3-10 yr, M:F, more common on right side

Clinical Presentation
- afebrile or low-grade fever, pain typically occurs in hips, knees (referred from hip); painful limp but full ROM (pain not as pronounced as in joint or bone infections), child does not look "toxic"
- pain is not disabling and gradually worsens over few days, can have sudden onset of symptoms
- symptoms resolve over 7-10 d

Investigations
- WBC within normal limits; ESR and CRP may be mildly elevated
- joint effusions may be seen on ultrasound
  - aspirate joint and examine synovial fluid if suspicious for septic arthritis
  - MRI if suspicious for osteomyelitis or periarticular pyomyositis
- diagnosis of exclusion

Treatment
- symptomatic and anti-inflammatory medications
  - usually resolves with 24-48 h

Complications
- Legg-Calve-Perthes Disease

Red Flags for Limb Pain
- Fever
- Pinpoint pain/tenderness
- Pain out of proportion to degree of inflammation
- Night pain
- Weight loss
- Erythema
**Septic Arthritis and Osteomyelitis**

- MEDICAL EMERGENCY
- see Orthopedics, OR

### Table 43. Microorganisms and Treatment Involved in Septic Arthritis/Osteomyelitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate: GBS, S. aureus, Gram negative bacilli</td>
<td>cloxacillin + gentamicin OR cloxacillin + cefotaxime</td>
<td></td>
</tr>
<tr>
<td>Infant (1-3 mo): Strep. spp., Staph. spp., H. influenzae</td>
<td>Pathogens as per neonate cefoxitin OR cefotaxime</td>
<td></td>
</tr>
<tr>
<td>Child: S. aureus, S. pneumoniae, GAS</td>
<td>Cefazolin OR cloxacillin OR clindamycin</td>
<td></td>
</tr>
<tr>
<td>Adolescent: As above; also N. gonorrhoeae</td>
<td>Ceftriaxone OR cefixime + azithromycin</td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease: As above; also Salmonella</td>
<td>Cefotaxime</td>
<td></td>
</tr>
</tbody>
</table>

GAS = group A Strep; GBS = group B Strep

Adapted from Tse SML, Laxer RM. Pediatrics in Review 2006;27:170-179

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**Juvenile Idiopathic Arthritis**

- a heterogeneous group of conditions characterized by persistent arthritis in children <16 yr
- diagnosis: arthritis in ≥1 joint(s); duration ≥6 wk; onset age <16 yr old; exclusion of other causes of arthritis; classification defined by features/number of joints affected in the first 6 mo of onset

### Systemic Arthritis (Still’s Disease)

- onset at any age, M=F
- onset or twice daily fever spikes (>38.5°C) ≥2 d/wk with temperature returning below baseline; children usually acutely unwell during fever episodes
- extra-articular features: erythematous “salmon-coloured” maculopapular rash, lymphadenopathy, hepatosplenomegaly, thrombocytosis, anemia, arthritis
- arthritis may occur weeks to months later
- high ESR, CRP, WBC, platelet count

### Oligoarticular Arthritis (1-4 joints)

- most common type of JIA
  - onset early childhood (<5 years of age), F>M
  - persistent: affects no more than 4 joints during the disease course
  - extended: affects more than 4 joints after the first 6 mo
  - typically affects large joints: knee most common, elbows, wrists; hip involvement unusual
  - ANA positive ~60-80%, RF negative
  - screening eye exams for asymptomatic anterior uveitis (occurs in ~30%)
  - complications: knee flexion contracture, quadriiceps atrophy, leg-length discrepancy, growth disturbances, uveitis

### Polyarticular Arthritis (5 or more joints)

- ANA positive in 50%, uveitis in 10%
- RF negative (usually negative)
  - onset: 2-4 yr and 6-12 yr, F>M
- symmetrical involvement of large and small joints of hands and feet, TMJ, cervical spine
- RF positive
  - onset late childhood/early adolescence, F>M
  - similar to the aggressive form of adult rheumatoid arthritis
  - severe, rapidly destructive, symmetrical arthritis of large and small joints
  - may have rheumatoid nodules at pressure points (elbows, knees)
  - unremitting disease, persists into adulthood

### Enthesitis-Related Arthritis

- onset: late childhood/adolescence, M>F
- arthritis and/or enthesitis (inflammation at the site where tendons or ligaments attach to the bone)
- weight bearing joints, especially hip and intertarsal joints
- risk of developing ankylosing spondylitis in adulthood

### Psoriatic Arthritis

- onset: 2-4 yr and 9-11 yr, F>M
- arthritis and psoriasis OR arthritis and at least two of:
  - dactylitis, nail pitting or other abnormalities, or family history of psoriasis in a 1st degree relative
  - asymmetric or symmetric small or large joint involvement
Management
- goals of therapy: eliminate inflammation, prevent joint damage, promote normal growth and development as well as normal function, minimize medication toxicity
- exercise to maintain ROM and muscle strength
- multidisciplinary approach: OT/PT, social work, orthopedics, ophthalmology, rheumatology
- 1st line drug therapy: NSAIDs, intra-articular corticosteroids
- 2nd line drug therapy: DMARDs (methotrexate, sulfasalazine, leflunamide), corticosteroids (acute management of severe arthritis, systemic symptoms of JIA, topical eye drops for uveitis), biologic agents (IL1, IL6 inhibition for systemic arthritis, TNF antagonist for polyarticular JIA)

Reactive Arthritis
- see Rheumatology, RH24
- arthritis (typically the knee) follows bacterial infection, especially with Salmonella, Shigella, Yersinia, Campylobacter, Chlamydia, and most commonly Streptococcus (post-streptococcal reactive arthritis)
- typically resolves spontaneously
- may progress to chronic illness or Reiter's syndrome (urethritis, conjunctivitis)

Lyme Arthritis
- see Infectious Diseases, ID23
- caused by spirochete Borrelia burgdorferi
- incidence highest among 5-10 yr olds
- do not treat children <8 yr old with doxycycline (may cause permanent tooth discoloration)

Systemic Lupus Erythematosus
- see Rheumatology, RH11
- autoimmune illness affecting multiple organ systems
- incidence 1/1,000, more commonly age >10, F:M = 10:1
- childhood-onset SLE vs. adult-onset SLE: children have more active disease, are more likely to have renal disease, and children receive more intensive drug therapy and have a poorer prognosis

Vasculitides
HENOCHE-SCHÖNLEIN PURPURA
most common vasculitis of childhood, peak incidence 4-10 yr, M:F = 2:1
- vasculitis of small vessels
- often have history of URTI 1-3 wk before onset of symptoms

Clinical Presentation
- clinical triad: 1) palpable purpura, 2) abdominal pain, 3) arthritis
- skin: palpable, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthritis involving large joints associated with painful edema
- GI: abdominal pain, GI bleeding, intussusception
- renal: microscopic hematuria, IgA nephropathy, proteinuria, HTN, renal failure in <5%

Investigation
- urinalysis (blood, protein creatinine ratio), serum (urea/ electrolytes, creatinine, albumin, elevated IgA)
- skin/renal biopsy – IgA deposition
- ultrasound – intussusception/perforation, testicular pain/swelling
- rule out other autoimmune conditions/vasculitides

Management
- mainly supportive (e.g. elevation for edema)
- anti-inflammatory medications for joint pain, corticosteroids for select patients
- monitor for protein on urinalysis and hypertension every month for 6 mo, checking for renal disease, which may develop late (immunosuppressive therapy if severe)

Prognosis
- self-limited, resolves within 4 wk
- recurrence in about one-third of patients
- long-term prognosis dependent on severity of nephritis
KAWASAKI DISEASE
• acute vasculitis of unknown etiology (likely triggered by infection)
• medium-sized vasculitis with predilection for coronary arteries
• most common cause of acquired heart disease in children in developed countries
• peak age: 3 mo-5 yr; Asians > Blacks > Caucasians

Diagnostic Criteria
• fever persisting ≥5 d AND ≥4 of the following features
  1. bilateral, non-exudative conjunctival injection
  2. oral mucous membrane changes (fissured lips, strawberry tongue, injected pharynx)
  3. changes of the peripheral extremities
    • acute phase: extremity changes including edema of hands and feet or erythema of palms or soles
    • subacute phase: periungual desquamation
  4. polymorphous rash
  5. cervical lymphadenopathy >1.5 cm in diameter (usually unilateral)
• exclusion of other diseases (e.g. scarlet fever, measles)
• atypical Kawasaki disease: fever persisting ≥5 d and 2-3 of the above criteria
  • further evaluation dictated by CRP, ESR, and supplemental laboratory criteria

Management
• initial therapy: IVIG (2g/kg) and high (anti-inflammatory) dose of ASA
• once afebrile >48 h: low (anti-platelet) dose of ASA until platelets normalize, or longer if coronary artery involvement
• IVIg within 10 d of onset reduces risk of coronary aneurysm formation
• baseline 2D-Echo and follow-up periodic 2D Echo (usually at 2, 6 wk)

Complications
• coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children, <5% if receive IVIg within 10 d of fever
• 50% of aneurysms regress within 2 yr
• anticoagulation for multiple or large coronary aneurysms
• risk factors for coronary disease: male, age <1 or >9 yr, fever >10 d, Asian or Hispanic ethnicity, thrombocytopenia hyponatremia

Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen</td>
<td>10-15 mg/kg/dose PO q4-6h prn</td>
<td>Analgesic, antipyretic</td>
<td>Not to exceed 60 mg/kg/d in neonates or 75 mg/kg/d in older children to a max of 4 g/d Causes hepatotoxicity at high doses</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>80-90 mg/kg/d PO divided q8h</td>
<td>Otitis media</td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>0.6 mg/kg PO x 1 0.6 mg/kg/d PO for 2 d</td>
<td>Croup Acute asthma</td>
<td></td>
</tr>
<tr>
<td>fluticasone (Flovent®)</td>
<td>Moderate dose – 250-500 µg/d divided bid High dose – &gt;500 µg/d divided bid</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>ibuprofen</td>
<td>5-10 mg/kg/dose PO q6-8h</td>
<td>Analgesic, antipyretic Cautious use in patients with liver impairment, history of GI bleeding or ulcers</td>
<td></td>
</tr>
<tr>
<td>iron</td>
<td>6 mg/kg/d elemental iron OD or divided tid</td>
<td>Anemia SE: dark stoo constipation, dark urine</td>
<td></td>
</tr>
<tr>
<td>omeprazole</td>
<td>0.7-3.3 mg/kg/d (max dose 20 mg/d) OD or divided bid/tid</td>
<td>GERD SE: headache, diarrhea, nausea, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>ondansetron</td>
<td>0.15 mg/kg/dose (max dose 16 mg) q4-8h up to 3x</td>
<td>Post-operative N/V Gastroenteritis Cyclic vomiting SE: QTc prolongation, orally disintegrating tablets contain phenylalanine (caution in PKU patients)</td>
<td></td>
</tr>
<tr>
<td>phenobarbital</td>
<td>3-5 mg/kg/d PO or bid</td>
<td>Seizures SE: CNS depression</td>
<td></td>
</tr>
<tr>
<td>polyethylene glycol 3350 (PEG)</td>
<td>Disimpaction: 1-1.5 g/kg/d x 3 d Maintenance: starting dose at 0.4-1 g/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prednisone/ prednisilone</td>
<td>1-2 mg/kg/d PO x 5 d 3-4 mg/kg/d PO then taper to 1-2 mg/kg/d PO once platelet count &gt;30 x 10⁹/L 60 mg/m²/d PO</td>
<td>Asthma ITP Nephrotic syndrome Oral prednisone is bitter tasting, consider using prednisilone</td>
<td></td>
</tr>
<tr>
<td>salbutamol (Ventolin®)</td>
<td>0.01-0.03 mL/kg/dose in 3 mL NS via nebulizer q0.5-4h prn 100-200 µg/dose pm, max 4-8 puffs frequency q4h</td>
<td>Acute asthma Can cause tachycardia, hypokalemia, restlessness Maintenance treatment for asthma</td>
<td></td>
</tr>
</tbody>
</table>

Acronyms

ABI ankle brachial index  DM diabetes mellitus  IP interphalangeal
ABG arterial blood gas  EMG electromyography  IVG intravenous immunoglobulin
AFL abductor pollicis longus  ENT ear, nose, throat  MC metacarpal
ARDS acute respiratory distress syndrome  EOM extracranial movement  MCP metacarpal phalangeal joint
ATLS advanced trauma life support  EPB extensor pollicis brevis  NCV nerve conduction velocity
BMR basal metabolic rate  FDP flexor digitorum profundus  NS normal saline
CHF congestive heart failure  FDS flexor digitorum superficialis  NSAIDs nonsteroidal anti-inflammatory drugs
CMC carpo-metacarpal  FTSG full thickness skin graft  OTM otitis media
CO carbon monoxide  GBG group B Streptococcus  OR operating room
CSF cerebrospinal fluid  GBS group B streptococcus  ORIF open reduction internal fixation
CVS cerebrovascular disease  HTN hypertension  PIP proximal interphalangeal joint
CXR chest x-ray  I&d incision and drainage  PMN polymorphonuclear
D5W 5% dextrose in water  ID intracranial pressure  PVD peripheral vascular disease
DIEP deep inferior epigastric perforator  IGAP inferior gluteal artery perforator  RA rheumatoid arthritis
DIP distal interphalangeal joint  IGAP inferior gluteal artery perforator

Basic Anatomy Review

Skin

Figure 1. Split and full thickness skin grafts

Hand

BONES AND NERVES

1. Radius
2. Scaphoid
3. Trapezium
4. Trapezoid
5. Capitate
6. Lunate
7. Pisiform
8. Triquetrum
9. Hamate
10. Metacarpal bones

11. Metacarpal bones

Figure 2. Arterial supply in the hand

Figure 3. Carpal bones

Figure 4. Sensory distribution in the hand
**Figure 5. Flexor tendon insertion at PIP and DIP**

- Distal interphalangeal joint
- Flexor digitorum profundus
- Proximal interphalangeal joint
- Camper’s chiasm
- Flexor digitorum superficialis
- Metacarpal phalangeal joint

**Figure 6. Extensor mechanism of digits**

- Lateral bands
- Central slip
- DIP
- PIP
- MCP
- Extensor hood
- Oblique fibres
- Sagittal fibres
- Lumbrical
- Interosseous muscles
- Extensor digitorum communis

**Figure 7. Nail anatomy**

1. Hyponychium
2. Sterile matrix
3. Germinial matrix
4. Ventral floor
5. Lunula
6. Eponychium
7. Dorsal root
8. Distal phalanx
9. Extensor tendon
10. Flexor tendon

**Figure 8. Carpal tunnel**

- Flexor retinaculum
- Median nerve
- Flexor carpi radialis tendon
- Flexor pollicis longus tendon
- Trapezius
- Trapezoid
- Trapezium

**Figure 9. Extensor compartment of the wrist (dorsal view and cross-sectional view)**

1. Extensor retinaculum
   - **Compartment 1**
      2. Abductor pollicis longus
      3. Extensor pollicis brevis
   - **Compartment 2**
      4. Extensor carpi radialis brevis
      5. Extensor carpi radialis longus
   - **Compartment 3**
      6. Extensor pollicis longus
      (EPL tendon passes around Lister’s tubercle)
   - **Compartment 4**
      7. Extensor digitorum
      8. Extensor indicis
   - **Compartment 5**
      9. Extensor digiti minimi
   - **Compartment 6**
      10. Extensor carpi ulnaris
Brachial Plexus

Figure 10. Brachial plexus anatomy

Face

Figure 11. Skull and facial bones

1. Lacrimal bone
2. Zygomatic bone
3. Maxilla
4. Mandible
5. Nasal bone
6. Sphenoid bone
7. Temporal bone
8. Parietal bone
9. Occipital bone
10. Frontal bone
Skin Lesions and Masses

Differential Diagnosis of Skin Lesions/Masses

- for background information and medical management, see Dermatology, D5
- for biopsy techniques, see Skin Biopsy Types and Techniques, PL7

Surgical Management of Malignant Skin Lesions

- surgical treatment for all malignant skin lesions involve total excision of the primary lesion
- excision margin of lesion depends on the type of lesion, the lesion diameter, and (for melanoma) the lesion depth
- for decisions regarding reconstruction using flaps or skin grafts, see Reconstruction, PL11

Precursors of Malignant Lesions

Table 1. Precursors

<table>
<thead>
<tr>
<th>Basal Cell Carcinoma</th>
<th>Squamous Cell Carcinoma</th>
<th>Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevus sebaceous of Jadassohn</td>
<td>Actinic keratosis</td>
<td>Lentigo maligna</td>
</tr>
<tr>
<td>Bowen's disease</td>
<td>Giant congenital nevus</td>
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</tr>
<tr>
<td>Bowenoid papulosis</td>
<td>Dysplastic nevus</td>
<td></td>
</tr>
<tr>
<td>Lentigo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoplakia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythroplasia</td>
<td></td>
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</tr>
</tbody>
</table>

Surgical Margins

Table 2. Surgical Margins for Basal Cell Carcinoma

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>3 mm</td>
</tr>
<tr>
<td>High Risk*</td>
<td>3-5 mm</td>
</tr>
</tbody>
</table>

*High risk features include: diameter and location (>20 mm trunk, >6 mm face, hands, and feet), poorly defined borders, recurrent lesion, poor differentiation, and type of lesion (e.g. morpheiform)

Table 3. Surgical Margins for Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>4 mm</td>
</tr>
<tr>
<td>High Risk*</td>
<td>5-10 mm</td>
</tr>
</tbody>
</table>

*High risk features include: depth >2 mm, facial lesions, poorly defined borders, recurrent lesion, perineural invasion, poor differentiation, and type of lesion (e.g. morpheiform)

Table 4. Surgical Margins for Malignant Melanoma

<table>
<thead>
<tr>
<th>Depth of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01-1.99 mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>≥2 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>
Basic Surgical Techniques

Sutures and Suturing

ANESTHESIA
- irrigate before injecting anesthetic, followed by debridement and more vigorous irrigation

Table 5. Toxic Limit and Duration of Action (1 cc of 1% solution contains 10 mg lidocaine)

<table>
<thead>
<tr>
<th></th>
<th>Without Epinephrine</th>
<th>With Epinephrine (vasoconstrictor, limits bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (Xylocaine)*</td>
<td>5 mg/kg, lasts 45-60 min</td>
<td>7 mg/kg, lasts 2-6 h</td>
</tr>
<tr>
<td>Bupivicaine (Marcaine)* for longer analgesic effect</td>
<td>2 mg/kg, lasts 2-4 h</td>
<td>3 mg/kg, lasts 3-7 h</td>
</tr>
</tbody>
</table>

*Lidocaine toxicity symptoms include: circumoral numbness, light-headedness, and drowsiness followed by tremors and seizures. Cardiac and respiratory signs are late findings.

- for example when using 1% lidocaine without epinephrine in a 70 kg patient:
  - toxic limit = 5 mg x 70 kg = 350 mg
  - max bolus injection = 350 mg / 10 mg/cc = 35 cc (may add more after 30 min)

IRRIGATION AND DEBRIDEMENT
- irrigate copiously with a physiologic solution such as Ringer’s lactate or normal saline to remove surface clots, foreign material, and bacteria
- use a 19 gauge needle and 35 cc syringe to generate ~25-35 psi when irrigating
- debride all obviously devitalized tissue; irregular or ragged wounds must be excised to produce sharp wound edges that will assist healing when approximated
- wounds left unapproximated ≥8 h should be debrided and copiously irrigated to ensure wound edges are optimized for healing
- there is high risk of infection for any wound closed primarily after 8 h

SUTURES
- use of a particular suture material is highly dependent on surgeon preference; however, skin should be closed with a non-absorbable material when traumatic mechanisms are involved

Table 6. Suture Materials: Absorbable vs. Non-absorbable and Monofilament vs. Multifilament

<table>
<thead>
<tr>
<th>Suture Materials</th>
<th>Uses</th>
<th>Examples</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbable</td>
<td>Deep sutures under short-term tension</td>
<td>Plain gut®, Vicryl®, Polysorb®, Biosyn®, Monocryl®, Caproyn®, chromic gut, fast absorbing gut</td>
<td>Loses at least 50% of their strength in 4 wk; eventually absorbed</td>
</tr>
<tr>
<td>Non-absorbable</td>
<td>Skin closure</td>
<td>Nylon, polypropylene (Prolene®), stainless steel, silk, ticon, ethibond</td>
<td>Lower likelihood of wound dehiscence, more difficult to tie, makes track marks</td>
</tr>
<tr>
<td>Monofilament</td>
<td>Everyday use and optimal for contaminated and infected wounds (lower likelihood of bacterial trapping in suture material)</td>
<td>Monosof®, Monocryl®, Biosyn®, Prolene®</td>
<td>Slides through tissue with less friction; more memory/stiffness; more difficult to tie; requires multiple throws (lower knot security)</td>
</tr>
<tr>
<td>Multifilament</td>
<td>AVOID in contaminated wounds (increased likelihood of bacterial trapping)</td>
<td>Vicryl® and Silk, Ticon, Ethibond</td>
<td>Less memory/stiffness, thus easier to work with (higher knot security)</td>
</tr>
</tbody>
</table>

BASIC SUTURING TECHNIQUES

Basic Suture Methods
- simple interrupted: can be used in almost all situations
- sub-cuticular: good cosmetic result but weak, used in combination with deep sutures; not used in trauma
- vertical mattress: for areas difficult to evert (e.g. volar hand)
- horizontal mattress: evertting, time-saving
- continuous over and over (i.e. “running”, “baseball stitch”): time-saving, good for hemostasis

Other Skin Closure Materials
- tapes: may be indicated for superficial wounds and those with opposable edges. Tape cannot be used on actively bleeding wounds. When placed across the incision, will prevent surface marks and can be used primarily or after surface sutures have been removed
- skin adhesives: e.g. 2-octylcyanoacrylate (e.g. Dermabond®) works well on small areas without much tension or shearing; may cause irreversible tattooing
- staples: steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture)
Excision

- plan your incision along relaxed skin tension lines to minimize appearance of scar
- use elliptical incision to prevent “dog ears” (heaped up skin at end of incision), so the length of the ellipse should be approximately 3x the width
- if needed, undermine skin edges to decrease wound tension
- use layered closure including dermal sutures decreases tension

Skin Biopsy Types and Techniques

SHAVE BIOPSY
- used for superficial lesions where sampling of the full thickness of the dermis is not necessary or practical
- most suitable for shave biopsies are benign lesions either elevated above the skin or have pathology confined to the epidermis (e.g. seborrheic or actinic keratoses, skin tags, and warts)
- high risk of recurrence with shave biopsy for any lesions, including actinic or seborrheic keratoses
- rapid, requires little training, and does not require sutures for closure
- heals by secondary intent (moist dressings should be used)
- should not be used for pigmented lesions – an unsuspected melanoma cannot be properly staged if partially removed

NEEDLE BIOLOGY
- 21 G for lymph node biopsy
- Trucut® needle biopsy for breast masses suspected for carcinoma

INCISIONAL BIOPSY
- can be a punch biopsy, an ellipse within the lesion, or a narrow margin excision of the lesion
- gives pathologists a portion of the lesion and the border with normal skin
- punch biopsies involve the removal of a core-shaped piece of tissue to allow sampling of the deep dermis; performed with round, disposable knives ranging in diameter from 2-10 mm
- punch biopsy wounds can be closed with suture or left to heal by secondary intention. Punches greater than 3 mm may produce scarring and are best closed with one or two sutures
- punch biopsies have a low incidence of infection, bleeding, non-healing, and significant scarring

EXCISIONAL BIOPSY
- performed for lesions that require complete removal for diagnostic purposes
- performed for lesions that cannot be adequately punch biopsied due to size or depth
- for small pigmented lesions and atypical moles; if concerned about melanoma, can do a narrow margin excision for the diagnosis and treatment of small pigmented lesions and atypical moles
- best for small lesions that are easily removed and primarily closed
- requires the greatest amount of expertise and time
- always requires sutures for closure

TECHNIQUE

General
- all shave and punch biopsies performed in clinic are done using aseptic technique, but are not sterile
- sterile gloves are indicated for biopsies and excisions in all patients

Preparing the Site
- common skin antisepsics (Betadine®, chlorhexidine) can be used to prepare the biopsy site
- chlorhexidine is used in concentrations ranging from 0.5-4% The higher concentration cannot be used on the face, as it could get into the eyes or ears and may burn or cause damage. Most chlorhexidine preps also contain alcohol, which can be flammable, so allow to dry before the biopsy and certainly before using any cautery
- Betadine® (7.5% povidone–iodine) may be safer for the head and neck (as to avoid the above problems with chlorhexidine) and around the eyes and ears
- mark the intended lesion and surgical margins with a surgical marker, since they may be temporarily obliterated following injection of the anesthetic
- for all biopsies, a sterile drape technique is indicated. A fenestrated surgical drape is placed around the biopsy site after the area is cleansed and anesthetized

Anesthesia
- most commonly used local anesthetic is 1% or 2% lidocaine (with epinephrine)
- small amounts of epinephrine are added to constrict blood vessels, decrease bleeding, prolong anesthesia, and limit lidocaine toxicity. The local with epinephrine can be injected directly into the lesion
- local anesthetics with epinephrine may be used anywhere in the body, including the digits (except if the digits have been significantly injured and could have vascular compromise – e.g. saw injury)
- epinephrine should only be avoided in patients with history of vascular compromise if injecting into an area that is compromised
Wounds

• wound: disruption of the normal anatomical relationships of tissue as a result of injury

Types of Wounds

• laceration: cut or torn tissue
• abrasion: superficial skin layer is removed, variable depth
• contusion: injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact, yet injured
• avulsion: tissue/limb forcefully separated from surrounding tissue, either partially or fully; “de-gloving”
• puncture wounds: cutaneous opening relatively small as compared with depth (e.g. needle), including bite wounds
• crush injuries: caused by compression
• burns: thermal, chemical, electrical
• ulcers

Principles of Wound Healing

Table 7. Factors Influencing Wound Healing

<table>
<thead>
<tr>
<th>Local (reversible/controllable)</th>
<th>General (often irreversible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical (local trauma, significant crush, avulsion, tension)</td>
<td>Age (affects healing rate)</td>
</tr>
<tr>
<td>Blood supply (ischemia/circulation)</td>
<td>Nutrition (protein, vitamin C, O₂)</td>
</tr>
<tr>
<td>Temperature</td>
<td>Tobacco smoking</td>
</tr>
<tr>
<td>Technique and suture materials</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Retained foreign body</td>
<td>Chronic illness (e.g. DM, cancer, CVD, renal failure)</td>
</tr>
<tr>
<td>Infection</td>
<td>Imunosuppression (steroids, chemo)</td>
</tr>
<tr>
<td>Venous HTN</td>
<td>Tissue irradiation</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Genetic predisposition to abnormal healing (e.g. hypertrophic or keloid scarring, collagen vascular disease)</td>
</tr>
<tr>
<td>Hematoma/seroma (↑ infection rate)</td>
<td>Skin type</td>
</tr>
</tbody>
</table>

STAGES OF WOUND HEALING

• growth factors released by tissues play an important role
• scar is mature once it has completed the final stage, usually after 1-2 yr

PHASE

1. Inflammatory Phase (Reactive) (Days 1-6)
   • Limits damage, prevents further injury
   • Debris and organisms cleared via inflammatory response:
     • Neutrophils (24-48 h)
     • Macrophages: critical to wound healing by orchestrating growth factors for collagen production (48-96 h)
     • Lymphocytes: role poorly defined (5-7 d)

2. Proliferative Phase (Regenerative) (Day 4 – Week 3)
   • Fibroblasts attracted and activated by macrophage growth factors
   • Reparative process: re-epithelialization, matrix synthesis, angiogenesis (relieves ischemia)
   • Tensile strength begins to increase at 4-5 d

3. Remodeling Phase (Maturation) (Week 3 – Year 1)
   • Increasing collagen organization and stronger crosslinks
   • Type I collagen replaces Type III until normal 4:1 ratio achieved
   • Peak tensile strength at 60 d – 80% of pre-injury strength

PROCESS

1. Hemostasis – vasoconstriction + platelet plug
   2. Chemotaxis – migration of macrophages and PMN

1. Collagen synthesis (mainly type III)
   2. Angiogenesis
   3. Epithelialization

1. Contraction
   2. Scarring
   3. Remodeling of scar

Figure 15. Stages of wound healing
TYPES OF WOUND HEALING

Primary (1°) Healing (First Intention)
- definition: wound closure by direct approximation of edges within hours of wound creation (i.e. with sutures, staples, skin graft, etc.)
- indication: recent (<6 h, longer with facial wounds) clean wounds
- contraindications: animal/human bites (except on face), crush injuries, infection, long time lapse since injury (>6-8 h), retained foreign body

Secondary (2°) Healing/ Spontaneous Healing (Second Intention)
- definition: wound left open to heals spontaneously (epithelialization occurs at 1 mm/d from wound margins in concentric pattern, contraction [myofibroblasts], and granulation) – maintained in inflammatory phase until wound closed; requires dressing changes; inferior cosmetic result
- indication: when 1° closure not possible or indicated (see Primary Healing)

Tertiary (3°) Healing/ Delayed Primary Healing (Third Intention)
- definition: intentionally interrupts healing process (e.g. with packing, sharp debridement), then wound can be closed primarily at 4-10 d post-injury after granulation tissue has formed and there is <105 bacteria/gram of tissue
- indication: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization, closure of fasciotomy wounds
- prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

ABNORMAL HEALING

Hypertrophic Scar
- definition: scar remains roughly within boundaries of original scar
- red, raised, widened, frequently pruritic
- common sites: back, shoulder, sternum
- treatment: scar massage, pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur)
- often improve slowly over time

Keloid Scar
- definition: scar grows outside boundaries of original scar
- red, raised, widened, frequently pruritic
- caused by:
  - genetic factors (highest rates in African Americans, Asians)
  - endocrine factors
  - excess tension on wound or delayed closure (as in burn wounds)
- common sites: central chest, back, shoulders, deltoid, ear, angle of mandible
- treatment: multimodal therapy including: pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision with post-surgical management if other options fail (however, there is a high chance of recurrence), fractional carbon dioxide ablative laser, radiation

Spread Scar
- characterized by having exactly the same order of collagen fibres as normal scars
- clinically, a typical spread scar is flat, wide, and often dent
- treatment: surgical excision and closure

Chronic Wound
- wound fails to achieve primary wound healing within 4-6 wk
- common chronic wounds include: diabetic, pressure, and venous stasis ulcers
- treatment: may heal with meticulous wound care; may also require surgical intervention
- Marjolin’s ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation → always consider biopsy of chronic wound

Infected Wounds

Definitions
- the presence of bacteria within a wound may be divided into 4 categories:
  - contamination: the presence of non-replicating microorganisms within a wound
  - colonization: the presence of replicating microorganisms within a wound
  - critical colonization: increasing bacterial burden; have delayed healing but may not exhibit classic signs of infection
  - infection: the presence of >10⁵ microorganisms in a wound without intact epithelium or small amounts of a very virulent organism (e.g. GBS); have delayed healing and exhibit classic signs of infection
- signs of infection: redness, swelling, pain, clinically unwell

Risk Factors for Infection
- Virulence of the infecting microorganism
- Amount of bacteria present
- Host resistance
- Immunocompromised host
Management of Acute Contaminated Wound (<24 h)
- cleanse and irrigate open wound with physiologic solution (NS or RL) using sufficient pressure
- evaluate for injury to underlying structures (vessels, nerve, tendon, and bone)
- control active bleeding; previously closed wounds may require suture removal in order to drain any pus and allow for thorough irrigation and debridement
- debridement: removal of foreign material, devitalized tissue, old blood
- surgical debridement: blade and irrigation if indicated
- systemic antibiotics are commonly indicated for obvious infection. Risk factors include: wound >8 h, severely contaminated, human/animal bites, immunocompromised, involvement of deeper structures (e.g., joints, fractures)
- tetanus prophylaxis (see Table 8 and Figure 16)
- ± post-exposure treatment of:
  - hepatitis B, HIV, hepatitis C (if titres confirmed at 6 mo)
- re-evaluate in 24-48 h for signs of superficial or deep infection
- if evidence of infection (i.e., erythema, warmth, pain, discharge), open infected portion of wound by removing sutures, swab sample for culture and sensitivity, irrigate wound and allow healing by secondary intention

Management of Late Contaminated Wounds (>24 h, including ulcers)
- tetanus prophylaxis (see Table 8 and Figure 16)
- irrigation and debridement
- traumatic tattooing can occur if foreign materials left in wound
- systemic antibiotics
- topical antimicrobials: beneficial for minor wounds, but no additional benefit for wounds requiring systemic antibiotics. May aid in healing of chronic wounds
- closure: final closure via secondary intention (most common), delayed wound closure (3rd closure), skin graft, or flap; successful closure depends on bacterial count of ≤105/cm3 prior to closure and frequent dressing changes
Table 8. Risks for Tetanus Infection

<table>
<thead>
<tr>
<th>Wound Characteristics</th>
<th>Tetanus-Prone</th>
<th>Not Tetanus-Prone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since injury</td>
<td>&gt;6 h</td>
<td>&lt;6 h</td>
</tr>
<tr>
<td>Depth of injury</td>
<td>&gt;1 cm</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>Mechanism of Injury</td>
<td>Crush, burn, gunshot, frostbite, puncture through clothing, farming injury</td>
<td>Sharp cut (e.g. clean knife, clean glass)</td>
</tr>
<tr>
<td>Devitalized tissue</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Contamination (e.g. soil, dirt, saliva, grass)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Retained foreign body</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

BITES
- see Emergency Medicine, ER47

Dog and Cat Bites
- pathogens: *Pasteurella multocida, S. aureus, S. viridans*
- investigations
  - radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  - culture for aerobic and anaerobic organisms, Gram stain
- treatment: Clavulins® (amoxicillin + clavulanic acid) 500 mg PO q8h started immediately
  - consider rabies prophylaxis if animal has symptoms of rabies or unknown animal
  - ± rabies Ig (20 IU/kg around wound, or IM) and 1 of the 3 types of rabies vaccines (1.0 mL IM in deltoid, repeat on days 3, 7, 14, 28)
- aggressive irrigation with debridement
- healing by secondary intention is mainstay of treatment
- only consider primary closure for bite wounds on the face; otherwise primary closure is contraindicated
- contact Public Health if animal status unknown

Human Bites
- pathogens: *Staphylococcus*, β-hemolytic *Streptococcus*, *Eikenella corrodens*, *Bacteroides*
- mechanism: most commonly over dorsal MCP from a punch in mouth; “fight-bite”
- serious, as mouth has 109 microorganisms/mL, which get trapped in joint space when fist unclenches and overlying skin forms an air-tight covering ideal for anaerobic growth – can lead to septic arthritis
- investigations
  - radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  - culture for aerobic and anaerobic organisms, Gram stain
- treatment
  - urgent surgical exploration of joint, drainage, and debridement of infected tissue
  - wound must be copiously irrigated
  - Clavulin® 500 mg PO q8h or (if penicillin allergy) clindamycin 300 mg PO q6h + ciprofloxacin 500 mg PO q12h + secondary closure
  - splint

Dressings
- dressing selection depends on the wound characteristics and surgeon preference
  - as the wound progresses through healing, it will require different types of dressings; therefore, routine inspection is recommended
  - principles of dressing clean vs. infected wounds
    - clean wounds can be dressed with non-adherent dressing (which is non-adhering to epithelializing tissue); requires secondary dressing
    - infected wounds may need debridement and antibiotics and can be dressed with iodine gauze, silver-containing dressings, or antimicrobial dressings
  - moist vs. dry wounds
    - purpose of dressings should be to promote moist wound healing i.e. moistening dry wounds or drying (removing excess exudate/blood) wet wounds
  - wide-based vs. cavitary/tunnelling wounds
    - cavity or tunnelling wounds (i.e. through a fascial layer) can be packed with saline-soaked ribbon gauze (non-infected) or Betadine®-soaked ribbon gauze (infected)

Negative-pressure wound therapy or vacuum-assisted closure (VAC) uses sealed vacuum dressings that suction wound fluid and promote increased blood flow to enhance the healing process. VACs may be placed under deep wounds or to enhance skin graft take.
Table 9. Recommended Dressings for Wound Type

<table>
<thead>
<tr>
<th>Wound Depth</th>
<th>Exudate Level</th>
<th>Dressing Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>Light to moderately exuding wounds</td>
<td>Amorphous gels, hydrogels, hydrocolloids (Duoderm®, Tegaderm®), collagen, hypertonic saline gauze (Mesalt®)</td>
</tr>
<tr>
<td>Superficial</td>
<td>Any exudate level</td>
<td>Contact layers</td>
</tr>
<tr>
<td>Deep</td>
<td>Light to moderately exuding wounds</td>
<td>Foams (Mepilex®, Allevyn®), alginates (Sorbsan®, Kalto-stat®), hypertonic saline gauze, hydrofibre (Aquacel®)</td>
</tr>
<tr>
<td>Deep</td>
<td>Moderately to heavily exuding wounds</td>
<td>Foams (Mepilex®, Allevyn®), alginates (Sorbsan®, Kalto-stat®), hypertonic saline gauze, hydrofibre (Aquacel®)</td>
</tr>
</tbody>
</table>

Adapted from Grabb & Smith’s Plastic Surgery, 6th ed. Chapter 3, Table 3.3

Reconstruction

**RECONSTRUCTION LADDER**

**Definition**
- an approach to wound management with successively more complex methods of treatment
- surgeons should start with the least complex method and progressively increase in complexity as appropriate

**SKIN GRAFTS**

**Definition**
- tissue composed of epidermis and varying degrees of dermis, that does not carry its own blood supply. Survival requires the generation of new blood vessels from the recipient site bed

**Donor Site Selection**
- must consider size, hair pattern, texture, thickness of skin, and colour (facial grafts best if taken from “blush zones” above clavicle e.g. pre/post auricular or neck)
- partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)

**Partial Thickness Skin Graft Survival**
- 3 phases of skin graft “take”
  1. plasmatic imbibition: diffusion of nutrition from recipient site (first 48 h)
  2. inosculation: vessels in graft connect with those in recipient bed (d 2-3)
  3. neovascular ingrowth: graft revascularized (d 3-5)
- requirements for graft survival
  - well-vascularized bed (recipient site). Unsuitable beds include: bone, tendon, heavily irradiated, infected wounds, etc.
  - good contact between graft and recipient bed. Staples, sutures, splinting, and pressure dressings are used to prevent movement/ shearing of graft and hematoma or seroma formation
  - low bacterial count at recipient site (<10^5/cm^3, to prevent infection)
  - common reasons for graft loss: hematoma/seroma, infection, mechanical force (e.g. shearing, pressure)

**Classification of Skin Grafts**
1. by species
   - autograft: from same individual
   - allograft (homograft): from same species, different individual
   - xenograft (heterograft): from different species (e.g. porcine)
2. by thickness: see Table 10
## Table 10. Skin Grafts

<table>
<thead>
<tr>
<th></th>
<th>Split Thickness Skin Graft</th>
<th>Full Thickness Skin Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Epidermis and part of dermis</td>
<td>Epidermis and all of dermis</td>
</tr>
<tr>
<td><strong>Donor Site</strong></td>
<td>More sites</td>
<td>Donor sites limited by the ability to use primary closure</td>
</tr>
<tr>
<td><strong>Healing of Donor Site</strong></td>
<td>Re-epithelialization via dermal appendages in graft and wound edges</td>
<td>Primary closure</td>
</tr>
<tr>
<td><strong>Re-Harvesting</strong></td>
<td>~10 d (faster on scalp)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Graft Take</strong></td>
<td>More reliable and better survival; shorter nutrient diffusion distance</td>
<td>Lower rate of survival (thicker, slower vascularization)</td>
</tr>
<tr>
<td><strong>Contraction</strong>*</td>
<td>Less 1° contraction, greater 2° contraction (less with thicker graft)</td>
<td>Greater 1° contraction, less 2° contraction</td>
</tr>
<tr>
<td><strong>Aesthetic</strong></td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Can be meshed for greater area</td>
<td>May use on face and fingers</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Takes well in less favourable conditions</td>
<td>Resists contraction, better colour match</td>
</tr>
<tr>
<td></td>
<td>Can cover a larger area</td>
<td>May use on face and fingers</td>
</tr>
<tr>
<td></td>
<td>Can be meshed for greater area</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allows for extravasation of blood/serum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large number of donor sites</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Contracts significantly, abnormal pigmentation, high susceptibility to trauma</td>
<td>Requires well vascularized bed</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>Large areas of skin, granulating tissue beds</td>
<td>Face (colour match), site where thick skin or decreased contracture is desired (e.g. finger)</td>
</tr>
</tbody>
</table>

*Primary: immediate reduction in size upon harvesting; Secondary: reduction in size once graft placed on wound bed and healing has occurred

### Meshed Grafts (split thickness grafts can be meshed after harvest by a mesher to a variety of ratios)
- **advantages**
  - prevents accumulation of fluids (e.g. hematoma, seroma)
  - covers a larger area
  - best for contaminated recipient site
- **disadvantages**
  - poor cosmesis (“alligator hide” appearance)
  - has significant contraction

### OTHER GRAFTS

## Table 11. Various Tissue Grafts

<table>
<thead>
<tr>
<th>Graft Type</th>
<th>Use</th>
<th>Preferred Donor Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Repair rigid defects</td>
<td>Cranial, rib, iliac, fibula, scapula</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Restore contour of ear and nose</td>
<td>Ear, nasal septum, costal cartilage</td>
</tr>
<tr>
<td>Tendon</td>
<td>Repair or replace a damaged tendon</td>
<td>Palmaris longus plantaris (present in 85% population)</td>
</tr>
<tr>
<td>Nerve</td>
<td>Conduct for regeneration across nerve gap</td>
<td>Sural, antebrachial cutaneous, medial brachial cutaneous</td>
</tr>
<tr>
<td>Vessel</td>
<td>Bridge vascular gaps</td>
<td>Forearm or foot vessels for small vessels, saphenous vein for larger vessels</td>
</tr>
<tr>
<td>Dermis</td>
<td>Contour restoration (+ fat for bulk)</td>
<td>Thick skin of buttoc or abdomen</td>
</tr>
<tr>
<td>Fat</td>
<td>Contour restoration</td>
<td>Abdomen, any area with fat available</td>
</tr>
<tr>
<td>Nipple</td>
<td>To create a new nipple on a reconstructed breast</td>
<td>Nipple</td>
</tr>
</tbody>
</table>

## FLAPS
- **definition**: tissue of varying composition (skin and fat, muscle and fat, bone and fat, muscle only, etc.), that has a known blood supply (random, pedicled, or named); not dependent on neovascularization, unlike a graft
- **may consist of**: skin, subcutaneous tissue, fascia, muscle, tendon, bone, other tissue (e.g. omentum)
- **classification**: based on tissue composition, blood supply to skin (random, axial), and location of the donor site (local, regional, distant)
- **indications for flaps**
  - replaces tissue loss due to trauma or surgery (reconstruction)
  - provides skin and temporary soft tissue coverage through which surgery can be carried out later
  - to aid healing or treatment of infection by providing vascularized tissue to a poorly vascularized bed
- **complications**: flap loss due to hematoma, seroma, infection, poor flap design, extrinsic compression (dressing too tight) or vascular failure/thrombosis, fat necrosis (in free and pedicled flaps)
Random Pattern Flaps
- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply (typically 3:1 in the head and neck, 1-2:1 elsewhere)
- flap choice is often a combination of available tissue, type of tissue needed, location of reconstruction site with respect to donor site, blood supply, ability to close the donor site and surgeon preference
- types
  - rotation: semicircular tissue rotated around a pivot point for defect closure; commonly used on sacral pressure sores, scalp, and cheek defects
  - transposition: tissue is transposed (i.e. lifted up from its native location and brought into the defect) around a pivot point from one location to another; commonly used on certain areas of the face using adjacent areas of excess skin laxity
  - Z-plasty: two triangular flaps are repositioned; used to reorient a scar, lengthen the line of a scar, or to break up a scar
  - advancement flaps (V-Y, Y-V): defect is closed with uni-directional tissue advancement
    - single/bipedicle V-Y flaps: wounds with lax surrounding tissue; the pedicle is the deep tissue underlying the flap

Axial Pattern Flaps (Arterialized)
- flap contains a well-defined artery and vein
- allows greater length:width ratio (5-6:1)
- types
  - peninsular flap: skin and vessel intact in pedicle
  - island flap: vessel remains intact, but is skeletonized such that the pedicle is better defined
  - free flap: vessel is cut and re-anastomosed in a different anatomical location by microsurgical techniques
- can be sub-classified according to tissue content of flap
  - e.g. musculocutaneous/myocutaneous (e.g. transverse rectus abdominal myocutaneous) vs. fasciocutaneous

Free Flaps
- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and vein to a flap, and performing a microsurgical anastomosis between these and the vessels in the recipient wound
- survival rates >95%
- types: muscle and skin (common), bone, jejunum, omentum, fascia
  - e.g. radial forearm, scapular, latissimus dorsi

Table 12. Characteristics of Healthy Free Flap

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Arterial Insufficiency</th>
<th>Venous Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>Pink</td>
<td>Pale</td>
<td>Purple or blue</td>
</tr>
<tr>
<td>Temperature</td>
<td>Warm</td>
<td>Cool</td>
<td>Warm or cool</td>
</tr>
<tr>
<td>Arterial Pulse (Doppler)</td>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Turgor</td>
<td>Soft, but with some firmness</td>
<td>Decreased tissue firmness</td>
<td>Increased (tissue firmness with tissue stiffness)</td>
</tr>
<tr>
<td>Capillary Refill</td>
<td>2-5 s</td>
<td>&gt;5 s</td>
<td>&lt;2 s</td>
</tr>
</tbody>
</table>
Soft Tissue Infections

Table 13  Classification of Soft Tissue Infections by Depth

<table>
<thead>
<tr>
<th>Infection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erysipelas</td>
<td>Superficial, with upper dermis and superficial lymphatics involvement</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Full thickness of skin with subcutaneous tissue involvement</td>
</tr>
<tr>
<td>Fasciitis</td>
<td>Fascia</td>
</tr>
<tr>
<td>Myositis</td>
<td>Muscle</td>
</tr>
</tbody>
</table>

**Erysipelas**

**Definition**
- acute skin infection that is more superficial than cellulitis

**Etiology**
- typically caused by Group A β-hemolytic Streptococcus

**Clinical Features**
- intense erythema, induration, and **sharply demarcated borders** (differentiates it from other skin infections)

**Treatment**
- penicillin or first-generation cephalosporin (e.g. cefazolin or cephalixin)

**Cellulitis**

**Definition**
- non-suppurative infection of skin and subcutaneous tissues

**Etiology**
- skin flora are most common organisms: S. aureus, β-hemolytic Streptococcus
- immunocompromised: Gram-negative rods and fungi

**Clinical Features**
- source of infection
  - trauma, recent surgery
  - PVD, DM – cracked skin in feet/toes
  - foreign bodies (IV, orthopedic pins)
  - systemic symptoms (fever, chills, malaise)
- pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (visible red streaking in skin proximal to area of cellulitis)

**Investigations**
- CBC, blood cultures
- culture and Gram stain a collection/aspirate from wound if open wound
- plain radiographs show soft tissue edema only

**Treatment**
- antibiotics: first line – cephalexin 500 mg PO q6h or cloxacillin 500 mg PO q6h x 7 d; if complicated (e.g. lymphangitis, DM, severe infection, oral antibiotic therapy failure), consider IV cefazolin 1-2 g q8h or IV cloxacillin, IV penicillin. All patients should have reassessment in 48 h for resolution if on oral antibiotic
- outline area of erythema to monitor success of treatment
- immobilize and splint (hands)

**Necrotizing Fasciitis**

**Definition**
- rapidly spreading, very painful infection of the fascia with necrosis of surrounding tissues
- some bacteria create gas that can be felt as crepitus and can be seen on x rays
- infection spreads rapidly along deep fascial plane and is limb-and life-threatening

**Etiology**
- Type I: polymicrobial (less aggressive)
- Type II: monomicrobial, usually β-hemolytic Streptococcus
Ulcers

Clinical Features

• pain out of proportion to clinical findings and beyond border of erythema
• edema, tenderness, ± crepitus (subcutaneous gas from anaerobes), ± flu-like symptoms (e.g. nausea, fever, diarrhea, dizziness, malaise)
• overlying skin changes including blistering and ecchymoses
• patients may look deceptively well at first, but may rapidly become very sick/toxic
• late findings
  • skin turns dusky blue and black (secondary to thrombosis and necrosis)
  • induration, formation of bullae
  • cutaneous gangrene, subcutaneous emphysema

Investigations

• a clinical diagnosis
• CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, gas collection, myonecrosis and possible source of infection)
• severely elevated CK: usually means myonecrosis (late sign)
• bedside incision, exploration, and incisional biopsy when ruling out conditions, clinical presentation is not supportive, or difficult exam
• during incisional biopsy, often see “dish water pus” (Group A infection) and a hemostat easily passed along fascial plane (fascial biopsy to rule out in equivocal situations)

Treatment

• vigorous resuscitation (ABCs)
• urgent surgical debridement: remove all necrotic tissue, copious irrigation with plans for repeat surgery in 24-48 h
• IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4h and/or clindamycin 900 mg IV q6h until final cultures available (the combination can be synergistic if Group A strep)
• urgent consultation with infectious disease specialist is recommended

Lower Limb Ulcers

Traumatic Ulcers (Acute)

• failure of wound to heal, usually due to compromised blood supply and unstable scar, secondary to pressure or bacterial colonization/infection
• usually over bony prominence ± edema ± pigmentation changes ± pain
• treatment: involvement of vascular surgery. Any debridement of ulcer and compromised tissues must be preceded by ABIs and vascular Doppler. Ulcers or compromised tissues left to heal via secondary intention with dressings may need reconstruction with local or distant flap in select cases, vascular status of limb must be assessed clinically and via vascular studies (i.e. ABI, duplex Doppler)

Non-Traumatic Ulcers (Chronic)

Table 14. Venous vs. Arterial vs. Diabetic Ulcers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venous (70% of vascular ulcers)</th>
<th>Arterial</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Valvular incompetence</td>
<td>2° to small and/or large vessel disease (be aware of risk factors)</td>
<td>Peripheral neuropathy: decreased sensation</td>
</tr>
<tr>
<td></td>
<td>Venous HTN</td>
<td></td>
<td>Atherosclerosis: microvascular disease</td>
</tr>
<tr>
<td>History</td>
<td>Dependent edema, trauma</td>
<td>Arteriosclerosis, claudication</td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Rapid onset ± thrombophlebitis, varicities</td>
<td>Usually &gt;45 yr Slow progression</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trauma/pressure</td>
</tr>
<tr>
<td>Common Distribution</td>
<td>Medial malleolus (“Gaiter” locations)</td>
<td>Distal locations (e.g. lower limb, feet)</td>
<td>Pressure point distribution (more likely metatarsal heads)</td>
</tr>
<tr>
<td>Appearance</td>
<td>Yellow exudates</td>
<td>Pale/white, necrotic base ± dry eschar covering</td>
<td>Necrotic base</td>
</tr>
<tr>
<td></td>
<td>Granulation tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varicose veins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brown discoloration of surrounding skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound Margins</td>
<td>Irregular</td>
<td>Irregular or “punched out” or deep</td>
<td></td>
</tr>
<tr>
<td>Depth</td>
<td>Superficial</td>
<td>Deep</td>
<td>Superficial/deep</td>
</tr>
<tr>
<td>Surrouding Skin</td>
<td>Venous stasis discolouration (brown)</td>
<td>Thin shiny, dry skin; hairless, cool</td>
<td>Thin, dry skin ± hyperkeratotic border</td>
</tr>
</tbody>
</table>

ABI in diabetics can be falsely normal due to incompressible arteries secondary to plaques/calciﬁcation

Necrotizing Soft-Tissue Infection: Diagnosis and Management


Summary: Necrotizing soft tissue infections (NSTIs) are highly lethal. Establishing the diagnosis of NSTI can be the main challenge in treating patients with NSTI. The mainstay of treatment is early and complete surgical debridement, combined with antimicrobial therapy, close monitoring, and physiologic support. Novel therapeutic strategies, including hyperbaric oxygen and intravenous immunoglobulin, have been described, but their effect is controversial. Identification of patients at high risk of mortality is essential for selection of patients that may benefit from future novel treatments and for development and comparison of future trials.
Table 14. Venous vs. Arterial vs. Diabetic Ulcers (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venous (70% of vascular ulcers)</th>
<th>Arterial</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulses</strong></td>
<td>Normal distal pulses</td>
<td>Decreased or no distal pulses</td>
<td>Decreased pulses likely (take caution in calcified vessels)</td>
</tr>
<tr>
<td><strong>Vascular Exam</strong></td>
<td>ABI &gt;0.9 Doppler; abnormal venous system</td>
<td>ABI &lt;0.9 Pallor on elevation, rubor on dependency Delayed venous filling</td>
<td>ABI is inaccurately high (due to PVD) Usually associated with arterial disease (microvascular/macrovascular disease)</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>Moderately painful Increased with leg dependency, decreased with elevation No rest pain</td>
<td>Extremely painful Decreased with dependency, increased with leg elevation and exercise (claudication) Rest pain</td>
<td>Painless (if neuropathy) No claudication or rest pain Associated paresthesia, anesthesia</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Leg elevation, rest Compression at 30 mmHg (stockings or elastic bandages) Moist wound dressings ± topical, systemic antibiotics if infected ± skin grafts</td>
<td>Rest, no elevation, no compression Moist wound dressing ± topical and/or systemic antibiotics if infected Modify risk factors (smoking, diet, exercise, etc.) Vascular surgical consultation (angioplasty or bypass) Treat underlying conditions (DM, proximal arterial occlusion, etc.)</td>
<td>Control DM Careful wound care Foot care Orthotics, off loading Early intervention for infections (topical and/or systemic antibiotics if infected) Vascular surgical consultation</td>
</tr>
</tbody>
</table>

Pressure Ulcers

**Common Sites**
- over bony prominences; 95% on lower body

**Stages of Development**
1. hyperemia: disappears 1 h after pressure removed
2. ischemia: follows 2-6 h of pressure
3. necrosis: follows >6 h of pressure
4. ulcer: necrotic area breaks down – N.B. skin is like tip of an iceberg

**Classification** (National Pressure Ulcer Advisory Panel 2014)
- Stage I: non-blanchable erythema present >1 h after pressure relief, skin intact
- Stage II: partial-thickness skin loss
- Stage III: full-thickness skin loss into subcutaneous tissue
- Stage IV: full-thickness skin loss into muscle, bone, tendon, or joint
- if an eschar is present, must fully debride before staging possible
- Stage X: unstageable ulcer

**Prevention**
- good nursing care (clean dry skin, frequent repositioning), special beds or pressure relief surface, proper nutrition, activity early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, immunocompromised, DM, etc.)

**Treatment**
- depends on individual patient and condition
- treat underlying medical issues including nutrition
- continue with preventative measures (pressure relief, assess for pressure points e.g. wheelchairs; manage continence issues, divert contaminants e.g. urine and feces)
- wound debridement, moisture retentive or antimicrobial dressing, regular reassessment
- systemic antibiotics for infections
- assess for possible reconstruction

**Complications**
- cellulitis, osteomyelitis, sepsis, gangrene
Burns

Burn Injuries

Causal Conditions
- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

Most Common Etiology
- children: scald burns
- adults: flame burns

Table 15. Skin Function and Burn Injury

<table>
<thead>
<tr>
<th>Skin Function</th>
<th>Consequence of Burn Injury</th>
<th>Intervention Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoregulation</td>
<td>Prone to lose body heat</td>
<td>Must keep patient covered and warm</td>
</tr>
<tr>
<td>Control of fluid loss</td>
<td>Loss of large amounts of water and protein from the skin and other body tissues</td>
<td>Adequate fluid resuscitation is imperative</td>
</tr>
<tr>
<td>Mechanical barrier to bacterial invasion</td>
<td>High risk of infection</td>
<td>Antimicrobial dressings (systemic antibiotics if signs of specific infection present)</td>
</tr>
<tr>
<td>and immunological organ</td>
<td></td>
<td>Tetanus prophylaxis if not already administered</td>
</tr>
</tbody>
</table>

Pathophysiology of Burn Wounds

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent
- zone of hyperemia: vasodilation from inflammation; entirely viable, cells recover within 7 d; contributes to systemic consequences seen with major burns
- zone of stasis (edema): decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24–48 h without proper treatment
- factors favouring cell survival: moist, aseptic environment, rich blood supply
- zone where appropriate early intervention has most profound effect in minimizing injury zone of coagulation (ischemia): no blood flow to tissue → irreversible cell damage → cellular death/necrosis

Diagnosis and Prognosis

- burn size
  - % of TBSA burned: rule of 9s for 2nd and 3rd burns only (children <10 yr old use Lund-Browder chart)
  - for patchy burns, surface area covered by patient’s palm (fingers closed) represents approximately 1% of TBSA
- age: more complications if <3 yr or >60 yr old
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see Table 16)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see Indications for Transfer to Burn Centre, PL21)
- inhalation injury: can severely compromise respiratory system, affect fluid requirement estimation (underestimate), mortality secondary to ARDS
- associated injuries (e.g. fractures)
- comorbid factors (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure) can exacerbate extent of injury, other trauma

Figure 19. Zones of thermal injury

Blood vessels and nerves are found in the dermis

Prognosis best determined by burn size (TBSA), age of patient, presence/absence of inhalation injury

Circumferential burns can restrict respiratory excursion and/or blood flow to extremities and require escharotomy

TBSA does not include areas with 1st burns
Burn Size And Survival Probability In Paediatric Patients In Modern Burn Care: A Prospective Observational Cohort Study
Lancet 2012 Mar 17;379(9820):1013-21
Study: Single-centre prospective observational cohort study using clinical data for paediatric patients with burns of at least 30% of their total body surface area (TBSA). Patients were stratified by burn size in 10% increments, ranging from 30% to 100% TBSA.
Results: 952 severely burned paediatric patients were admitted to the centre between 1998 and 2008. 123 (13%) patients died, 154 (16%) developed multiorgan failure, and 89 (9%) had sepsis. Burn size of 62% TBSA was a crucial threshold for mortality.
Conclusions: In a modern paediatric burn care setting, a burn size of roughly 60% TBSA is a crucial threshold for postburn morbidity and mortality. We recommend that paediatric patients with greater than 60% TBSA burns be immediately transferred to a specialised burn centre. Furthermore, patients should be treated with increased vigilance and improved therapies at the burn centre, in view of the increased risk of poor outcome associated with this burn size.

Table 16. Burn Depth (1st, 2nd, 3rd degree)

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Traditional Nomenclature</th>
<th>Depth</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema/Superficial</td>
<td>First degree</td>
<td>Epidermis</td>
<td>Painful, sensation intact, erythema, blanchable</td>
</tr>
<tr>
<td>Superficial-Partial</td>
<td>Second degree</td>
<td>Into superficial demis</td>
<td>Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present</td>
</tr>
<tr>
<td>Thickness</td>
<td>Second degree</td>
<td>Into deep (reticular) demis</td>
<td>Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn</td>
</tr>
<tr>
<td>Deep-Partial Thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Thickness</td>
<td>Third degree</td>
<td>Through epidermis and dermis injury to underlying tissue structures (e.g. muscle, bone)</td>
<td>Insensate (nerve endings destroyed), hard leathery eschar that is black, grey, white, or cherry red in colour; hairs do not stay attached, may see thrombosed veins</td>
</tr>
<tr>
<td></td>
<td>Fourth degree</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Indications for Transfer to Burn Centre

American Burn Association Criteria

- patients with partial or full-thickness burns that involve the hands, feet, genitalia, face, eyes, ears, and/or major joints or perineum
- partial thickness burns ≥20% TBSA in patients aged 10-50 yr old
- partial thickness burns ≥10% TBSA in children aged ≤10 or adults aged ≥50 yr old
- full thickness burns ≥5% TBSA in patients of all ages
- electrical burns, including lightning (internal injury underestimated by TBSA), and chemical burns
- inhalation injury (high risk of mortality and may lead to respiratory distress)
- burn injuries in patients with medical comorbidities, could complicate management and recovery
- any patient with simultaneous trauma plus burns should be stabilized for trauma first, then triaged appropriately to burn centre
- any patients with burn injury and who will require special emotional, social, and rehabilitation intervention
- children with burns in a hospital not equipped with pediatric care specialists

Acute Care of Burn Patients

- adhere to ATLS protocol
- resuscitation using Parkland formula to restore plasma volume and cardiac output. Parkland formula is a starting estimate and patients may require more volume. Other formulas exist, but the Parkland formula is predominately used in North America
  - 4 cc/kg x %TBSA (greater than first degree) x wt(kg) (1/2 within first 8 h of sustaining burn, 1/2 in next 16 h)
- extra fluid administration required if
  - burn >80% TBSA
  - 4° burns
  - associated traumatic injury
  - electrical burn
  - inhalation injury
  - delayed start of resuscitation
  - pediatric burns
- monitor resuscitation
  - urine output is best measure: maintain at >0.5 cc/kg h (adults) and 1.0 cc/kg/h in children <12 yr
  - maintain a clear sensorium, HR <120/min, MAP >70 mmHg
- burn specific care
  - relieve respiratory distress: intubation and/or escharotomy
  - escharotomy in circumferential extremity burn, including digits
  - prevent and/or treat burn shock: 2 large bore IVs for fluid resuscitation
  - insert Foley catheter to monitor urine output
  - identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
  - determine TBSA affected first, since depth is difficult to determine initially (easier to determine after 24 h)
- tetanus prophylaxis if needed
  - all patients with burns >10% TBSA, or deeper than superficial-partial thickness, need 0.5 cc tetanus toxoid
  - also give 250 U of tetanus Ig if prior immunization is absent/unclear, or the last booster >10 yr ago
- baseline laboratory studies (Hb, U/A, BUN, CXR, electrolytes, Cr, glucose, CK, ECG, cross-match if traumatic injury, ABG, carboxyhemoglobin)
- cleanse, debride, and treat the burn injury (antimicrobial dressings)
- early excision and grafting important for outcome

Respiratory Problems

3 major causes

- burn eschar encircling chest
  - distress may be apparent immediately
  - perform escharotomy to relieve constriction
- CO poisoning
  - may present immediately or later
  - treat with 100% O₂ by facemask (decreases half-life of carboxyhemoglobin from 210 to 59 min) until carboxyHb <10%
- smoke inhalation leading to pulmonary injury
  - chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
  - risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
  - watch for secondary bronchopneumonia (3-25 d) leading to progressive pulmonary insufficiency
  - intubate patient with any signs of inhalation injuries

Inhalation Injuries 101

- Indicators of inhalation injury
- Injury in a closed space
- Facial burn
- Singed nasal hair/eyebrows
- Soot around nares/oral cavity
- Hoarseness
- Conjunctivitis
- Tachypnea
- Carbon particles in sputum
- Elevated blood CO levels (i.e. brighter red)
- Suspected inhalation injury requires immediate intubation due to impending airway edema; failure to diagnose inhalation injury can result in airway swelling and obstruction, which, if untreated, can lead to death
- Neither CXR or ABG can be used to rule out inhalation injury
- Direct bronchoscopy now used for diagnosis
- Signs of CO poisoning (headache, confusion, coma, arrhythmias)
Burn Wound Healing

Table 17. Burn Shock Resuscitation (Parkland Formula)

<table>
<thead>
<tr>
<th>Hour 0-24</th>
<th>4 cc RL/kg/% TBSA with 1/2 of total in first 8 h from time of injury and 1/2 of total in next 16 h from time of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour 24-30</td>
<td>0.35-0.5 cc plasma/kg/%TBSA</td>
</tr>
<tr>
<td>&gt; Hour 30</td>
<td>DSW at rate to maintain normal serum sodium</td>
</tr>
</tbody>
</table>

*Do not forget to add maintenance fluid to resuscitation

Table 18. Burn Wound Healing

<table>
<thead>
<tr>
<th>Depth</th>
<th>Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>No scarring; complete healing</td>
</tr>
<tr>
<td>Second degree (Superficial partial)</td>
<td>Spontaneously re-epithelialize in 7-14 d from retained epidermal structures</td>
</tr>
<tr>
<td></td>
<td>± residual skin discoloration</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic scarring uncommon; grafting rarely required</td>
</tr>
<tr>
<td>Deep second degree (Deep partial)</td>
<td>Re-epithelialize in 14-35 d from retained epidermal structures</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic scarring frequent</td>
</tr>
<tr>
<td></td>
<td>Grafting recommended to expedite healing</td>
</tr>
<tr>
<td>Third degree (Full thickness)</td>
<td>Re-epithelialize from the wound edge</td>
</tr>
<tr>
<td></td>
<td>Grafting/flap necessary to replace dermal integrity, limit hypertrophic scarring</td>
</tr>
<tr>
<td>Fourth degree</td>
<td>Often results in amputations</td>
</tr>
<tr>
<td></td>
<td>If not requiring amputation, needs flap for coverage after debridement (do not re-epithelialize, cannot graft)</td>
</tr>
</tbody>
</table>

Treatment

- 3 stages
  1. assessment: depth determined
  2. management: specific to depth of burn and associated injuries
  3. rehabilitation
- first degree
  - treatment aimed at comfort
  - topical creams (pain control, keep skin moist) ± aloe
  - oral NSAIDs (pain control)
- superficial second degree/partial thickness
  - daily dressing changes with topical antimicrobials (such as polysporin); leave blisters intact unless circulation impaired or over joint and inhibiting motion
- deep second degree/deep partial thickness and third degree/full thickness
  - prevent infection and sepsis (significant complication and cause of death in patients with burns)
    - most common organisms: *S. aureus*, *P. aeruginosa*, and *C. albicans*
      - day 1-3 (rare): Gram-positive
      - day 3-5: Gram-negative (*Proteus, Klebsiella*)
    - topical antimicrobials: treat colonized wounds (from skin flora, gut flora, or caregiver)
    - remove dead tissue
    - surgically debride necrotic tissue, excise to viable (bleeding) tissue

Table 19. Antimicrobial Dressings for Burns

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pain with Application</th>
<th>Penetration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver nitrate (0.5% solution)</td>
<td>None</td>
<td>Minimal</td>
<td>May cause methemoglobinemia, stains (black), leaches sodium from wounds</td>
</tr>
<tr>
<td>Nanocrystalline silver-coated dressing (Acticoat®)</td>
<td>None or transient</td>
<td>Medium, does not penetrate eschar</td>
<td>May stain, producing a pseudoeschar or facial discolouration (argyria-like symptoms); raised liver enzymes</td>
</tr>
<tr>
<td>Silver sulfadiazine (cream) (Flamazine®, Silvadene®)</td>
<td>Minimal</td>
<td>Medium, penetrates eschar poorly</td>
<td>Most commonly used</td>
</tr>
<tr>
<td>(Sulfamylon®)</td>
<td>Moderate</td>
<td>Well, penetrates eschar</td>
<td>Mild inhibition of epithelialization</td>
</tr>
</tbody>
</table>

Risk Factors for Infection of Burn Wounds

**Patient Related**
- Extent >30% TBSA
- Depth: full-thickness and deep partial-thickness
- Patient age (higher risk with very young and very old)
- Comorbidities
- Wound dryness
- Wound temperature
- Secondary impairment of blood flow to wound
- Acidosis

**Microbial Factors**
- Density >10^5 organisms per gram of tissue
- Motility
- Virulence and metabolic products (endotoxin, exotoxin, permeability factors, other factors)
- Antimicrobial resistance
• early excision and grafting is the mainstay of treatment for deep/full thickness burns
• initial dressing should decrease bacterial proliferation
• prevention of wound contractures: pressure dressings, joint splints, early physiotherapy

Other Considerations in Burn Management

Figure 22. Systemic effects of severe burns

- nutrition
  • hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
  • consider nutritional supplementation e.g. calories, vitamin C, vitamin A, Ca++, Zn++, Fe++
- immunosuppression and sepsis
  • must keep bacterial count <105 bacteria/g of tissue (blood culture may not be positive)
  • signs of sepsis: sudden onset of hyper/hyperthermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 h post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
- GI bleed may occur with burns >40% TBSA (usually subclinical)
  • treatment: tube feeding or NPO if there is a GI bleed, antacids, H2 blockers (preventative)
  • renal failure secondary to under resuscitation, drugs, myoglobin, etc.
  • progressive pulmonary insufficiency
  • can occur after: smoke inhalation, pneumonia, cardiac decompensation, sepsis
- wound contracture and hypertrophic scarring (outcomes optimized with timely wound closure, splinting, pressure garments) and physiotherapy

Special Considerations

CHEMICAL
• major categories: acid burns, alkaline burns, phosphorous burns, chemical injection injuries
• common agents: cement, hydrofluoric acid, phenol, tar
• mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
  • acids → coagulation necrosis
  • alkalines → saponification followed by liquefactive necrosis
• severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
• burns are deeper than they initially appear and may progress with time

Treatment (General)
• ABCs, monitoring
• remove contaminated clothing and brush off any dry powders before irrigation
• irrigation with water for 1-2 h under low pressure (contraindicated in heavy metal burns, such as sodium, potassium, magnesium, and lithium; in these cases, soak in mineral oil instead)
• inspect eyes, if affected: wash with saline and refer to ophthalmology
• inspect nails, hair, and webspaces
• correct metabolic abnormalities and tetanus prophylaxis if necessary
• contact poison control line if necessary
• local wound care 12 h after initial dilution (debridement)
• wound closure same as for thermal burn
• beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

Special Burns and Treatments

<table>
<thead>
<tr>
<th>Burn Type</th>
<th>Treatment/Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Burn</td>
<td>Water irrigation, followed by dilute solution of sodium bicarbonate</td>
</tr>
<tr>
<td>Hydrofluoric Acid</td>
<td>Water irrigation; clip fingernails to avoid acid trapping; topical calcium gel ± subcutaneous injection of calcium gluconate ± 10% calcium gluconate IV depending on amount of exposure and pain</td>
</tr>
<tr>
<td>Sulfuric Acid</td>
<td>Eat with soap/lime prior to irrigation, as direct water exposure produces extreme heat</td>
</tr>
<tr>
<td>Tar</td>
<td>Remove with repeated application of petroleum-based antibacterial ointments (e.g. Polysporin®)</td>
</tr>
</tbody>
</table>
ELECTRICAL BURNS
- depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
- often presents as small punctate burns on skin, with extensive deep tissue damage which requires debridement
- electrical burns require ongoing monitoring, as latent injuries can occur
  - watch for system-specific damages and abnormalities
    - abdominal: intraperitoneal damage
    - bone: fractures and dislocations especially of the spine and shoulder
    - cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
    - muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
    - neurological: seizures and spinal cord damage
    - ophthalmology: cataract formation (late complication)
    - renal: ATN resulting from toxic levels of myoglobin and hemoglobin
    - vascular: vessel thrombosis → tissue necrosis (increased Cr, K+, and acidity), decrease in RBC (beware of hemorrhages/delayed vessel rupture)

Treatment
- ABCs, primary and secondary survey, treat associated injuries
- beware of cardiac arrhythmias (continue cardiac monitoring)
- monitor: hemorrhochromogenuria, compartment syndrome, urine output
- wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
- debride nonviable tissue early and repeat prn (every 48 h) to prevent sepsis
- amputations frequently required

FROSTBITE
- see Emergency Medicine, ER46

Hand

Traumatic Hand

Table 20. Key Features of the History and Physical Exam of the Injured Hand

<table>
<thead>
<tr>
<th>HISTORY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Questions</strong></td>
<td><strong>Tetanus status</strong></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Hand dominance</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Time and place of accident</td>
<td></td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td></td>
</tr>
<tr>
<td>Initial treatment received</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHYSICAL EXAM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation</strong></td>
<td>Abnormal cascade (fingers normally slightly flexed and point towards scaphoid), scissoring</td>
</tr>
<tr>
<td>Deformity</td>
<td>Bony protrusions or specific deformities (e.g. mallet, boutonnière, and swan neck deformity)</td>
</tr>
<tr>
<td>Bruising or swelling</td>
<td>May indicate underlying skeletal injury</td>
</tr>
<tr>
<td>Sweating pattern (usually felt more so than from observation)</td>
<td>May indicate denervation</td>
</tr>
<tr>
<td>Anatomical structures beneath</td>
<td>If open laceration, need to explore within wound (under sterile conditions)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular Status</th>
<th>Palpate pulses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial and ulnar arteries</td>
<td>Allen’s test</td>
</tr>
<tr>
<td>Digital arteries</td>
<td>Assess capillary refill (&lt; 2-3 s)</td>
</tr>
<tr>
<td>Temperature and skin turgor</td>
<td>For each test, need to compare both sides</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensory (see Figure 4)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median nerve</td>
<td>Volar radial tip of index finger</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>Volar ulnar tip of little finger</td>
</tr>
<tr>
<td>Radial nerve</td>
<td>Dorsal web space of the thumb</td>
</tr>
<tr>
<td>Digital nerves</td>
<td>2 point discrimination on both the radial and ulnar side of the DIPJ creases (static or moving 2 point discrimination)</td>
</tr>
</tbody>
</table>
Table 20. Key Features of the History and Physical Exam of the Injured Hand (continued)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Function</td>
<td></td>
</tr>
<tr>
<td>Median nerve</td>
<td>Flex DIP of index finger (to test the anterior interosseus nerve (AIN) branch)</td>
</tr>
<tr>
<td></td>
<td>Touch the tip of the index finger to the thumb trying to break through (“OK sign”) (to test the AIN branch)</td>
</tr>
<tr>
<td></td>
<td>Thumb to ceiling with palm up (to test the recurrent motor branch)</td>
</tr>
<tr>
<td></td>
<td>Thumb to tip of 5th digit (to test the recurrent motor branch)</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>Extrinsic muscles: flex DIP of little finger</td>
</tr>
<tr>
<td></td>
<td>Intrinsic muscles: abduct index finger (“Peace sign”) or patient able to hold piece of paper between adducted thumb and index finger and resist pulling (“Froment’s sign”)</td>
</tr>
<tr>
<td>Radial nerve</td>
<td>Extrinsic muscles: extend thumb (“thumb’s up”) and wrist</td>
</tr>
</tbody>
</table>

Range of Motion

| Tendons, bones, joints, nerves | Assess active and passive range of motion of wrist: extension/flexion/ulnar/radial deviation; finger abduction/adduction/flexion/extension, thumb flexion/extension/abduction/adduction/opposition |

Tendons

| FDP | Stabilize PIP in extension, ask patient to flex fingers (at DIP) |
| FDS | Stabilize non exam fingers in extension (neutralizes FDP) and ask patient to flex examination finger (at PIP) |

Palpation

| Bones | Focal tenderness or abnormal alignment |
| Joints | Instability may indicate ligamentous injury or dislocation |

General Management of Hand Injuries

Nerves

- test the nerve function BEFORE putting in local anesthesia
- primary repair for a clean injury within 7 d and without concurrent major injuries; secondary repair if >7 d (may require nerve graft)
- epineural repair of all digital nerves with minimal tension
- post-operative: dress wound, elevate hand, and immobilize
- Tinel’s sign (cutaneous percussion over the repaired nerve) produces paresthesias and defines level of nerve regeneration
  - Wallerian degeneration occurs in the first 2 wk, which is why there is no Tinel’s sign until after this time period
  - a peripheral nerve regenerates at 1 mm/d
  - paresthesias felt at area of percussion because regrowth of myelin (Schwann cells) is slower than axonal regrowth → percussion on exposed free-end of axon generates paresthesia

Vessels

- often associated with nerve injury (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 h
- close skin, then dress, immobilize, and splint hand with fingertips visible
- monitor colour, capillary refill, skin turgor, fingertip temperature post-revascularization

Tendons

- most tendon lacerations require primary repair
- many tendons are repaired in the emergency room, flexors are repaired in the operating room within 2 wk
- avoid excessive immobilization after repair (specific protocols for flexors to minimize stiffness and facilitate rehabilitation)

Bones

- see Fractures and Dislocations, PL27

Nailbed

- subungual hematomas >50% of the nail surface area need to be drained (trephination), done under a digital block by puncturing nail plate
- if suspecting greater severity of injury (e.g. distal phalanx displaced fracture, laceration of nail bed), remove nail plate to examine underlying nailbed under digital block anesthesia
- irrigate wound and nail thoroughly
- suture repair of nailbed with chromic suture
- replace cleaned nail, which acts as a splint for any underlying distal phalangeal fracture and prevents adhesion formation between nail fold and nailbed
Hand Infections

Principles
- trauma is most common cause
- 5 cardinal signs: rubor (red), calor (hot), tumour (swollen), dolor (painful), and functio laesa (loss of function)
- 90% caused by Gram-positive organisms
- most common organisms (in order) – S. aureus, S. viridans, Group A Streptococcus, S. epidermidis, and Bacteroides melaninogenicus (MRSA is becoming more common)

TYPES OF INFECTIONS

Deep Space Infections
- abscess formation in deep spaces of the hand, most commonly thenar or mid-palm space
- uncommon, there are 9 spaces in the hand

Felon
- definition: abscess in the pulp of a fingertip or thumb that occurs following a puncture wound into the pad of the digit; may be associated with osteomyelitis (akin to compartment syndrome and can lead to skin necrosis)
- treatment: elevation, warm soaks, cloxacillin 500 mg PO q6h (if in early stage); if obvious abscess or pressure on the overlying skin or failure to resolve with conservative measures, then needs I&D, take cultures/gram stain and adjust antibiotics to culture results

Flexor Tendon Sheath Infection
- Staphylococcus > Streptococcus > Gram-negative rods
- definition: abscess within the flexor tendon sheath (flexor tenosynovitis), commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated; it is often suppurative; however, there can be very little pus early on
- clinical features: Kanavel’s 4 cardinal signs
  1. point tenderness along flexor tendon sheath
  2. severe pain on passive extension of digit
  3. fusiform swelling of entire digit
  4. flexed posture (increased comfort)
- treatment
  - OR I&D, copious irrigation and debridement, IV antibiotics, resting hand splint until infection resolves, aggressive hand therapy after

Herpetic Whitlow
- HSV-1, HSV-2
- definition: painful vesicle(s) around fingertip or thumb
  - often found in medical/dental personnel and children
- clinical features: can be associated with fever, malaise and lymphadenopathy, prodromal phase
  - patient is infectious until lesion has completely healed
- treatment: diagnosed clinically, if in doubt confirm with viral culture/PCR or Tzanck smear, usually self-limited, consider oral acyclovir in severe cases; I&D is contraindicated

Paronychia
- acute = Staphylococcus; chronic = Candida
- definition: infection (granulation tissue) of soft tissue around fingernail (within the paronychium and/or beneath eponychial fold)
- etiology
  - acute paronychia: a “hangnail”, artificial nails, and nail biting
  - chronic paronychia: prolonged exposure to moisture
- treatment
  - acute paronychia: warm compresses and oral antibiotics if caught early; if abscess present, drainage with blade (avoid hitting nail bed) and oral/IV antibiotics; if abscess extends to below nail plate, nail plate removal may be required
  - chronic paronychia: anti-fungals, eponychial marsupialization, nail plate removal may be required
Amputations

Hand or Finger
- emergency management: injured patient and amputated part require attention
  - patient: x-rays (stump and amputated part), NPO, clean wound and irrigate with NS, dress stump with nonadherent dressing, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/erythromycin)
  - amputated part: x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice
- indications for replantation
  - age: children often better results than adults
  - level of injury: thumb and multiple digit amputations are higher priority; multiple level amputation is a contraindication to replant
  - nature of injury: clean cut injuries have greater success; avulsion and crush injuries are relative contraindications to replant
- if replant contraindicated, manage stump with revision amputation
  - involves debriding stump of wound, trimming back the bone and nerve endings, and gently closing the skin
  - commonly done in the ER under digital block

Tendons

Common Extensor Tendon Deformities

Table 21. Extensor Tendon Deformities

<table>
<thead>
<tr>
<th>Injury</th>
<th>Definition</th>
<th>Zone (see Figure 23)</th>
<th>Etiology/Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallet Finger</td>
<td>DIP flexed with loss of active extension</td>
<td>1</td>
<td>There are bony and non-bony mallets</td>
<td>Splint DIP in extension for 6 wk, followed by 2 wk of night splinting; if inadequate improvement after 6 wk, check splinting routine and recommend 4 more wk of continuous splinting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bony: Fracture of distal phalanx distal to tendon insertion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-bony: Forced flexion of the extended DIP leading to extensor tendon</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rupture at DIP (e.g. sudden blow to tip of the finger)</td>
<td></td>
</tr>
<tr>
<td>Boutonnière Deformity</td>
<td>PIP flexed, DIP hyperextended</td>
<td>3</td>
<td>Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Associated with RA or trauma</td>
<td>Splint PIP in extension and allow active DIP motion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>laceration, volar dislocation, acute forceful flexion of PIP</td>
<td></td>
</tr>
<tr>
<td>Swan Neck Deformity</td>
<td>PIP hyperextended, DIP flexed</td>
<td>1, 3</td>
<td>Trauma (PIP volar plate injury)</td>
<td>Corrective procedures involve tendon rebalancing or arthrodesis/arthroplasty</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Associated with RA and old, untreated mallet deformity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Splint to prevent PIP hyperextension or DIP flexion</td>
<td></td>
</tr>
</tbody>
</table>

Figure 23. (A) Mallet finger deformity (B) Boutonnière deformity (C) Swan neck deformity

De Quervain’s Tenosynovitis
- definition: tenosynovitis is inflammation of the tendon and/or its sheath. Most common is De Quervain’s tenosynovitis (inflammation of the extensor tendons in the 1st dorsal compartment [APL and EPB])
- clinical features
  - +ve Finkelstein’s test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)
  - pain localized to the 1st extensor compartment
  - tenderness and crepitation over radial styloid may be present
  - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)

Figure 24. Zone of extensor tendon injury (odd numbered zones fall over a joint)
• treatment
  • mild: NSAIDs, splinting and steroid injection into the tendon sheath (successful in over 60% of cases)
  • severe surgery to open 1st dorsal compartment and release stenotic tendon sheaths of APL and EPB

Ganglion Cyst
• definition
  • fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin
  • most common soft tissue tumour of hand and wrist (60% of masses)
• clinical features
  • most commonly on the dorsal wrist overlying the scapholunate ligament, followed by the volar surface of the wrist overlying the radioscaphoid or scaphotrapezial joints
  • 3 times more common in women than in men
  • more common in younger individuals (2nd to 4th decades)
  • can be large or small – may drain internally so size may wax and wane
  • often non-tender although tenderness increased when cyst is smaller (from increased pressure within smaller cyst sac)
• treatment
  • conservative treatment: do nothing
  • aspiration (recurrence rate 30-60%)
  • steroid injection if painful (done in combination with aspiration, as results alone are no better than aspiration)
  • consider operative excision of cyst and stalk (recurrence rate 5.9% for dorsal wrist ganglion, 30% for volar)

Common Flexor Tendon Deformities
• flexor tendon zones (important for prognosis of tendon lacerations)
  • "no-man’s land" (zone 2) (see Figure 24)
    • between distal palmar crease and mid-middle phalanx
    • zone where superficialis and profundus lie ensheathed together
    • recovery of glide very difficult after injury

Stenosing Tenosynovitis (trigger finger/thumb)
• definition: inflammation and thickening of tendon or tendon sheath/pulley (most commonly at A-1 pulley near MCP), preventing smooth gliding of tendon through the sheath/pulley and resulting in locking of thumb or finger in flexion/extension
• etiology: idiopathic or associated with RA, DM, hypothyroidism, gout, and pregnancy
• clinical features
  • ring finger is most commonly affected, then long finger and thumb
  • patient complains of catching, snapping, or locking of affected finger
  • tenderness to palpation/nodule at palmar aspect of MCP over A-1 pulley
  • women are 4 times more likely to be affected than men
• non-surgical treatment
  • NSAIDs
  • steroid injection; injections less likely to be successful in patients >60 yr, or symptoms greater than 6 mo
  • splint
• surgical treatment
  • indicated if no relief of symptoms or minimal relief with steroids
  • incise A-1 flexor pulley to permit unrestricted, full active finger motion

Fractures and Dislocations
• for fracture principles, see Orthopedics, OR4

FRACTURES
• about 90% of hand fractures are stable in flexion (splint to prevent extension)
• position of safety
  • wrist extension 0-30°
  • MCP flexion 70-90°
  • IP full extension
  • this is done if you want to immobilize a fracture but are not sure whether there are other injuries
• stiffness secondary to immobilization is the most important complication; Tx = early motion

Distal Phalanx Fractures
• most commonly fractured bone in the hand
• usual mechanism is crush injury, and thus accompanied by soft tissue injury
• subungual hematoma is common and must be decompressed, especially if there is involvement of >50% of the nail surface area
• injury involving >50% of the nail surface area often suggests a nail bed laceration, in which the patient would benefit from nail plate removal and nailbed repair surgery
• treatment consists of 3 wk of digital splinting (immobilize the DIP with a STAX splint); if intra-articular fracture displaced >30%, then percutaneous pinning (K-wires) and splint

Proximal and Middle Phalanx Fractures
• check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit
• non-displaced or minimally displaced: closed reduction (if extra-articular), buddy tape to neighbouring stable digit, elevate hand, motion in guarded fashion early, splinted for 2-3 wk
• displaced, non-reducible, not stable with closed reduction, or rotational or scissoring deformity: percutaneous pinning (K-wires) or ORIF, and splint

Metacarpal Fractures
• generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
• Boxer’s fracture: acute angulation of the neck of the 5th metacarpal into palm
  • mechanism: blow on the distal-dorsal aspect of closed fist
  • loss of prominence of metacarpal head, volar displacement of head
  • up to 30-40° angulation may be acceptable
  • if greater angulation, closed reduction should be considered to decrease the angle
  • if stable, ulnar gutter splint for 4-6 wk
• Bennett’s fracture: two-piece fracture/dislocation of the base of the thumb metacarpal, usually intra articular
  • unstable fracture
  • APL pulls MC shaft proximally and radially, causing adduction of thumb
  • treat with percutaneous pinning or ORIF, followed by thumb spica x 6 wk
• Rolando fracture: T- or Y-shaped fracture of the base of the thumb metacarpal
  • treated like a Bennett’s fracture

DISLOCATIONS
• must be reduced as soon as possible
• dislocation vs. subluxation
  • dislocation: severe injury where articular surfaces of a joint are no longer in contact with one another
  • subluxation: articular surfaces of a joint are partially out of place (i.e. “partial dislocation” – often unstable and requires reduction)

PIP and DIP Dislocations (PIP more common than DIP)
• usually dorsal dislocation (commonly from hyperextension)
  if closed dislocation: closed reduction and splinting in position of function for 1 wk or buddy taping, and early mobilization (prolonged immobilization causes stiffness)
• open injuries are treated with wound care, irrigation, and debridement, followed by closed or open reduction and antibiotics

MCP Dislocations (relatively rare)
• dorsal dislocations much more common than volar dislocations
• dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
  • two types of dorsal dislocation
    • simple (reducible with manipulation): treat with closed reduction and splinting for 2-4 wk at 60-70° MCP flexion
    • complex (irreducible - most commonly due to volar plate blocking the reduction): treat with open reduction

Ulnar Collateral Ligament (UCL) Injury
• forced abduction of thumb (e.g. ski pole injury)
• Skier’s thumb: acute UCL injury – if stable, treated with splint x 6-8 wk; if unstable, patient may have Stener lesion
• Gamekeeper’s thumb: chronic UCL injury, often requires open repair and tendon graft for stabilization
• Stener Lesion: the distal portion of the UCL can detach and flip superficial to the adductor aponeurosis and will not appropriately heal – requires open repair
• evaluation: radially deviate thumb MCP joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion
**Dupuytren’s Disease**

**Definition**
- proliferative disorder of the palmar fascia, forming nodules (usually painless), fibrous cords, and flexion contractures at the MCP and interphalangeal joints
- flexor tendons not involved
- Dupuytren's diathesis: male sex, early age of onset, strong family history (autosomal dominant inheritance), involvement of multiple digits, bilateral involvement, and involvement of sites other than palmar aspect of hand, including the plantar fascia (Ledderhose’s) and the penis (Peyronie’s) – (see Urology, U30)

**Epidemiology**
- unusual in patients from African and Asian countries, high incidence in northern Europeans, men > women, often presents in 5th-7th decade of life; associated with but not caused by alcohol use, smoking, and DM

**Clinical Features**
- nodules, cords and contractures of MCP, PIP, DIP
- order of digit involvement (most common to least common) ring > little > long > thumb > index
- risk of recurrence

**Treatment**
- palmar pit or nodule: no surgery (steroid injections for pain) palpable band/cord with no limitation of extension (i.e. no contracture) of either MCP or PIP: no surgery
- MCP contracture >30 degrees or PIP contracture of any degree: needle aponeurotomy, collagenase injection, or surgical fasciectomy
- contractures impeding function and/or hygiene: needle aponeurotomy, collagenase injection, or surgical fasciectomy
- MCP joints have better outcomes than PIP joints post-treatment (achievement of near full extension, lower risk of recurrence)

**Carpal Tunnel Syndrome**

**Definition**
- median nerve compression at the level of the flexor retinaculum/transverse carpal ligament

**Etiology**
- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumours, hypertrophic synovial tissue, fracture callus, and osteophytes), metabolic and physiological (pregnancy, hypothyroidism, acromegaly, and RA); job/hobby related repetitive trauma, especially forced wrist flexion

**Epidemiology**
- female:male = 4:1, most common entrapment neuropathy

**Clinical Features**
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/rubbing
- on exam, sensory loss in median nerve distribution (see Figure 4), but thenar eminence sensory loss is spared (palmar cutaneous branch given off prior to carpal tunnel)
- decreased light touch and 2-point discrimination at DIP adial and ulnar creases; discriminative touch often lost first
- advanced cases: thenar wasting/weakness due to involvement of the motor branch of the nerve
- ± Tinel's sign (tingling sensation on percussion of nerve)
- ± Phalen's sign (wrist flexion induces symptoms)

**Investigations**
- clinical diagnosis
- NCV and EMG studies may be used to objectively confirm the diagnosis

**Treatment**
- avoid repetitive wrist and hand motion, wrist splints at night and when repetitive wrist motion required
- conservative: night-time splinting to keep wrist in neutral position
- medical: NSAIDs local corticosteroids injection (relief from local corticosteroid injections is also diagnostic)
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: persistent signs and symptoms of median nerve compression not relieved by conservative management
Brachial Plexus

Etiology
- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumours, ectopic ribs

Common Palsies

Table 22. Named Neonatal Palsies of the Brachial Plexus

<table>
<thead>
<tr>
<th>Palsy</th>
<th>Location of Injury</th>
<th>Mechanism of Injury</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne-Erb Palsy</td>
<td>Upper brachial plexus (C5-C6)</td>
<td>Head/shoulder distraction (e.g., motorcycle)</td>
<td>“Waiter’s tip deformity” (shoulder internal rotation, elbow extension and pronation, wrist flexion)</td>
</tr>
<tr>
<td>Klumpke’s Palsy</td>
<td>Lower brachial plexus (C7-T1)</td>
<td>Traction on abducted arm</td>
<td>“Claw hand” May include Horner’s syndrome</td>
</tr>
</tbody>
</table>

Differential Diagnosis of Adult-Acquired Brachial Plexus Palsies
- trauma (blunt, penetrating)
  - associated with large cervical rib, anomalous first rib, strenuous arm work, neck muscle hypertrophy
  - neurogenic: compression of brachial plexus, resulting in upper limb paresthesia, pain, and weakness
  - vascular: compression/thrombosis of subclavian artery/vein, resulting in pain; pallor and Raynaud’s if arterial; swelling and cyanosis if venous
- tumour
  - schwannoma: well-defined margins enable total resection
  - neurofibromas: associated with neurofibromatosis type I
  - other: e.g., Pancoast syndrome (apical lung tumour)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

Investigations
- EMG
- MRI: gold standard for identifying soft tissue masses and nerve roots
- CT myelogram: controversial, although some people think that it is better than MRI for identification of nerve root avulsion
- closed injuries: if avulsion suspected, then CT myelogram or MRI initially; otherwise, EMG/NCS 6-12 weeks post-injury to assess healing progress
- open injuries: OR for exploration within a few days post-injury (once patient stable)

Management

Table 23. Management of Brachial Plexus Injuries

<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed Injuries</td>
<td>Concussive/compressive Usually improves (unless expanding mass, e.g., hematoma)</td>
</tr>
<tr>
<td></td>
<td>Traction/stretch If no continued insult, follow for 3-4 mo for improvement</td>
</tr>
<tr>
<td></td>
<td>Obstetric palsy Surgery if no significant improvement and/or residual paresis at 6 mo of age</td>
</tr>
<tr>
<td>Open Injuries</td>
<td>Sharp or vascular injury Explore immediately in OR</td>
</tr>
</tbody>
</table>
Craniofacial Injuries

- low velocity vs. high velocity injuries determine degree of damage
- fractures cause bruising, swelling, and tenderness → loss of function
- management: most can wait ~5 d for swelling to decrease before ORIF required

Approach to Facial Injuries

- ATLS protocol
- inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve, bony injuries, septal hematoma, ocular involvement, etc.)
- tetanus prophylaxis
- radiological evaluation: CT scan with fine cuts through the orbit
- wound irrigation with NS/RL and remove foreign materials
- conservative debridement of detached or nonviable tissue
- repair at the time of presentation with 4-0 nylon sutures when the patient's general condition allows
- consider intracranial trauma; rule out skull fracture

Investigations

- CT (gold standard)
  - axial and coronal (specifically request 1.5 mm cuts): for fractures of upper and middle face, as well as mandible
  - indicated for significant head trauma, suspected facial fractures, pre-operative assessment
- panorex radiograph: shows entire upper and lower jaw; best for isolated mandible fracture, but patient must be able to sit; however, if high clinical suspicion and negative panorex, CT should be done

Treatment Goals

- consultation when indicated (dentistry, ophthalmology)
- re-establish normal occlusion if occlusion is an issue
- normal eye function (extraocular eye movements and vision)
- restore stability of face and appearance

Mandibular Fractures

- two points of injury since it is a ring structure (includes fractures and dislocations)
- commonly at sites of weakness (condylar neck, angle of mandible)

Etiology

- anterior force: bilateral fractures
- lateral force: ipsilateral subcondylar and contralateral angle or body fracture
- note: classified as open if fracture into tooth bearing area (alveolus)

Clinical Features

- pain, swelling, difficulty opening mouth ("trismus")
- malocclusion, asymmetry of dental arch
- damaged, loose, or lost teeth
- palpable "step" along mandible
- numbness in V3 distribution
- intra-oral lacerations or hematoma (sublingual)
- chin deviating toward side of a fractured condyle

Classification

Table 24. Mandibular Fracture Classifications by Anatomic Region

<table>
<thead>
<tr>
<th>Areas/Boundaries</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symphysis</td>
<td>Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible</td>
</tr>
<tr>
<td>Body</td>
<td>From the symphysis to the distal alveolar border of the third molar</td>
</tr>
<tr>
<td>Angle</td>
<td>Triangular region between the anterior border of the masseter and the posterosuperior insertion of the masseter distal to the third molar</td>
</tr>
<tr>
<td>Ramus</td>
<td>Part of the mandible that extends posterosuperiorly into the condylar and coronoid processes</td>
</tr>
<tr>
<td>Condylar*</td>
<td>Area of condylar process of mandible</td>
</tr>
<tr>
<td>Subcondylar</td>
<td>Area below the condylar neck (i.e. sigmoid notch) of the mandible</td>
</tr>
<tr>
<td>Coronoid Process</td>
<td>Area of the coronoid process of mandible</td>
</tr>
</tbody>
</table>

*Most common mandibular fracture type

Signs of Basal Skull Fracture

- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (peri orbital bruising)
- CSF otorrhea/rhinorrhea

Patients with major facial injuries are at risk of developing upper airway obstruction (displaced blood clots, teeth, or fracture fragments; swelling of pharynx and larynx; loss of support of hyomandibular complex → retrusion of tongue); also at risk of ocular injury.

Figure 27. Mandibular fracture
Treatment
- maxillary and mandibular arch bars wired together (intramaxillary fixation) or ORIF ideally managed within 48 h as indicated by best current evidence
- antibiotics from initial presentation until at least 3 doses post-operatively; if late presentation, may consider treatment with antibiotics for an extended course

Maxillary Fractures

Table 25. Le Fort Classification

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Structures Involved</th>
<th>Anatomical Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Fort I</td>
<td>Maxillary sinus</td>
<td>Maxilla divided into 2 segments</td>
</tr>
<tr>
<td>Le Fort II</td>
<td>Pterygoid plates</td>
<td>Maxillary teeth and midsection of the maxilla separated from upper face</td>
</tr>
<tr>
<td>Le Fort III</td>
<td>Pterygoid plates</td>
<td>Detach entire midfacial skeleton from cranial base</td>
</tr>
</tbody>
</table>

Nasal Fractures

Etiology
- lateral force \(\rightarrow\) more common, good prognosis
- anterior force \(\rightarrow\) can produce more serious injuries
- most common facial fracture

Clinical Features
- epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum; crepitis, septal hematoma, respiratory obstruction, subconjunctival hemorrhage

Treatment
- treated for airway or cosmetic issues
- always inspect for and drain septal hematoma as this is a cause of septal necrosis and perforation – completed in the ER with small incision in the septal mucosa followed by packing
- closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with petroleum or nonadhesive gauze packing, nasal splint for 7 d
- best reduction immediately (<6 h) or when swelling subsides (5-7 d)
- rhinoplasty may be necessary later for residual deformity (30%)

Zygomatic Fractures

Classification
1. fracture restricted to zygomatic arch
2. depressed fracture of zygomatic complex (zygoma)
3. unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone, and orbital rim

Clinical Features
- 3 most common features (pathognomonic):
  - subconjunctival hemorrhage
  - periorbital ecchymosis (often associated with fractures of the orbital floor)
  - V2 numbness (infraorbital and superior dental nerves)
- flattening of malar prominence (view from above)
- pain over fractures on palpation
- palpable step deformity in bony orbital rim (especially inferiorly)
- ipsilateral epistaxis; trismus
- ophthalmologic evaluation if suspected globe injury

Treatment
- if undisplaced, stable, and no symptoms, then soft diet; no treatment necessary
- undisplaced zygomatic arch fractures can be elevated using Gillies approach (leverage on the anterior part of the zygomatic arch via a temporal incision) or Keane approach (elevation through upper buccal sulcus incision) only if arch is not comminuted
- if arch is comminuted, ORIF is required
- stabilization often unnecessary
- ORIF for displaced or unstable fractures of zygomatic complex
Orbital Floor Fractures

- see Ophthalmology, OP40

Definition
- fracture of floor of orbit: may be a "pure blow-out fracture", which has an intact orbital rim, or can be associated with other fractures (orbital rim fracture and/or zygoma)

Etiology
- blunt force to eyeball → sudden increase in intraorbital pressure (e.g. baseball or fist)

Clinical Features
- check visual fields and visual acuity for injury to globe
- periorbital edema and bruising, subconjunctival hemorrhage
- ptosis, exophthalmos, exorbitis, enophthalmos, or hypoglobus
- orbital rim step-offs with possible infraorbital nerve anesthesia
- vertical dystopia (abnormal displacement of the entire orbital cone in the vertical plane) – assessed by comparing the symmetry of the two pupils by a horizontal line running through the pupil of the unaffected eye
- orbital entrapment
  - clinical diagnosis that is a surgical emergency
  - diplopia with straight gaze: unable to look up or down (entrapment of inferior rectus), limited EOM
  - severe pain or nausea and vomiting with upward globe movement
  - requires urgent ophthalmology evaluation if there are associated visual acuity changes

Investigations
- CT (diagnostic): axial and coronal views – with fine cuts through orbit
- diagnostic maneuver for entrapment is forced duction test (pulling on inferior rectus muscle with forceps to ensure full ROM) under local anesthesia in the OR

Treatment
- surgical repair indicated if: entrapment (urgent), any size defect with enophthalmos (if patient is bothered by it) or persistent diplopia (>10 d)
- reconstruction of orbital floor with bone graft or alloplastic material
- after repair, assess for diplopia: may require additional surgery for strabismus

Complications
- persistent diplopia
- enophthalmos

Superior Orbital Fissure Syndrome
- fracture of SOF causing ptosis, proptosis, anesthesia in V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, VI)
- uncommon complication seen in Le Fort II and III fractures (1/130)
- recovery time reported as 4.8-23 wk following operative reduction of fractures

Orbital Apex Syndrome
- fracture through optic canal with involvement of CN II at apex of orbit
- symptoms are the same as SOF syndrome plus vision loss
- treatment is urgent decompression of fracture in optic canal (posterior craniotomy for decompression) or steroids
Breast

Anatomy

Vascular Supply

- Thoracodorsal artery
- Thoracolumbar artery
- Thoracoacromial artery
- Subclavian artery
- Axillary artery
- Lateral thoracic artery
- Internal thoracic artery
- Anterolateral intercostal perforators
- Medial intercostal perforators
- Internal thoracic perforating branches

Innervation

- Innervated in a dermatomal pattern from branches of the thoracic intercostal nerves (T3-6)
- Medially innervated from anterior cutaneous branches of I-VI intercostal nerves
- Laterally innervated from lateral cutaneous nerve branches of II-VII intercostal nerves
- Laterally and upper portions of the breast innervated by lower fibres of the cervical plexus (C3, C4)
- Nipple areolar complex (NAC)
  - Supplied by anterior and lateral cutaneous branches of intercostal nerve IV
  - Additional innervation by cutaneous branches of intercostal nerves III and VI

Breast Reduction

Indications

- Symptomatic (general symptoms)
  - Musculoskeletal pain (back, strap, neck), chronic headache, paresthesia in upper limb, rash under the breast, breast discomfort and physical impairment
- Breast reduction methods can be classified based on pedicle (i.e. blood supply to the nipple/areolar complex) and skin resection pattern (i.e. the resultant scar)
Table 26. Common Types of Pedicles

<table>
<thead>
<tr>
<th>Pedicle Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inferior Pedicle</strong></td>
</tr>
<tr>
<td>Most commonly used technique; versatile use in small-large breast reduction</td>
</tr>
<tr>
<td>Critiqued for boxy shape breast along with more extensive scarring (wise pattern skin resection)</td>
</tr>
<tr>
<td>Recommended pedicle width 6-8 cm, 8-10 cm in large breasts</td>
</tr>
<tr>
<td><strong>Superior Pedicle</strong></td>
</tr>
<tr>
<td>Pedicle derived from the internal mammary perforator of the second intercostal space</td>
</tr>
<tr>
<td>Must be thinned to permit inset</td>
</tr>
<tr>
<td><strong>Medial Pedicle</strong></td>
</tr>
<tr>
<td>Modified from horizontal bi-pedicle (Strombeck) techniques</td>
</tr>
<tr>
<td>Blood supplied from internal mammary perforator from third intercostal and potentially fourth intercostal space</td>
</tr>
<tr>
<td><strong>Superomedial Pedicle</strong></td>
</tr>
<tr>
<td>Incorporate the descending artery from second intercostal space as medial pedicle base extended superolaterally to breast meridian</td>
</tr>
</tbody>
</table>

Table 27. Type of Skin Resections/Scar Options

<table>
<thead>
<tr>
<th>Indications</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inverted T Pattern</strong></td>
<td>Commonly used in association with inferior pedicle</td>
</tr>
<tr>
<td>Large breasts</td>
<td>Large portion of skin removed in horizontal and vertical direction</td>
</tr>
<tr>
<td>Breasts with poor quality skin that are challenging to remodel</td>
<td>Skin integrity important to shape and hold breast parenchyma</td>
</tr>
<tr>
<td><strong>Vertical Pattern</strong></td>
<td>Used in association with superior or medial pedicle</td>
</tr>
<tr>
<td>Skin must be healthy and easy to remodel</td>
<td>Parenchyma needed to shape skin</td>
</tr>
<tr>
<td></td>
<td>No horizontal scar</td>
</tr>
<tr>
<td></td>
<td>Small to moderate reductions</td>
</tr>
</tbody>
</table>

Complications
- NAC necrosis
- sensory alteration of nipple (may vary with type of reduction pattern)
- unsatisfactory scarring, including hypertrophic or keloid scar
- wound healing complications (1-3% in healthy patients, higher in patients with elevated BMI)
- difficulty breastfeeding (potential issue in women of childbearing age)
- asymmetry
- hematoma
- wound infection
Mastopexy (Breast Lift)

Definition
- aesthetic procedure of the breast used to correct for breast ptosis by modifying the contour and size of the breast along with elevating the position of the nipple

Clinical Grading of Ptosis (Regnault Ptosis Grade Scale)
1. minor ptosis (1st degree)
   - nipple at inframammary fold
2. moderate ptosis (2nd degree)
   - nipple below inframammary fold, but above lower breast contour
3. severe ptosis (3rd degree)
   - nipple below inframammary fold and at lower breast contour
4. glandular ptosis
   - nipple above inframammary fold, but breast hangs below fold
5. pseudoptosis
   - nipple above inframammary fold, but breast is hypoplastic and hangs below the fold

Table 28 Type of Skin Resection/Scar Options

<table>
<thead>
<tr>
<th>Type of Skin Resection/Scar Options</th>
<th>Indications</th>
<th>Description</th>
</tr>
</thead>
</table>
| Circumareolar Mastopexy            | Nipple located 1-2.5 cm too low | Originally described as “donut mastopexy”
|                                    |             | Reduce areolar diameter while simultaneously raising nipple (<2 cm)
|                                    |             | Can correct nipple position asymmetry when used unilaterally
|                                    |             | Also increase infra-areolar skin display in ptotic breasts |
| Vertical Mastopexy                 | Grade I - III ptosis | Larger removal than circumareolar
|                                    |             | Raises nipple position and reduces circumareolar skin tension |
|                                    |             | Larger angle between vertical limb and limb length increases with more lower pole skin |
| Inverted T Mastopexy               | Most effective in grade II to III ptosis caused by skin excess attributed to large weight loss | Facilitate nipple elevation and parenchymal redistribution, fixation, and autoaugmentation techniques |
|                                    |             | Large removal of skin in return for greater scar burden |

- mastopexy can be performed through the same incisions as breast reductions

Breast Augmentation

Definition
- procedure designed to increase the size of the breast

Choice of Incision
- position of incision individualized since no single incision is best for all
- 3 commonly used types of incision: periareolar, inframammary crease, transaxillary

Type of Implant
- silicone or saline-filled
- subclassified into various styles of surface and shape

Location of Implant
- implants are commonly placed in the following positions:
  1. submuscular positions
     - implant placed below pectoralis major muscle
     - most commonly in patients that do not have enough tissue to cover the implant
  2. subglandular position
     - implant placed deep to glandular breast tissue but superficial to muscle
  3. subfascial
     - implant placed below the fascia
Gynecomastia

Definition
- benign enlargement of the male breast due to proliferation of the glandular tissue

Clinical Classification
- gynecomastia can be further classified into:
  1. idiopathic
  2. physiologic
     - neonatal: circulating maternal estrogens via placenta
     - pubertal: relative excess of plasma estradiol versus testosterone
     - elderly: decrease circulating testosterone, peripheral aromatization of testosterone to estrogen
  3. pathologic
     - endocrinopathies: excess estrogen, androgen deficiency, deficient production or action of testosterone
     - tumours
     - chronic disease: liver cirrhosis, renal
     - congenital/genetic: Klinefelter's syndrome, androgen resistance
  4. pharmacologic
     - drugs that may interfere with estrogen-testosterone balance including:
       - hormones (estrogens, gonadotropins, exogenous steroids)
       - antiandrogens
         - androgen receptor antagonists (steroidal and non-steroidal)
         - androgen synthesis inhibitors (5a-reductase inhibitors)
         - antagonidrotropins (GnRH analogs, estrogens)
       - recreational drugs (marijuana, heroin, amphetamines)
       - antihypertensives (spironolactone)
  5. massive weight gain
     - for physical exam, investigations, and medical management (see Endocrinology, E47)

Surgical Options
- surgery is the accepted management for gynecomastia
- surgery addresses the three components (breast, fat, skin)
- often involves a combination of liposuction (to remove the fatty portion) and surgical excision through a small periareolar incision (to remove the glandular component)
- patients with significant skin excess may require skin excision as well

Breast Reconstruction
- reconstruction of the breast after cancer or trauma to recreate the breast which is similar to the contralateral breast
- reconstruction can be performed immediately (at the same time as mastectomy), or delayed (as a separate surgery months or years after initial surgery)
- there are alloplastic and autogenous methods of reconstruction, each with its advantages and disadvantages

Table 29. Timing of Immediate Reconstruction vs. Delayed Reconstruction

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Reconstruction</td>
<td>Generally best aesthetic outcome; may possibly preserve nipple if oncologically advisable</td>
</tr>
<tr>
<td></td>
<td>Skin viability assessment can be compromised</td>
</tr>
<tr>
<td></td>
<td>Does not require creation of additional skin</td>
</tr>
<tr>
<td></td>
<td>Longer surgical time</td>
</tr>
<tr>
<td></td>
<td>Tissues are not damaged from scarring</td>
</tr>
<tr>
<td></td>
<td>Less time for patient to consider surgical options</td>
</tr>
<tr>
<td></td>
<td>Breast tissue retains size and shape of original breast</td>
</tr>
<tr>
<td></td>
<td>Loss of skin, volume, lateral border or breast and natural landmarks, including IMF</td>
</tr>
<tr>
<td></td>
<td>More time for patients to discuss surgical options</td>
</tr>
<tr>
<td></td>
<td>Resection of irradiated/scarred skin and associated wound healing complications, including risk of reconstructive failure</td>
</tr>
<tr>
<td>Delayed Reconstruction</td>
<td>Best for patients unable or unwilling to have immediate reconstruction</td>
</tr>
<tr>
<td></td>
<td>Likely requires more stages for completion</td>
</tr>
<tr>
<td>For patients who may be getting radiotherapy and undetermined post-surgery oncologic treatment</td>
<td>Provides option of contralateral surgery with reconstruction, if required (i.e. contralateral cancer)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 30. Alloplastic Reconstruction vs. Autogenous Reconstruction

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alloplastic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstruction</td>
<td>One stage reconstruction with implant</td>
<td>Shorter surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May give a more complete or final result</td>
</tr>
<tr>
<td></td>
<td>Two stage reconstruction with expander and implant</td>
<td>Size restriction in reconstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very few women meet criteria: grade 1 ptosis, small breast, skin-sparing mastectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires post-surgical procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(requires patient to come to clinic for inflations)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Size of reconstruction limited to size and vascularity of mastectomy flaps</td>
</tr>
<tr>
<td><strong>Autogenous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstruction</td>
<td>Latissimus Dorsi Flap</td>
<td>Reliably pedicle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uses patient’s own tissues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provides skin and muscles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible to do muscle sparing procedure without flap compromise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provides good amount of skin and muscle for reconstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good option for delayed reconstruction, larger women and to avoid complications using abdominal wall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May also require implants for adequate volume</td>
</tr>
<tr>
<td></td>
<td>TRAM (Transverse Rectus Abdominis Muscle) Flap</td>
<td>Second scar with second surgical site</td>
</tr>
<tr>
<td></td>
<td>Pedicled</td>
<td>Volume depends on patient’s donor site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pedicled TRAM: Weakness in rectus abdominis with higher bulge rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Free TRAM: Similar complications to DIEPs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less muscle used, decreased risk of hematomas or bulge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May not always be possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal scarring and second wound</td>
</tr>
<tr>
<td></td>
<td>DIEP (Deep Inferior Epigastric Perforator) Flap</td>
<td>Method sparing rectus abdominis muscle and should theoretically preserve innervation and continuity of abdominal wall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires microsurgical training for meticulous dissection of flap and appropriate choice of perforator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May not always be possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal scars and second wound</td>
</tr>
</tbody>
</table>

Nipple Areolar Complex Reconstruction

- nipple reconstruction is usually done as the final step when the patient is satisfied with breast mound creation
- reconstruction can be performed with local anesthetic since many women have decreased sensation in the mastectomy or breast flaps
- it can be done by either a flap, graft, or 3D tattoo

Table 31. Types of Nipple Reconstruction

<table>
<thead>
<tr>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skate flap</td>
<td>Pedicle elevated above breast mound</td>
<td>Low complication rates</td>
</tr>
<tr>
<td></td>
<td>Lateral aspects of flap are wrapped around central aspect of flap</td>
<td>Donor site morbidity</td>
</tr>
<tr>
<td></td>
<td>Defect mainly closed by skin graft</td>
<td>May have loss of projection over time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin graft required</td>
</tr>
<tr>
<td>CV flap</td>
<td>Utilizes C flap and two V flaps for nipple reconstruction</td>
<td>No grafts required</td>
</tr>
<tr>
<td></td>
<td>Diameter of C flap becomes diameter of reconstructed nipple</td>
<td>Nipple size limited by flap dimensions</td>
</tr>
<tr>
<td></td>
<td>Width of V flaps dictate projection of reconstructed nipple</td>
<td>May have loss of projection over time</td>
</tr>
<tr>
<td></td>
<td>CV closed with primary closure</td>
<td>Tattooing required to match natural areola</td>
</tr>
<tr>
<td>Nipple graft</td>
<td>Tissue commonly from contralateral nipple (nipple share) or labia</td>
<td>Nipple share is an excellent option in patients with contralateral nipple projection &gt; 1 cm</td>
</tr>
<tr>
<td></td>
<td>Two methods for nipple graft:</td>
<td>Donor site morbidity</td>
</tr>
<tr>
<td></td>
<td>• Distal aspect of nipple removed transversely and</td>
<td>Decreased contralateral nipple sensation</td>
</tr>
<tr>
<td></td>
<td>• Defect closed with purse string suture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nipple divided in half longitudinally, folded over, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>closed with primary closure</td>
</tr>
</tbody>
</table>
Table 32. Types of Areolar Reconstruction

<table>
<thead>
<tr>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tattoo</td>
<td>Conducted 3-4 months after nipple reconstruction when most of the projection has stabilized</td>
<td>Can provide more accurate colour matching</td>
</tr>
<tr>
<td>Skin graft</td>
<td>Full thickness skin grafts, commonly from inner aspect of thigh or opposite areola</td>
<td>Provides texture and pigment resembling a natural areola</td>
</tr>
</tbody>
</table>

* Tattoo and skin grafting can be used in conjunction

Aesthetic Surgery

Aesthetic Procedures

<table>
<thead>
<tr>
<th>Location</th>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/Neck</td>
<td>Hair transplants</td>
<td>Aesthetic improvement of hair growth patterns using hair follicle grafts or flaps</td>
</tr>
<tr>
<td></td>
<td>Otoplasty</td>
<td>Surgical correction of protruding ears</td>
</tr>
<tr>
<td></td>
<td>Forehead/Brow lift</td>
<td>Surgical procedure to lift the forehead and eyebrows</td>
</tr>
<tr>
<td></td>
<td>Rhinoplasty</td>
<td>Surgical procedure to reduce wrinkling and sagging of the face and neck; “face lift”</td>
</tr>
<tr>
<td></td>
<td>Blepharoplasty</td>
<td>Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin ± fat pads</td>
</tr>
<tr>
<td></td>
<td>Rhinoplasty</td>
<td>Surgical reconstruction of the nose ± nasal airway</td>
</tr>
<tr>
<td></td>
<td>Genioplasty</td>
<td>Chin augmentation via osteotomy or synthetic implant to improve contour</td>
</tr>
<tr>
<td>Skin</td>
<td>Chemical peel</td>
<td>Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration</td>
</tr>
<tr>
<td></td>
<td>Dermabrasion</td>
<td>Skin resurfacing with a rapidly rotating abrasive tool; often used to reduce scars, irregular skin surfaces, and fine lines</td>
</tr>
<tr>
<td></td>
<td>Laser resurfacing</td>
<td>Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening; often used to reduce scars and wrinkles</td>
</tr>
<tr>
<td></td>
<td>Injectable fillers</td>
<td>An injectable substance is used to decrease facial rhytids; can augment lips to create fuller appearance; substances include: collagen, fat, hyaluronic acid, and calcium hydroxyapatite (most common substances include hyaluronic acid and fat)</td>
</tr>
<tr>
<td>Other</td>
<td>Abdominoplasty</td>
<td>Removal of excess skin and repair of rectus muscle laxity (rectus diastasis); ‘tummy tuck’</td>
</tr>
<tr>
<td></td>
<td>Calf augmentation</td>
<td>Augmentation of calf muscle with implants</td>
</tr>
<tr>
<td></td>
<td>Liposuction</td>
<td>Surgical removal of adipose tissue for body contouring (not a weight loss procedure)</td>
</tr>
</tbody>
</table>

Pediatric Plastic Surgery

Craniofacial Anomalies

Table 34. Pediatric Craniofacial Anomalies

<table>
<thead>
<tr>
<th>Definition</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft Lip</td>
<td>Failure of fusion of maxillary and medial nasal processes</td>
<td>1 in 1000 live births (1 in 800 Caucasians, increased in Asians, decreased in Blacks) M:F = 2:1</td>
<td>Classified as incomplete/complete and uni/bilateral; 2/3 cases: unilateral, left-sided, male</td>
</tr>
<tr>
<td>Cleft Palate</td>
<td>Failure of fusion of lateral palatine/median palatine processes and nasal septum</td>
<td>Isolated cleft palate: 0.5 per 1000 (no racial variation) F &gt; M</td>
<td>Classified as incomplete/complete and uni/bilateral</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>Premature fusion of ≥1 cranial sutures</td>
<td>1 in 2000 live newborns; M:F = 52:48 Syndromes include: Crouzon’s, Apert’s, Saeftie-Chotzen Carpenter’s, Pfeiffer’s, Jackson-Weiss, and Boston-type syndromes</td>
<td>Primary (no known cause), or secondary (associated with a known cause or syndrome)</td>
</tr>
</tbody>
</table>
## Table 35. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of Formation</td>
<td>Transverse absence (congenital amputation)</td>
<td>At any level (often below elbow/wrist)</td>
<td>Early prosthesis</td>
</tr>
<tr>
<td></td>
<td>Longitudinal absence (phocomelia)</td>
<td>Absent humerus Thalidomide association</td>
<td>Physiotherapy + splinting Soft tissue release if splinting fails Distraction osteogenesis (Ilizarov) ± wedge osteotomy Tendon transfer Pollicization</td>
</tr>
<tr>
<td></td>
<td>Radial deficiency (radial club hand)</td>
<td>Radial deviation Thumb hypoplasia M&gt;F</td>
<td>Distraction osteogenesis (Ilizarov) ± wedge osteotomy Tendon transfer Pollicization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thumb hypoplasia</td>
<td>Degree ranges from small thumb with all components to complete absence</td>
<td>Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger</td>
</tr>
<tr>
<td></td>
<td>Ulnar club hand</td>
<td>Rare, compared to radial club hand Stable wrist</td>
<td>Splinting and soft tissue stretching therapies Soft tissue release (if above fails) Correction of angulation (Ilizarov distraction)</td>
</tr>
<tr>
<td></td>
<td>Cleft hand</td>
<td>Autosomal dominant Often functionally normal (depending on degree)</td>
<td>First web space syndactyly release Osteotomy/tendon transfer (if hypoplastic)</td>
</tr>
<tr>
<td>Failure of Differentiation/ Separation</td>
<td>Syndactyly</td>
<td>Fusion of ≥2 digits 1/3,000 live births M:F = 2:1 Classified as partial/complete Simple (skin only) vs. complex (osseous or cartilaginous bridges)</td>
<td>Surgical separation before 6-12 mo of age Usually good result May require a skin graft to cover the fingers</td>
</tr>
<tr>
<td></td>
<td>Symbrachydactyly</td>
<td>Short fingers with short nails at fingertips</td>
<td>Digital separation Webspace deepening</td>
</tr>
<tr>
<td></td>
<td>Camptodactyly</td>
<td>Congenital flexion contracture (usually at PIP especially 5th digit)</td>
<td>Early splinting Volar release Arthroplasty (rarely)</td>
</tr>
<tr>
<td></td>
<td>Clinodactyly</td>
<td>Radial or ulnar deviation Often middle phalanx</td>
<td>None (usually); if severe, osteotomy with grafting</td>
</tr>
<tr>
<td>Duplication</td>
<td>Polydactyly</td>
<td>Congenital duplication of digits May be radial (increased in Aboriginais and Asians) or central or ulnar (increased in Blacks)</td>
<td>Amputation of least functional digit Usually &gt;1 yr of age (when functional status can be assessed)</td>
</tr>
<tr>
<td>Overgrowth</td>
<td>Macrodactyly</td>
<td>Rare</td>
<td>None (if mild) Soft tissue/bony reduction</td>
</tr>
<tr>
<td>Undergrowth</td>
<td>Brachydactyly</td>
<td>Short phalanges</td>
<td>Removal of nonfunctional stumps Osteotomies/tendon transfers Distraction osteogenesis Phalangeal/free toe transfer</td>
</tr>
<tr>
<td></td>
<td>Symbrachydactyly</td>
<td>Short webbed fingers</td>
<td>As above + syndactyly release</td>
</tr>
<tr>
<td></td>
<td>Brachysyndactyly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constriction Band Syndrome</td>
<td>i.e. amniotic (annular) band syndrome</td>
<td>Variety of presentations</td>
<td>Urgent release for acute, progressive edema distal to band in newborn Other reconstruction is case specific</td>
</tr>
<tr>
<td>Generalized Skeletal Abnormality</td>
<td>Achondroplasia, Marfan’s, Madelung’s</td>
<td>Variety of presentations</td>
<td>Treatment depends on etiology</td>
</tr>
</tbody>
</table>
References

Acronyms ................................................. 2
Public Health Context ............................... 2
Public Health Services in Canada
Legislation and Public Health in Canada
Determinants of Health ............................. 3
Concepts of Health
Vulnerable Populations
Disease Prevention
Measurements of Health and Disease in a Population ............................. 7
Epidemiology ............................................ 8
Interpreting Test Results
Effectiveness of Interventions
Types of Study Design ............................... 11
Qualitative vs Quantitative
Observational Study Designs
Experimental Study Designs
Summary Study Designs
Methods of Analysis ............................... 14
Distributions
Data Analysis
Common Statistical Tests
Causation
Assessing Evidence
Health Services Research ......................... 17
Continuous Quality Improvement
Cost Analysis
Outbreak of Infectious Diseases ................. 18
Definitions
Steps to Control an Outbreak
Infection Control Targets
Environmental Health ............................. 20
Risk Assessment
Air
Water
Soil
Food
Occupational Health ............................... 23
Taking an Occupational Health History
Occupational Hazards
Workplace Legislation
Workplace Health Promotion and Protection
Workplace Disease Prevention and Identification
Workplace Treatment and Rehabilitation
Appendix – Mandatory Reporting ............... 24
Reportable Diseases
Other Reportable Conditions
References ............................................. 26

For more detail on topics covered in this chapter, use website http://phprimer.afmc.ca/ as a resource
Public Health Context

- see Ethical, Legal, and Organizational Medicine, ELOM2 Overview of Canadian Healthcare System for the organization of health care in Canada including the legal foundation and historical context

Definitions

- population health
  - refers to the health of defined groups of people, their health determinants, trends in health, and health inequalities
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; health care services
  - broader scope vs. public health, accounts for socio-economic, policy, historical issues

- public health
  - "efforts organized by society to protect, promote, and restore the peoples’ health" and prevent morbidity and mortality
  - refers to the practices, programs, policies, institutions, and disciplines required to achieve the desired state of population health

- epidemiology
  - "study of the distribution […] of determinants of disease, health-related states, and events in populations" 

- public health and preventive medicine (formerly called community medicine)
  - the postgraduate study of health and disease in the population or a specified community
  - 5 year Royal College specialty training
  - goal: to identify and address health problems and evaluate the extent to which health services and others address these issues


Public Health Services in Canada

Mission: to promote and protect the health of Canadians through leadership, partnership, innovation, and action in public health (Public Health Agency of Canada)

- local public health units and services within regional health authorities (in most provinces except Ontario, where local public health units are either autonomous or within local government) provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range widely (100s–1,000,000s), covering areas of 15 km² to 1.5 million km²
- the "core functions" of public health include six essential activities (The Organization of Health Services in Canada. AFMC Primer on Population Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003.): preparing for the LMCC

Preparing for the LMCC

- the AFMC Primer on Population Health is the core text for the LMCC and is available as an online resource on the AFMC website (http://phprimer.afmc.ca)
- For the LMCC exam, it is recommended that you also read Chapter 15 in Shah CP. Public health and preventive medicine in Canada, 5th ed. Toronto: Elsevier, 2003.

Historical Perspective

Over the last century, Public Health has evolved through three main epidemiological phases:

- Infectious diseases: controlled in the more developed world but an issue in less developed countries (e.g. polio, malaria)
- Chronic diseases: chronic diseases and other noncommunicable conditions have increased morbidity and mortality (e.g. heart disease and cancer due to risk factors and/or exposures)
- Re-emerging infectious diseases: new or re-emergent infections emerge due to unfamiliar or new pathogens, inefficient or inappropriate antibiotic use, travel, and global warming (e.g. HIV, drug resistant TB and malaria)


The Association of Faculties of Medicine of Canada Public Health Educators’ Network. The Organization of Health Services in Canada. AFMC Primer on Population Health.
### Legislation and Public Health in Canada

#### Table 1. Legislation and Public Health in Canada

<table>
<thead>
<tr>
<th>Federal</th>
<th>Provincial</th>
<th>Municipal (Ontario)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Provides health services to First Nations, Aboriginal peoples, the Canadian military, and veterans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Approves new drugs and medical devices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian Food Inspection Agency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Monitors food products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Deals with animal-related infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Regulates food labeling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public Health Agency of Canada (main Government of Canada agency responsible for public health)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• An independent body created to strengthen public health capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Focuses on preventing chronic diseases preventing injuries, and responding to public health emergencies and infectious disease outbreaks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oversees immigration screening, protects Canadian borders (e.g. airport health inspection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Liaises with the World Health Organization (WHO) on global health issues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legislation is in the form of Acts and Regulations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Each province has its own Public Health Act or equivalent (e.g. the Health Protection and Promotion Act in Ontario)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Designates the creation of geographic areas for the provision of public health services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gives powers to the Chief Medical Officer of Health to control public health hazards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Specifies infectious diseases to be reported to public health units by physicians, laboratories, and hospitals (see Appendix, PH24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Has the ability to mandate programs that address public health issues, environmental health, and chronic disease prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local boards of health deliver programs mandated by provincial and municipal or regional legislation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boards of health are responsible for the delivery of most public health services, such as:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Infectious disease control, including the follow up of reported diseases and management of outbreaks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inspection of food premises including those in hospitals, nursing homes, and restaurants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Family health services including pre-conception, preschool, school-aged, and adult health programs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tobacco control legislation enforcement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Assessment and management of local environmental health risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Collection and dissemination of local health status reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Public dental health services to children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• By-laws may be approved by municipal governments to facilitate public health issues</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Determinants of Health

#### Concepts of Health

- **wellness:** “state of dynamic physical, mental, social, and spiritual well-being that enables a person to achieve full potential and have an enjoyable life”
- **disease:** “abnormal, medically-defined changes in the structure or function of the human body”
- **illness:** “an individual’s experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles”
- **illness behaviour:** an individual’s actions resulting from and responding to their illness, including their interactions or avoidance of the health care system
- **sickness:** views the individual and their society hold towards a health condition, affecting their thoughts and actions
- **impairment:** “any loss or abnormality of psychological, physiological, or anatomical structure or function”
- **disability:** “any restriction or lack of ability to perform an activity within the range considered normal for a human being”
- **handicap:** a disadvantage for an individual arising due to impairment or disability
- **health:** “the ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not merely the absence of disease or infirmity”

#### Definitions of Health

- **First multidimensional definition of health, as defined by the WHO in 1948:** “state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”
- **WHO updated the definition (socio-ecological definition) of health in 1986:** “The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasising social and personal resources, as well as physical capacities”
- **Ottawa Charter for Health Promotion**
- **Other definitions of health have since been proposed that incorporate other dimensions of health (e.g. “Health is a social, economic, and political issue and above all a fundamental human right” – The People’s Charter for Health)**

#### Determinants of Health

- **1974:** The Honourable Marc Lalonde, federal Minister of Health, publishes *A New Perspective on the Health of Canadians* which outlines four factors that determine health: “human biology, environment, lifestyle, and health care organizations.” The idea of determinants of health has since been expanded and refined to include many additional factors

Sources:
- Aspc.gc.ca/ph-sp/determinants/determinants-eng.php
- Toronto Notes 2018
### Table 2. Health Determinants of Vulnerable Populations

<table>
<thead>
<tr>
<th>Definition</th>
<th>Psychosocial/Socioeconomic</th>
<th>Physical</th>
<th>Environment</th>
<th>Individual Behaviour</th>
<th>Population-Specific Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aboriginal Peoples</strong></td>
<td>Four specific groups: First Nations Status Indians (registered under the Indian Act), non-Status Indians, Métis, and Inuit</td>
<td>Low income</td>
<td>Crowded housing</td>
<td>Smoking</td>
<td>Mental health awareness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family violence</td>
<td>Inefficient ventilation</td>
<td>Substance misuse</td>
<td>Aboriginal-specific DM initiatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low education status</td>
<td>Environmental toxins (botulism)</td>
<td>Excessive gambling</td>
<td>Substance abuse treatment programs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unemployment</td>
<td>TB declining</td>
<td>Poor nutrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homelessness</td>
<td>but prevalence higher than rest of population</td>
<td>Sedentary lifestyle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Longer length of disability</td>
<td></td>
<td>High BMI</td>
<td></td>
</tr>
<tr>
<td><strong>Isolated Seniors</strong></td>
<td>Individuals &gt;65 yr</td>
<td>Elder abuse</td>
<td>Low hazard tolerance</td>
<td>Aging in place of choice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of emotional support</td>
<td>Institutionalization</td>
<td>Falls and injury prevention</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isolation</td>
<td>Mobility issues</td>
<td>Mental health promotion</td>
<td></td>
</tr>
<tr>
<td><strong>Children in Poverty</strong></td>
<td>Based on Low Income Cut Offs (LICO) LICO is an income threshold below which a family will likely devote a larger share of its income on the necessities of food, shelter and clothing than the average family</td>
<td>Low income</td>
<td>Housing availability</td>
<td>Poor supervision</td>
<td>Improvements in family income most significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family dysfunction</td>
<td>Unsafe housing</td>
<td>Food insecurity</td>
<td>Early childhood education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of educational opportunities</td>
<td>Lack of recreational space</td>
<td>High risk behaviours</td>
<td></td>
</tr>
</tbody>
</table>

### Social Determinants: Indigenous People’s Health in Canada

- Colonization: subjugation of Indigenous peoples by the Europeans, leading to the loss of lands, cultural practices, and self-government
- Residential schools: placement of children from Indigenous groups in church run, government-funded schools for the purpose of assimilation, resulting in loss of identity, alienation, and abuse, with long-lasting consequences of higher rates of addictions, abusive relationships, and suicide
- Treaties and land claims: inadequate services for those living on reserves leading to poverty and poor quality infrastructure, reflected in disproportionate burden of infectious diseases (e.g. pertussis, Chlamydia, hepatitis, shigellosis)
- Traditional approach to healing: restoring balance in the four realms of spiritual, emotional, mental and physical health of a person acting as an individual, as well as a member of a family, community and nation
- Ideas represented by medicine wheel of First Nations peoples, the Learning Blanket of Inuit peoples, and the Metis tree model of Holistic Lifelong Learning
- Contrast to Western medicine focus of treating illness, leading to challenges for practitioners of Western medicine to meet Aboriginal patients’ needs
- National Aboriginal Health Organization (NAHO) offers 8 guidelines on practicing culturally safe health care for Aboriginal patients including need to allow Aboriginal patients access to ceremony, song, and prayer; the need for information and for family support; guidelines for the appropriate disposal of body parts and for handling death

### New Immigrants to Canada

- Mandatory medical exams on entry to Canada by a designated medical practitioner
- Complete medical examination for all persons of all ages
- Chest x-ray and tape for persons 11 yr of age and over
- Urinalysis for persons 5 yr of age and over
- Syphilis serology for persons 15 yr of age and over
- HIV testing for applicants 15 yr of age and over as well as for those children who have received blood or blood products, have a known HIV-positive mother, or have an identified risk. An ELISA HIV screening test should be done for HIV 1 and HIV 2
- Serum creatinine if the applicant has hypertension (resting blood pressure greater than 140/90 mmHg), a history of treated hypertension, DM, autoimmune disorder, persistent proteinuria, or kidney disorder

Table 2. Health Determinants of Vulnerable Populations (continued)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Psychosocial/ Socioeconomic</th>
<th>Physical</th>
<th>Environment</th>
<th>Individual Behaviour</th>
<th>Population-Specific Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with Disabilities</td>
<td></td>
<td>Low income</td>
<td>Institutionalization</td>
<td>Substance misuse</td>
<td>Transportation support</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low education status</td>
<td>Barriers to access Transportation</td>
<td>Poor nutrition</td>
<td>Multidisciplinary care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discrimination</td>
<td>challenges</td>
<td>Inactivity</td>
<td>Unique support for individuals with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dependency for ADLs</td>
<td>specific disabilities (e.g. Trisomy 21)</td>
</tr>
<tr>
<td>New Immigrants</td>
<td>Person born outside of</td>
<td>Access to community</td>
<td>Exposure to diseases and conditions</td>
<td>Employment, ESL</td>
<td>Women’s health</td>
</tr>
<tr>
<td></td>
<td>Canada who has been granted</td>
<td>services Cultural</td>
<td>in country of origin</td>
<td>Healthy Newcomer</td>
<td>Mental health</td>
</tr>
<tr>
<td></td>
<td>the right to live in Canada</td>
<td>perspectives (including</td>
<td>(e.g. smoke from wood fires, incidence</td>
<td>Effect (health worsens over time to</td>
<td>Infectious diseases</td>
</tr>
<tr>
<td></td>
<td>permanently by immigration</td>
<td>reliance on alternative</td>
<td>of TB, etc.)</td>
<td>that of the general population)</td>
<td>(syphilis blood test, CXR, HIV)</td>
</tr>
<tr>
<td></td>
<td>authorities</td>
<td>health practices</td>
<td></td>
<td>Cultural or religious expectations</td>
<td>Dental and vision screening</td>
</tr>
<tr>
<td>Homeless Persons</td>
<td>An individual who lacks</td>
<td>Low income</td>
<td>Exposure to temperature</td>
<td>Substance misuse</td>
<td>Vaccinations</td>
</tr>
<tr>
<td></td>
<td>permanent housing</td>
<td>Food insecurity</td>
<td>extremes</td>
<td>Violence</td>
<td>Vaccinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental illness</td>
<td></td>
<td></td>
<td>Women’s health</td>
</tr>
<tr>
<td>Refugee Health</td>
<td>Forced to flee country</td>
<td>Post-traumatic stress</td>
<td>Diseases and conditions in country</td>
<td>Employment ESL</td>
<td>Mental health</td>
</tr>
<tr>
<td></td>
<td>of origin because of a</td>
<td>disorders Depression</td>
<td>of origin (e.g. malaria, TB,</td>
<td>Longstanding prior lack of access to</td>
<td>Infectious diseases</td>
</tr>
<tr>
<td></td>
<td>well-founded fear of</td>
<td>Adjustment problems</td>
<td>onchocerciasis, etc.)</td>
<td>health care (chronically neglected</td>
<td>Dental and vision screening</td>
</tr>
<tr>
<td></td>
<td>persecution and given</td>
<td>Partial health</td>
<td></td>
<td>problems)</td>
<td>Political advocacy</td>
</tr>
<tr>
<td></td>
<td>protection by the</td>
<td>coverage via Interim</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Government of Canada</td>
<td>Federal Health Program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Refugee claimant:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrive in Canada and ask</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>to be considered refugee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population.

Disease Prevention

Natural History of Disease
• course of a disease from onset to resolution
  1. pathological onset
  2. presymptomatic stage: from onset to first appearance of symptoms/signs
  3. clinical manifestation of disease: may regress spontaneously, be subject to remissions and relapses, or progress to death

Disease Prevention Strategies
• measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

Table 3. Levels of Disease Prevention

<table>
<thead>
<tr>
<th>Level of Prevention</th>
<th>Goal</th>
<th>Sample Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Protect health and prevent disease onset</td>
<td>Immunization programs (e.g. measles, diphtheria, pertussis, tetanus, polio, see Pediatrics, P4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking Cessation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sea belt use</td>
</tr>
<tr>
<td>Secondary</td>
<td>Early detection of disease to minimize morbidity and mortality</td>
<td>Mammography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine Pap smears</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Treatment and rehabilitation of disease to prevent progression, permanent disability, and future disease</td>
<td>DM monitoring with HbA1c, eye exams, foot exams</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medication</td>
</tr>
</tbody>
</table>

Screening (Secondary Prevention)
- "presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly"

Types of Screening
- Mass screening: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
- Selective screening: screening of targeted subgroups of the population at risk for a disease (e.g. mammography in women >50 yr old)
- Multiphasic screening: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)

Bias in Screening
- Lead-time: false improvement in survival time caused by changing the starting point of measurement, as opposed to real improvements measured from the original starting point (e.g. due to better therapy)
- Lead-time bias: overestimation of survival time ‘from diagnosis’ when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening
- Length-time bias: overestimation of the survival time due to screening at one time point including more stable cases than aggressive cases of disease, who may have shorter survival times

![Figure 2. Lead-time bias](image)

Table 4. Ideal Criteria for Screening Tests

<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
<th>Health Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes significant suffering and/or death</td>
<td>High specificity and sensitivity</td>
<td>Adequate capacity for reporting, follow-up, and treatment of positive screens</td>
</tr>
<tr>
<td>Natural history must be understood</td>
<td>Safe, rapid, easy, relatively inexpensive</td>
<td>Cost effective</td>
</tr>
<tr>
<td>Must have an asymptomatic stage that can be detected by a test</td>
<td>Acceptable to providers and to population</td>
<td>Sustainable program</td>
</tr>
<tr>
<td>Early detection and intervention must result in improved outcomes</td>
<td>Incidence is not too high or too low</td>
<td>Clear policy guidelines</td>
</tr>
</tbody>
</table>


The Association of Faculties of Medicine of Canada Public Health Educators’ Network. Concepts of Health and Illness. AFMC Primer on Population Health

Health Promotion Strategies

Table 5. Disease Prevention vs. Health Promotion Approach

<table>
<thead>
<tr>
<th>Disease Prevention</th>
<th>Health Promotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health = absence of disease</td>
<td>Health = positive and multidimensional concept</td>
</tr>
<tr>
<td>Medical model (passive ole)</td>
<td>Participatory model of health</td>
</tr>
<tr>
<td>Aimed mainly at high risk groups in the population</td>
<td>Aimed at the population in its total environment</td>
</tr>
<tr>
<td>One-shot strategy, aimed at a specific pathology</td>
<td>Diverse and complementary strategies aimed at a network of issues/determinants</td>
</tr>
<tr>
<td>Directive and persuasive strategies enforced in target groups</td>
<td>Facilitating and enabling approaches by incentives offered to the population</td>
</tr>
<tr>
<td>Focused mostly on individuals and groups of subjects</td>
<td>Focused on a person’s health status and environment</td>
</tr>
<tr>
<td>Led by professional groups from health disciplines</td>
<td>Led by non-professional organizations, civic groups, local, municipal, regional, and national governments</td>
</tr>
</tbody>
</table>


Healthy Public Policy
- characterized by an explicit concern for health and equity in all areas of policy and by an accountability for health impact
- main aim: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- government sectors must take into account health as an essential factor when formulating policy and should be accountable for the health consequences of their policy decisions
- methods
  - Fiscal: imposing additional costs (e.g. taxes on tobacco and alcohol)
  - Legislative: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  - Social: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)
Measurements of Health and Disease in a Population

MEASURES OF DISEASE OCCURRENCE

Incidence Rate

- number of new cases in a population per unit of person-time

Prevalence

- total number of cases in a population over a defined period of time
- two forms of prevalence
  - point prevalence: assessed at one point in time
  - period prevalence: as above, but all cases over defined time window (including ‘incident’ ones) are included:
    - depends on incidence rate and disease duration from onset to termination (cure or death)
    - favours the inclusion of chronic over acute cases and may underestimate disease burden if those with short disease duration are missed
- prevalence studies are cross-sectional and provide weak evidence for causal inferences
- prevalence figures are useful for determining the extent of a disease and can aid in the planning of facilities and services

Risk Reduction Strategies

- risk reduction: lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
- harm reduction: tolerance of some degree of risk behaviour, while aiming to minimize the adverse outcomes associated with these behaviours (e.g. needle exchange programs)

Example of Harm Reduction Strategy – Evaluation of a Pilot Medically Supervised Safer Injection Facility

CMAJ 2006;175:1399-1404

Purposes: To evaluate the outcomes of a supervised safer injecting facility facilitating pre-obtaining illicit drugs under supervision of medical staff, conducted over a 2 year period.

Methods: IDUs who used the safer injecting facility included age <30 yr, history of drug use, homelessness, daily heroin and/or cocaine injection, and recent history of overdose. Mean measures of public order problems were taken 6 wk before and 12 wk after initiation of the safer injecting facility. It was found that the mean number of IDUs injecting daily in public, along with the mean number of publicly discarded syringes were reduced by approximately half.

Conclusion: Overall it has been found that the safer injecting facility in Vancouver has been successful in attracting IDUs at increased risk of HIV, overdose, and public injection of substances. This has resulted in lower incidences of public drug use, publicly discarded syringes and sharing of needles. Other studies associated with this one have demonstrated that there has been no increase in the drug dealing, drug related crimes, or rates of new IDUs in the area surrounding the safer injecting facility.

Incidence and Prevalence

Incidence = # of new cases in a time interval

Prevalence = # of existing cases at a point in time

e.g. For Canada in 2011:

HIV incidence rate is 9.5 per 100,000 people
HIV prevalence is 213 per 100,000 people

Top 5 Causes of Mortality in Canada, 2012, by Sex

Female
- Cancer
- Heart disease
- Stroke
- COPD/chronic lower respiratory disease
- Alzheimer’s

Male
- Cancer
- Heart disease
- Accidents
- Stroke
- COPD/chronic lower respiratory disease


Behavior Change

- health education serves to:
  - increase knowledge and skills
  - encourage positive behaviour changes and discourage unhealthy choices
- health education is an important component of eliciting behaviour change
- behaviour is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community

Health Belief Model (1975)

- “behaviours undertaken by individuals in order to remain healthy […] are a function of a set of interacting beliefs”
- beliefs include: (i) individual’s perception of their susceptibility to a disease; (ii) severity of the disease; (iii) efficacy of proposed change/action; (iv) benefits and costs of health-related actions
- beliefs are modified by socio-demographic and psychosocial variables
- individuals must be in a state of readiness
- behaviour can be stimulated by cues to action, which are triggers that can encourage preventive health decisions and actions (e.g. physician recommendation, public advertising)

Stages of Change Model

- provides a framework in which the Health Belief Model is applied to facilitating behaviour change (e.g. quitting smoking)

Figure 3. Stages of change model


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- Heart disease
- Accidents
- Stroke
- COPD/chronic lower respiratory disease

Age Standardized Rate
• adjustment of the crude rate of a health-related event using a “standard” population
• standard population is one with a known number of persons in each age and sex group
• standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time)

MEASURES OF MORTALITY

Life Expectancy
• “the expected number of years to be lived by a newborn based on age-specific mortality rates at a selected time”
• usually qualified by country, gender, and age

Crude Death Rate
• mortality from all causes of death per 1,000 in the population

Infant Mortality Rate (IMR)
• number of deaths among children >1 yr of age reported during a given time period divided by the number of live births reported during the same time period and expressed per 1000 live births per year

Maternal Mortality Rate (MMR)
• “number of deaths of women during pregnancy and due to puerperal causes […] per 1000 live births in the same year”

MEASURES OF DISEASE BURDEN

Potential Years of Life Lost (PYLL)
• calculated for a population using the difference between the actual age at death and a standard/expected age at death
• increased weighting of mortality at a younger age

Disability Adjusted Life Year (DALY)
• life expectancy weighted by amount of disability experienced
• both premature death and time spent with disability accounted for; these disabilities can be physical or mental

Quality Adjusted Life Year (QALY)
• years of life weighted by utility (similar to quality of life), ranging from 0-1 assigned to a year of life based on perceived quality of life; a yr in “perfect” health is considered equal to 1 QALY, the value of a year in ill health would be lowered based on the burden of disease
• it is possible to have “states worse than death” for example QALY <0 for extremely serious conditions

For additional rate calculations see Outbreak of Infectious Diseases, PH19
Consult the Public Health Agency of Canada for examples and latest statistics

Sources: Shah, CP. Health Indicators and Data Sources. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003

Epidemiology

Population
• a defined collection of individuals/regions/institutions/etc (e.g. individuals defined by geographic region, sex, age)

Sample
• a selection of individuals from a population
• types
  • random: all members are equally likely to be selected
  • systematic: an algorithm is used to select a subset
  • stratified: population is divided into subgroups that are each sampled
  • cluster: grouped in space/time to reduce costs
  • convenience: non-random inclusion, usually volunteers

Sample Size
• sample size contributes to the statistical precision of the observed estimate
• increasing the sample size decreases the probability of type I and type II errors
• increasing sample size does not reduce bias/confounding
Bias
- systematic error causing results to differ from correct values/inferences
- can occur at any point in study execution (e.g. collection, analysis, interpretation, publication, or review of data)
  - sampling bias: occurs with the selection of a sample that does not truly represent the population
  - sampling procedures should be chosen to prevent or minimize bias
  - measurement bias: systematic error arising from inaccurate measurements of subjects
  - recall bias: bias in individuals’ responses when reporting on past exposures/events
    - e.g. individuals with disease may be more likely to incorrectly recall/believe they were exposed to a possible risk factor than those who are free of disease

Confounder
- a variable that is related to both the exposure and outcome but is not a mediator in the exposure-outcome relationship
- distorts the estimated effect of an exposure if not accounted for in the study design/analysis (e.g. late maternal age could be a confounder in an investigation of birth order >4 and risk of developing Trisomy 21)
- randomization, stratification, matching, and regression modelling can help minimize confounder effects

Interpreting Test Results

<table>
<thead>
<tr>
<th></th>
<th>TP = True positive</th>
<th>TN = True negative</th>
<th>FP = False positive</th>
<th>FN = False negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Result</td>
<td>Positive</td>
<td>Sensitivity = TP/(TP+FN)</td>
<td>Specificity = TN/(TN+FP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Likelihood Ratio (LR)
- Likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
- LR+ indicates how much the probability of disease increases if the test is positive
- LR- indicates how much the probability of disease decreases if the test is negative

Positive Predictive Value (PPV)
- Proportion of people with a positive test who have the disease

Negative Predictive Value (NPV)
- Proportion of people with a negative test who are free of disease

Advanced Neoplasia

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>68</td>
<td>147</td>
</tr>
<tr>
<td>Negative</td>
<td>216</td>
<td>2234</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>2381</td>
</tr>
</tbody>
</table>

Sensitivity = 68/284 = 23.9%
Specificity = 2234/2381 = 93.8%

LR+ = Sensitivity = 0.239
LR- = 1 - Sensitivity = 0.761
PPV = 68/(68+147) = 31.6%
NPV = 2234/(2234+216) = 91.2%

Figure 4. Understanding sensitivity and specificity

SPIN: use a Sspecific test to rule IN a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive

SNOUT: use a SENitive test to rule OUT a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative

Sensitivity
- proportion of people with disease who have a positive test

Specificity
- proportion of people without disease who have a negative test

Pre-Test Probability
- the probability a particular patient has a given disease before a test/assessment results are known
Post-Test Probability
- a revision of the probability of disease after a patient has been interviewed/examined/tested
- calculation process can be explicit using results from epidemiologic studies, knowledge of the accuracy of tests, and a nomogram/Bayes' theorem
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
- after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

Effectiveness of Interventions
Effectiveness, Efficacy, Efficiency
- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - **efficacy**: the extent to which a specific intervention produces a beneficial result under ideal conditions (e.g. RCT)
    - ideal conditions include adherence, close monitoring, access to health resources, etc.
  - **effectiveness**: measures the benefit of an intervention under usual conditions of clinical care
    - considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it its proper administration, acceptance of intervention, and degree of adherence to intervention
  - **efficiency**: a measure of economy of an intervention with known effectiveness
    - considers the optimal use of resources (e.g. money, time, personnel, equipment, etc.)

<table>
<thead>
<tr>
<th>Disease (e.g. lung CA)</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure</strong> (e.g. smoking)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>A</td>
<td>B</td>
<td>A + B</td>
</tr>
<tr>
<td>Absent</td>
<td>C</td>
<td>D</td>
<td>C + D</td>
</tr>
<tr>
<td>Total</td>
<td>A + C</td>
<td>B + D</td>
<td>A + B + C + D</td>
</tr>
</tbody>
</table>

**Case-Control Study**

\[
\text{odds ratio (OR)}^* = \frac{A}{C} = \frac{B}{D} = \frac{A \times D}{B \times C}
\]

**Cohort Study**

\[
\frac{A}{A + B} = \text{incidence rate of health outcome in exposed} \quad \frac{C}{C + D} = \text{incidence rate of health outcome in non-exposed}
\]

relative risk (RR)** = \frac{A}{A + B} - \frac{C}{C + D} 

attributable risk (AR)** = \frac{A}{A + B} - \frac{C}{C + D}

*Ratio of the odds in favour of the health outcome among the exposed to the odds in favour among the unexposed
**Ratio of the risk of a health outcome among exposed to the risk among the unexposed
***Ratio of health outcome in exposed individuals that can be attributed to the exposure

**Number Needed to Treat (NNT)**
- number of patients who need to be treated to achieve one additional favourable outcome
- only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility of intervention)
- a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

**Number Needed to Harm (NNH)**
- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

**Adherence (formerly compliance)**
- degree to which a patient follows a treatment plan

**Coverage**
- extent to which the services rendered cover the potential need for these services in a community

Sources: Shah, CP. Health Indicators and Data Sources. Public Health and Preventive Medicine in Canada. 5e. Toronto: Brever, 2003

Equations to Assess Effectiveness

\[
\begin{align*}
\text{CER} & = \text{control group event rate} \\
\text{EER} & = \text{experimental group event rate} \\
\text{RR} & = \frac{\text{EER}}{\text{CER}} \\
\text{ARR} & = \text{CER} - \text{EER} \\
\text{NNT} & = \frac{1}{\text{ARR}} \\
\end{align*}
\]

**Figure 6. Fagan's likelihood ratio nomogram: Practical example using PSA levels to calculate post-test probability of prostate cancer**


**Figure 7. Measures of effect by study type**

**Figure 8. Sensitivity and specificity are characteristics of the test**

**PPV and NPV depend on the prevalence of the disease in the population**

NNT
Consult http://www.thennt.com for quick summaries of evidence-based medicine (includes NNT, LR, and risk assessments)
**Types of Study Design**

### Qualitative vs. Quantitative

**Table 6. Qualitative vs. Quantitative Study Designs**

<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Quantitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often used to generate hypothesis (Why? What does it mean?)</td>
<td>Often tests hypothesis (What? How much/many?)</td>
</tr>
<tr>
<td>“Bottom up” approach</td>
<td>“Top down” approach</td>
</tr>
<tr>
<td>Observation → pattern → tentative hypothesis → theory</td>
<td>Theory → hypothesis → observation → confirmation</td>
</tr>
<tr>
<td>Sampling approach to obtain representative coverage of ideas, concepts, or</td>
<td>Sampling approach to obtain representative coverage of people</td>
</tr>
<tr>
<td>experiences</td>
<td>in the population</td>
</tr>
<tr>
<td>Narrative: rich, contextual, and detailed information from a small number</td>
<td>Numeric: frequency, severity, and associations from a large</td>
</tr>
<tr>
<td>of participants</td>
<td>number of participants</td>
</tr>
</tbody>
</table>

Source: Adapted from [http://phprimer.afmc.ca](http://phprimer.afmc.ca)


### Quantitative Research Methods

![Figure 8. Quantitative study designs](http://phprimer.afmc.ca)

**Formulating a Research Question**

**PICO**
- **Population/Patient Characteristics**
- **Intervention/Exposure of Interest**
- **Comparison Group or Control Group**
- **Outcome that you are trying to prevent or achieve**

### Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study subjects
- there are two main subtypes of observational studies: descriptive and analytic studies

#### Descriptive Studies
- describe the events and rates of disease with respect to person, place and time; estimates disease frequency and time trends
- can be used to generate an etiologic hypothesis and for policy planning

#### Analytic Studies
- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

An example of an ecological fallacy would be concluding that red wine drinking leads to lower risk of death from CVS disease after an ecological study shows that countries with a higher rate of red wine consumption have a lower rate of death from CVS causes.
Table 7. Observational Study Designs

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Ecological</th>
<th>Cross-Sectional</th>
<th>Case Control</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Units of analysis are populations or groups of people, rather than individuals</td>
<td>Use individual data on exposures and outcomes gathered at the same time</td>
<td>Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)</td>
<td>Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor</td>
</tr>
<tr>
<td>Subjects</td>
<td>Aggregated groups (e.g. cities)</td>
<td>Sample of a population</td>
<td>Two or more samples of individuals with and without the outcome(s) of interest (i.e. cases and controls)</td>
<td>One or more cohorts Cohort: group of people with common characteristics (e.g. year of birth, region of residence) Divided into measured exposed vs. non-exposed groups</td>
</tr>
<tr>
<td>Methods</td>
<td>Descriptions of the average exposure or risk of disease for a population Can use regression models to test associations between area-level predictors and aggregate outcomes Collect information from each person at one particular time Tabulate the numbers in groups (e.g. by presence or absence of disease/factor of interest) Make tables and compare groups Estimate prevalence Use regression models to test associations between predictors and outcomes of interest Select sample of cases of a specific disease during a specific time frame Representative of spectrum of clinical disease Select control(s) Represent the general population To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender) Assess past exposures (e.g. EMR, questionnaires) Association can be concluded between the risk factor and the disease (odds ratio) Collect information on factors from all persons at the beginning of the study Subjects are followed for a specific period of time to determine development of disease in each exposure group Prospective: measuring from the exposure at present to the future outcomes Retrospective: measuring forward in time from exposures in the past to later outcomes Use statistical models to test associations between exposures and disease or other measured outcomes Provides estimates of incidence, relative risk, attributable risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advantages</td>
<td>Quick, easy to do Uses readily available data Generates hypothesis Determines association between variables Quick and uses fewer resources Surveys with validated questions allows comparison between studies Often used when disease in population is rare (less than 10% of population) due to increased efficiency or when time to develop disease is long Less costly and time consuming Shows an association between risk factor(s) and outcome(s) Stronger evidence for causation Can consider a variety of exposures and outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Poor generalizability to individual level (not direct assessment of causal relationship) Ecological fallacy: an incorrect inference from groups to individuals Confounding Does not allow for assessment of temporal relationship or offer strong evidence for causation between variables Recall bias (see Bias, PH9) Confounding Selection bias for cases and controls Only one outcome can be measured Confounding may occur due to individuals self-selecting the exposure, or unknown/unmeasured factors are associated with the measured exposure and outcome Cost and duration of time needed to follow cohort Selection bias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>A study looking at the association between smoking rates and lung cancer rates in different countries at the population level without individual data on both factors A study that examines the distribution of BMI by age in Ontario at a particular point in time A famous case control study published by Sir Richard Doll demonstrated the link between tobacco smoking exposure and lung cancer cases at the individual level A famous cohort study is the Framingham Heart Study, which assessed the long-term cardiovascular risks of diet, exercise, medications such as ASA, etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Experimental Study Designs

not discussed here are non-randomized control trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible)

RANDOMIZED CONTROLLED TRIAL (RCT)

Definition
- subjects are assigned by random allocation to two or more groups, one of which is the control group, the other group(s) receive(s) an intervention

Subjects
- individuals are selected using explicit inclusion/exclusion criteria with recruitment targets guided by sample size calculations

Methods
- random allocation of individuals into two or more treatment groups through a centralized concealed process
- method of assessment to reduce bias
  - single-blind: subject does not know group assignment (intervention or placebo)
  - double-blind: subject and observer both unaware of group assignment
  - triple-blind: subject, observer, and analyst unaware of group assignment
- one group receives placebo or standard therapy
- one or more groups receive(s) the intervention(s) under study
- baseline covariates and outcome(s) are measured and the groups are compared
- all other conditions are kept the same between groups

Advantages
- “gold standard” of studies, upon which the practice of EBM is founded
- provides the strongest evidence for effectiveness of intervention
- threats to validity are minimized with sufficient sample size and appropriate randomization
- randomization is one of few methods that can address selection bias and confounding (including unmeasured confounders)
- allows prospective assessment of the effects of intervention

Disadvantages
- some exposures are not amenable to randomization (e.g. cannot randomize subjects to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
- can be difficult to randomly allocate groups (e.g. communities, neighbourhoods)
- difficult to study rare events, since RCTs would require extremely large sample sizes
- contamination, co-intervention, and loss to follow-up can all limit causal inferences
- can have poor generalizability
- costly


Summary Study Designs

META-ANALYSIS

Definition
- a form of statistical analysis that synthesizes the results of independent studies addressing a common research question, as identified through systematic review

Subjects
- all the studies identified through the review (or all subjects used in original studies for individual level meta-analysis)

Methods
- selection of relevant studies from the published literature which meet quality criteria
- statistical models used to combine the results of each independent study
- provides a summary statistic of overall results as well as graphic representation of included studies (forest plot)

Advantages
- attempts to overcome the problem of reduced power due to small sample sizes of individual studies
- ability to control for inter-study variation
- can address questions (e.g. subgroup analyses) that the original studies were not powered to answer

Analysis
- Per-Protocol Analysis (PP): Strategy of analysis in which only patients who complete the entire study are counted towards the results

Intention-to-Treat Analysis (ITT)
- When groups are analyzed exactly as they existed upon randomization (i.e. using data from all patients, including those who did not complete the study)

An example of a meta-analysis is one that compares the effects of ACE inhibitors, CCBs, and other antihypertensive agents on mortality and major cardiovascular events by compiling and analyzing data from a full set of reported RCTs
Methods of Analysis

Distributions

- distribution describes the probability of events
- normal (Gaussian) or non-normal (binomial, gamma, skewed, etc.)
- characteristics of the normal distribution
  - mean = median = mode
  - 67% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - mean: sum of each observations' data (e.g. ages) divided by total number of observations
  - median: value of the 50th percentile; a better reflection of the central tendency for a skewed distribution
  - mode: most frequently observed value in a series
- measures of dispersion
  - range: the largest value minus the smallest value
  - variance: a measure of the spread of data
  - standard deviation: the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

Data Analysis

Statistical Hypotheses

- null (H0): the default hypothesis; often states there is no relationship between two variables
- alternative (H1): the hypothesis that we are interested in; often states there is a relationship between two variables
  - we can find evidence against H0 but we can never 'prove' H1

Type I Error (α Error)

- the null hypothesis is falsely rejected (i.e. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error, since a type I error can have larger clinical significance than a type II error

Type II Error (β Error)

- the null hypothesis is falsely accepted (i.e. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- by convention a higher level of error is often accepted for most studies
- can also be used to calculate statistical power

Power

- probability of correctly rejecting a null hypothesis when it is in fact false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
- power increases with an increase in sample size
- power = 1 – β, and is therefore equal to the probability of a true positive result

Statistical Significance

- the probability that the statistical association found between variables is due to random chance alone (i.e. there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently p<0.05
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (denoted by the α-value)

Disadvantages

- sources of bias may not be controlled for
- reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)
- the decision to include/reject a particular study is subjective

Sources:

Example Calculation

Data set: 17, 14, 17, 10, 7
Mean = (17 + 14 + 17 + 10 + 7) ÷ 5 = 13
Median (write the list in order, median is the number in the middle) = 7, 10, 14, 17 = 14
Mode (number repeated more often) = 17
Range = 17 – 7 = 10
Variance = [(17 – 13)² + (14 – 13)² + (17 – 13)² + (10 – 13)² + (7 – 13)²] ÷ 4 = 19.5
Standard Deviation = √variance = √19.5 = 4.42

Type I (α) Error

"There Is An Effect" where in reality there is none

Consult the Cochrane Library of Systematic Reviews (http://www.cochranelibrary.com) for high-quality systematic reviews and meta-analyses
Clinical Significance
- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient compliance, and side effects in addition to statistical significance

Confidence Interval (CI)
- provides a range of values within which the true population result (e.g. the mean) lies
- frequently reported as 95% CI (i.e. 95% chance that the true value is within this data range)
- bounded by the upper and lower confidence limits

Data
- information collected from a sample of a population
- there are 4 overall levels of measurement for quantitative data
  - categorical (e.g. blood type, marital status)
  - ordinal (e.g. low, medium, high)
  - interval (e.g. °C, time of day)
  - ratio (e.g. serum cholesterol, hemoglobin, age)

Validity/Accuracy (of a measurement tool)
- how closely a measurement reflects the entity it claims to measure

Reliability/Precision
- how consistent multiple measurements are when the underlying subject of measurement has not changed
- may be assessed by different observers at the same time (inter-rater reliability) or by the same observer under different conditions (test-retest reliability)

Internal Validity
- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the reliability, accuracy, and absence of other biases

External Validity (i.e. Generalizability)
- degree to which the results of the study can be generalized to other situations or populations

Common Statistical Tests

<table>
<thead>
<tr>
<th>Table 8. Statistical Tests</th>
<th>Two-sample t-Test</th>
<th>Analysis of Variance (ANOVA)</th>
<th>Chi-Squared Test ($\chi^2$)</th>
<th>Linear Regression</th>
<th>Logistic Regression</th>
<th>Pearson product-moment correlation (Pearson’s r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are you trying to show?</td>
<td>Compare the mean values of an outcome variable between two groups (e.g. difference in average BP between men and women)</td>
<td>Compare the mean values of an outcome variable between two or more groups (e.g. difference in average BP between persons in three towns)</td>
<td>Test the correspondence between a theoretical frequency distribution and an observed frequency distribution (e.g. if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test determines if this variation is more than expected due to chance alone)</td>
<td>Looks at associations between two or more variables (e.g. age and blood pressure)</td>
<td>Shows how a change in one explanatory variable affects the status (e.g. if vs. non-ill) of the outcome variable</td>
<td>Assesses the strength of the linear relationship between two variables. Ranges from -1 (negative association, i.e. increases in one variable are associated with decreases in another) to 1 (positive association, increases in one variable are associated with increases in the other). A correlation of 0 indicates no relationship</td>
</tr>
</tbody>
</table>

What kind of variables do you measure?

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Continuous data</th>
<th>Continuous data</th>
<th>Categorical (2 or more)/ ordinal</th>
<th>Continuous</th>
<th>Categorical (outcomes usually dichotomous)</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent Variable</td>
<td>Dichotomous</td>
<td>Categorical/Ordinal (2 or more)</td>
<td>Categorical/Ordinal (2 or more)</td>
<td>Continuous/Ordinal/ Categorical</td>
<td>Continuous/Ordinal/ Categorical</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

Assumptions

| Data follow a normal distribution | Equal variances | Data are independent | The Normal distribution of dependent variable’s error term | Expected counts must be at least 5 for all cells in n by m table | Data are independent | Dependent variable’s error term has a normal distribution | Linear relationship between variables | Homoskedasticity | No influential values | Data are independent | Underlying relationship is linear | Data for both variables are Normally distributed | Data are independent |

Good reliability
- Good accuracy
- Poor reliability
- Good accuracy

Figure 12. Validity vs. reliability

What’s the difference between Pearson and Spearman correlation?
Different types of correlation are used for different levels of measurement. Pearson is for continuous and Normal data, Spearman is for ordinal or non-Normal data. There are other forms of correlation for other levels of measurement (e.g. Tetrachoric/polychoric)
Causation

Criteria for Causation (Sir Bradford Hill)
1. strength of association: the frequency with which the factor is found in the disease, and the frequency with which it occurs in the absence of disease
2. consistency: is the same relationship seen with different populations or study design?
3. specificity: is the association particular to your intervention and measured outcome?
4. temporal relationship: did the exposure occur before the onset of the disease?
5. biological gradient: finding a dose response relationship between the exposure-outcome
6. biological plausibility: does the association/causation make biological sense?
7. coherence: can the relationship be explained/accounted for based on what we know about science, logic, etc.?
8. experimental evidence: does experimental evidence support the association (e.g. is there improvement?)
9. analogy: do other established associations provide a model for this type of the relationship?

Note: Not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes ‘experimental evidence’ as superior to other criteria for experimental causation review. However, many causation questions in health cannot be answered with experimental methods.


Assessing Evidence

• critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision

Figure 13. Pyramid of pre-appraised evidence

Validity
• The degree to which the outcome observed in the study can be attributed to the intervention

5 Questions About the Validity of Primary Studies
• Were the patients randomized?
• Were the follow-up of patients sufficiently long and complete?
• Were all patients analyzed in the groups to which they were randomized?
• Were the groups treated equally except for the intervention?
• Were the patients and clinicians kept blind to treatment?

Other Questions to Consider
• Were the groups similar (i.e. demographics, prognostic factors) at the start of the trial?
• Were the appropriate and valid exposure and outcome measures obtained?
• Were outcome assessors aware of group allocation?
• Was contamination reported?
• Were ethical issues continuously upheld?

Levels of Evidence Classifications Cited in Guidelines/Consensus Statements

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results.</td>
</tr>
<tr>
<td>II</td>
<td>Based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results.</td>
</tr>
<tr>
<td>III</td>
<td>Based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies.</td>
</tr>
<tr>
<td>IV</td>
<td>Based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines.</td>
</tr>
<tr>
<td>V</td>
<td>Opinions of the authors who have written/reviewed the guidelines.</td>
</tr>
</tbody>
</table>

Notes: These 5 levels of evidence are not direct evaluations of evidence quality or credibility; they reflect the nature of the evidence. While RCTs tend to be most credible (with <III), level III evidence gains credibility when multiple studies from different locations and/or time periods report consistent findings. Level IV and V evidence reflects decision-making that is necessary but in the absence of published evidence.

Figure 14. Levels of evidence classifications

Note: This is only one method of classifying evidence. Various systems exist, but operate within the same premise that certain types of evidence carry more weight than others.

Health Services Research

Continuous Quality Improvement

Quality Improvement (QI)
- A means of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to cause variation in quality.
- Measures to increase efficiency of action with the purpose of achieving optimal quality.

Quality Assurance
- Process to guarantee the quality of health care through improvement and attainment of set standards.
- “Five-stage process of quality assurance” (Public Health and Preventative Medicine in Canada, Shah)
  1. Formulation of working goals
  2. Procedural changes to implement those goals
  3. Regular comparison of current performance with original goals
  4. Development of solutions to bring performance closer to goals
  5. Documentation of quality assurance activities

Quality Control
- A process of analyzing the quality of all factors involved in the process to maintain standards.

Continuous Quality Improvement
- The process of ongoing service/product refinement via the vigilant review of expectant issue detrimental to the system and regular incorporation of improvements.

Quality Management
- Combination of several processes (assurance, control, improvement) to maintain consistent quality.

Total Quality Management
- Management principle for advancing quality while minimizing additional expenditures.
- Focuses on the entire system rather than discrete elements.

Audit
- Methodical analysis of a quality system by quality auditor.
- To determine whether quality processes and results comply with goals, and whether processes have been implemented effectively.

Systems Analyses Tools
1. 5 Whys: Brainstorming to simplify the process of change; continue asking ‘why’ until the root of the problem is discovered.
2. Ishikawa Diagrams (i.e. Fishbone Diagrams): Identify generic categories of problems that have an overall contribution on the effect.
3. Defect check sheets: Consider all defects and tally up the number of times the defect occurs.
4. Pareto Chart: X vs. Y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis; purpose is to highlight most important among large set of factors contributing to defects/poor quality.
Outbreak of Infectious Diseases

**Precede-Proceed Model**
- tool for designing, implementing, and evaluating health interventions/programs

**Table 9. Precede-Proceed Model**

<table>
<thead>
<tr>
<th>PRECEDE Phase</th>
<th>PROCEED Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 – Identify the ultimate desired result</td>
<td>Phase 5 – Implementation (design and conduct the intervention)</td>
</tr>
<tr>
<td>Phase 2 – Identify health issues and their behavioural and environmental determinants. Set priorities among them</td>
<td>Phase 6 – Process Evaluation (determine if the program is implemented as planned)</td>
</tr>
<tr>
<td>Phase 3 – Identify the predisposing, enabling, and reinforcing factors that affect the behaviours and environmental determinants</td>
<td>Phase 7 – Impact Evaluation (measure intermediate objectives – predisposing, enabling, and reinforcing factors)</td>
</tr>
<tr>
<td>Phase 4 – Identify the administrat ve and policy factors that influence what can be implemented</td>
<td>Phase 8 – Outcome Evaluation (measure desired result)</td>
</tr>
</tbody>
</table>

**Cost Analysis**

**Cost Benefit Analysis (CBA)**
- an analysis which compares the total expected costs with the total expected benefits of actions in order to choose the most profitable or beneficial options
- costs are controlled for inflation and market changes so that the effect of the change is evaluated over a consistent, preset financial value

**Cost Effectiveness Analysis (CEA)**
- ratio of the change in cost (numerator) to change in effect (denominator) in response to a new strategy or practice
  - some examples of changes in effect (denominator) could be years of life gained or sight-years gained
  - the numerator highlights the cost of the health gain
  - the most commonly used outcome measure is quality-adjusted life years (QALY) (see *Quality Adjusted Life Year, PH8*)
- can be used where an extensive cost benefit analysis is not applicable or appropriate

**Outbreak of Infectious Diseases**

**Definitions**

**Endemic**
- consistent existence of infectious agent or disease in a given population or area (i.e. usual rate of disease)

**Outbreak**
- incidence of new cases beyond the usual frequency of disease in a particular population or community over a given period of time
- an epidemic that is in a confined location, has a short duration, or begins acutely

**Epidemic**
- an outbreak or excessive rate of disease that rapidly spreads to a large number of individuals (e.g. SARS epidemic)

**Pandemic**
- epidemic over a wide area, crossing international boundaries, and affecting an even larger number of people
Attack Rate
- cumulative incidence of infection within a defined group observed during a specific period of time in an epidemic
- calculated by dividing the total number of people who develop clinical disease by the population at risk, usually expressed as a percentage

Secondary Attack Rate
- the proportion of individuals who develop disease as a result of exposure to primary contacts during the incubation period
- infectiousness reflects the ease of disease transmission and is usually measured by the secondary attack rate

Virulence
- extent of sickness caused in host by a disease-causing agent
- ratio comparing those with the disease who are critically affected over the total number of individuals in the population who have the disease

Case-Fatality Rate (CFR)
- proportion of individuals with the disease who perish as a result of the illness
- most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths
- must be clearly differentiated from the mortality rate

Mortality Rate/Crude Death Rate
- estimation of the portion of the population that dies during a specified period from all causes of death

Steps to Control an Outbreak

Adopted from AFMC Primer on Population Health

1. Determine whether an outbreak

2. Develop case definitions and identify outbreak cases
- consider history, signs, symptoms, test results, and timing to balance sensitivity and specificity in case definition
- consider engaging in active surveillance to identify additional cases

3. Develop hypotheses regarding outbreak cause/source and implement initial control measures
- identify source, population at risk
- manage cases, including appropriate isolation
- reinforce importance of routine and additional precautions

4. Test hypotheses using surveillance data or special studies
- describe cases by person, place, and time to create a line listing
- plot an epidemic curve:
  - histogram with time on the x-axis and number of cases on the y-axis
  - often follows a characteristic pattern based on the nature of the exposure and/or infectious agent:
    - point source epidemic: exposure is brief and not continuous or propagated (e.g. single contaminated dish at a picnic)
    - extended source epidemic: exposure may be continuous (or intermittent if peaks are irregular) and lasts for days or weeks (e.g. ongoing or intermittent contamination of drinking water)
    - propagated epidemic: series of peaks demonstrating only a few cases initially, but then ongoing person-to-person transmission (e.g. influenza virus)

5. Re-evaluate hypothesis and adjust control measures

6. Create and implement plans for future prevention and control
- examples include prevention of transmission in the environment (e.g. handwashing and sterilization techniques), immunization of hosts, and education of healthcare professionals and the public


Active Surveillance
- Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection)

Passive Surveillance
- A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered)
Environmental Health

Definition
- study of the association between environmental factors, both constructed and natural, and health
- environmental exposures
  - four common hazards: chemical, biological, physical, and radiation
  - four main reservoirs: air, food, water, and soil
  - three main routes: inhalation, ingestion, or absorption (skin)
  - usually divided into two main settings:
    - workplace (including schools): may see high level exposure in healthy individuals (see Occupational Health, PH23)
    - non-workplace: lower levels of exposure over longer period of time. Affects vulnerable populations more severely, such as at extremes of age, immuno-suppressed. May be teratogenic
- health impacts of the environment also include factors such as urban planning and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths can facilitate more active lifestyles)

Table 10. Environmental Health Jurisdiction

<table>
<thead>
<tr>
<th>Public Health Unit</th>
<th>Enforcement of water and food safety regulations (including restaurant food safety)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sanitation</td>
</tr>
<tr>
<td></td>
<td>Assessment of local environmental risks</td>
</tr>
<tr>
<td></td>
<td>Monitoring and follow-up of reportable diseases</td>
</tr>
<tr>
<td>Municipal Government</td>
<td>Waste disposal</td>
</tr>
<tr>
<td></td>
<td>Recycling</td>
</tr>
<tr>
<td></td>
<td>Water and sewage treatment/collection/distribution</td>
</tr>
<tr>
<td>Provincia and Territorial Government</td>
<td>Water and air quality standards</td>
</tr>
<tr>
<td></td>
<td>Industrial emission regulation</td>
</tr>
<tr>
<td></td>
<td>Toxic waste disposal</td>
</tr>
<tr>
<td>Federal Government</td>
<td>Designating and regulating toxic substances</td>
</tr>
<tr>
<td></td>
<td>Regulating food products (e.g. Health Canada)</td>
</tr>
<tr>
<td></td>
<td>Setting policy for pollutants that can travel across provincial boundaries</td>
</tr>
<tr>
<td>International</td>
<td>Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change, International Joint Commission)</td>
</tr>
</tbody>
</table>
Risk Assessment

Adapted from p.250 Sixth Edition of "A Dictionary of Epidemiology" by Miquel Porta

Hazard Identification
- what is the hazard involved?
- assess potential hazards by taking environmental health history

Risk Characterization
- is the identified agent likely to elicit the patient’s current symptoms?
- review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. evaluate threshold levels)

Exposure Assessment
- is the patient’s exposure to the environmental agent sufficient to have caused the current symptoms?
- quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard

Air

Biological Hazards
- moulds thrive in moist areas; 10-15% of the population allergic
- bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. Legionella)
- dust mites (year-round) and pollens (seasonal) can trigger upper and lower-airway symptoms

Chemical Hazards
- ground-level ozone
  - main component of smog with levels increasing in major cities
  - worsens asthma, irritates upper airway
- carbon monoxide (fossil fuel related, common byproduct of combustion)
  - aggravates cardiac disease at low levels
  - headache, nausea, dizziness at moderate levels
  - fatal at high levels
- sulphur dioxide (fossil fuel-related), nitrogen oxides
  - contribute to acid rain and exacerbate breathing difficulties
- organic compounds at high levels (e.g. benzene, methylene chloride, tetrachloroethylene)
  - tend to be fat-soluble, easily absorbed through skin and difficult to excrete
- heavy metal emissions (e.g. nickel, cadmium, chromium)
  - variety of health effects: upper airway disease, asthma, decreased lung function
  - second-hand tobacco smoke
    - respiratory problems, increase risk of lung cancer
  - particulates associated with decreased lung function, asthma, upper airway irritation

Radiation Hazards
- sound waves
  - ionizing radiation
  - radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with a small proportion of lung cancers
- ultraviolet radiation is increasing due to ozone layer destruction and increases risk of skin cancer
  - non-ionizing radiation
  - visible light, infrared, microwave

Water

Biological Hazards
- mostly due to human and animal waste
  - Aboriginal Canadians, rural Canadians at higher risk
  - bacteria: Escherichia coli (e.g. Walkerton, ON), Salmonella, Pseudomonas, Shigella
  - protozoa: Giardia, Cryptosporidium (e.g. North Battleford, SK)

Chemical/Industrial Hazards
- chlorination by-products (e.g. chloroform can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides, and other industrial waste products can be present in groundwater
- fluoride at high levels (greater than that of municipal fluoridation) can cause skeletal fluorosis

BPA, The Toxic Concern of 2009
Bisphenol A (BPA) is a chemical compound found in some hard, clear, lightweight plastics and resins. According to the NIH, animal studies suggest that ingested BPA may mimic estrogen and other hormones. In October 2008, Canada became the first country in the world to ban the import and sale of polycarbonate baby bottles containing BPA, stating that although exposure levels are below levels that cause negative effects, current safety margins need to be higher. The US FDA does not consider normal exposure to BPA to be a hazard, however the NIH has some concern that fetuses, infants, and children exposed to BPA may be at increased risk for early-onset puberty, prostate, and breast cancer.

Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement from the American Heart Association
Circulation 2010 Jun 1;121(21):2331-78
A scientific statement by the American Heart Association in 2004 reported that exposure to particulate matter air pollution contributes to cardiovascular morbidity and mortality. An updated American Heart Association statement in 2010 confirmed a causal relationship between particulate matter exposure and cardiovascular morbidity and mortality. The statement reported that such an exposure over several hours to weeks may trigger cardiovascular disease-related mortality and non-fatal events, whereas longer exposures over several years may further increase cardiovascular mortality and reduce life expectancy within highly-exposed populations by several months to years.

The Walkerton Tragedy

To Fluoridate or Not
At the recommended concentration of 0.8-1.0 mg/L, fluoride reduces cavities by 18-40%, and there is little risk of fluorosis unless other exposures (e.g. toothpaste, rinses, mouthwash, etc.) are swallowed. Opposition raises concern that fluoride is not easily controlled and that children, and others may be more susceptible to health problems. However, public health experts strongly support fluoridation as an effective measure to prevent dental caries at the community level and reduce dental health inequities.
Soil

**Biological Hazards**
- biological contamination: tetanus, *Pseudomonas*

**Chemical Hazards**
- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, residue of industrial waste/development (e.g. urban agriculture), lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- infants and toddlers at highest risk of exposure due to hand-mouth behaviours
- dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue

Food

**Biological Hazards**

<table>
<thead>
<tr>
<th>Source</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em></td>
<td>Raw eggs, poultry, meat</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Raw poultry, raw milk</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Various including meat, sprouts</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Unpasteurized cheeses, prepared salads, cold cuts</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Unpasteurized honey, canned foods</td>
</tr>
<tr>
<td>Prion (BSE*)</td>
<td>Beef and beef products</td>
</tr>
</tbody>
</table>

Table 11. Comparison of Select Biological Contaminants of Food and Effects on Human Health

- other biological food contaminants include
  - viruses, mould toxins (e.g. aflatoxin has been associated with liver cancer), parasites (e.g. *Toxoplasmosis*, tapeworm), paralytic shellfish poisoning (rare), genetically modified organisms (controversial as to health risks/benefits)

**Chemical Hazards**
- many persistent organic pollutants are fat-soluble and undergo bioamplification
- drugs (antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrates highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
- pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects
  - polychlorinated biphenyls (PCBs)
  - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
- dioxins and furans
  - levels highest in fish and marine mammals, also present in breast milk can cause immunosuppression, liver disease, respiratory disease

---

Honey and Botulism
Although exceedingly rare, infant botulism has been documented as a form of food poisoning from *C. botulinum* found in honey. When an infant swallows spores of this bacterium, they grow and produce a toxin in the baby’s intestine. By the time an infant is 1, its gut has a healthy colony of “good” bacteria that prevents this from occurring.

Organic Foods
- Foods designated as “organic” in Canada must conform to the Organic Products Regulations enforced by the Canadian Food Inspection Agency
- Organic foods are not free of synthetic pesticide residues but typically contain smaller amounts compared to conventionally grown foods
- Currently, there has not been strong evidence to suggest that eating organic foods is safer or more nutritious compared to eating conventionally grown food

Organic foods and children, 2009
**Occupational Health**

- a field involved in the prevention of illness or injury and the promotion of health in the work environment
- services encompass “health promotion and protection (primary prevention), disease prevention (secondary prevention), and treatment and rehabilitation (tertiary prevention)” (Shah)
- occupational disease may be more difficult to recognize than occupational injury

**Taking an Occupational Health History**

- current and previous duties at place of employment
- exposures
  - identification: screen for chemical, metal, dust, biological, and physical hazards as well as psychological stressors; review relevant workplace MSDS
  - assessment: duration, concentration, route, exposure controls (e.g. ventilation, personal protective equipment)
  - temporal relationship: changes in symptoms in relationship to work environment
  - presence of similar symptoms in co-workers
  - non-work exposures: home, neighbourhood, hobbies

**Table 12. Occupational Hazards**

<table>
<thead>
<tr>
<th>Physical</th>
<th>Chemical</th>
<th>Biological</th>
<th>Psychosocial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma (e.g. fractures, lacerations)</td>
<td>Organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride)</td>
<td>Exposure to bacteria, viruses, fungi, protozoa, Rickettsia</td>
<td>Workload stressors</td>
</tr>
<tr>
<td>Noise (e.g. hearing loss)</td>
<td>Silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Responsibility</td>
</tr>
<tr>
<td>Temperature</td>
<td>Heavy metals (e.g. nickel, cadmium, mercury, lead)</td>
<td>Consider exposure to disease in endemic countries, travellers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. malaria, SARS, TB)</td>
<td>Fear of job loss</td>
</tr>
<tr>
<td>Hypothermia, frostbite</td>
<td>Gases (e.g. halogen gases, sulphur dioxide, carbon monoxide, nitrogen oxides)</td>
<td></td>
<td>Geographical isolation</td>
</tr>
<tr>
<td>Air pressure (barotrauma, decompress on sickness)</td>
<td>Second-hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage)</td>
<td></td>
<td>Shift work</td>
</tr>
<tr>
<td></td>
<td>Skin diseases (major portion of compensations, e.g. contact dermatitis, occupational acne, pigmentation disorders)</td>
<td></td>
<td>Bullying</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Harassment (sexual/non-sexual)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
</tbody>
</table>

**Workplace Legislation**

- universal across Canada for corporate responsibility in the workplace: due diligence, application of Workplace Hazardous Materials Information System (WHMIS), existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally regulated industries (e.g. airports, banks, highway transport) under the Canada Labour Code
- Ontario’s Occupational Health and Safety Act
  - sets out rights of workers and duties of employers, procedures for workplace hazards, and law enforcement
  - workers have the right to:
    - participate (e.g. have representatives on joint health and safety committees)
    - know (e.g. be rained and have information about workplace hazards)
    - refuse work (e.g. workers can decline tasks they feel are overly dangerous)
      - note: For some occupations, this right is restricted if, for example, danger/risk is normal part of work or refusal would endanger others (e.g. police, firefighters, some health care workers)
    - stop work (e.g. ‘certified’ workers can halt work they feel is dangerous to other workers)
employers must take precautions to protect the health and safety of employees and investigate
concerns
enforced by Ministry of Labour via inspectors
Health Protection and Promotion Act (HPPA) (Ontario)
Medical Officer of Health has right to investigate and manage health hazards where workplace
exposures may impact non-workers (e.g. community members living close to the work site)

Workplace Health Promotion and Protection

pro-active preventative health measures can reduce workplace illness or injury
identifying workplace hazards (e.g. through material safety data sheets [MSDS])
assessing risk
reducing exposure: changes to work environment including elimination, substitution, and
isolation of hazard (e.g. engineering controls) more effective than changes to how people work (e.g.
administrative controls) and personal protective equipment

Workplace Disease Prevention and Identification

avoid the development of disease with pro-active worker health surveillance
periodic examinations to facilitate diagnosis before symptoms develop:
PFT for asthma (e.g. occupational dust exposure)
audiograms for hearing loss (e.g. occupational noise exposure)
substance misuse screening useful if concern surrounds decreased employee functioning

Workplace Treatment and Rehabilitation

treatment of the disease or injury to facilitate safe and timely return to the workforce
may require rehabilitation: retraining, change in job duties, and/or workers’ compensation (WSIB)
advice relevant authorities if necessary (e.g. report notifiable diseases to public health, conditions
impeding driving to Ministry of Transportation, see Other Reportable Conditions, PH25)

Appendix – Mandatory Reporting

Reportable Diseases

As an essential part of the health system, physicians in Canada are required by law to report certain
diseases to public health for the following reasons:
1. to control the outbreak
   if the disease presents an outbreak threat (e.g. measles, Salmonella, respiratory diseases in
   institutions)
2. to prevent spread
   if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa
   Fever)
3. for surveillance
   if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment and/or partner notification (e.g. gonorrhea, TB)
5. reporting details (website, office etc.)
   some are more urgent than others (must contact MOH)
   physicians should also report unlisted diseases that appear in clusters
The following list is based on the reportable diseases in Ontario for 2015. Each province will have a similar legislation.

Note: Diseases marked * (and Influenza in institutions) should be reported immediately to the Medical Officer of Health by either telephone (24 hours a day, 7 days a week) or fax (Mon Fri, 8:30 am – 4:30 pm only). Other diseases can be reported the next working day by fax, phone or mail.

Source: Health Protection and Promotion Act, O. Reg. 559/91, amended to O. Reg 49/07 (update)

<table>
<thead>
<tr>
<th>Acquired Immunodeficiency Syndrome (AIDS)</th>
<th>Haemophilus influenzae b disease, invasive*</th>
<th>Q Fever*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute flaccid paralysis &lt;15 yr</td>
<td>Hemorrhagic fevers*, including:</td>
<td>Rabies*</td>
</tr>
<tr>
<td>Amoebiasis</td>
<td>1. Ebola virus disease*</td>
<td>Respiratory infection outbreaks in institutions*</td>
</tr>
<tr>
<td>Anthrax*</td>
<td>2. Marburg virus disease*</td>
<td>Rubella*</td>
</tr>
<tr>
<td></td>
<td>3. Other viral causes*</td>
<td>Rubella, congenital syndrome</td>
</tr>
<tr>
<td>Botulism*</td>
<td>Hepatitis, viral*:</td>
<td>Salmoneiosis</td>
</tr>
<tr>
<td>Brucellosis*</td>
<td>1. Hepatitis A*</td>
<td>Severe Acute Respiratory Syndrome (SARS)*</td>
</tr>
<tr>
<td></td>
<td>2. Hepatitis B</td>
<td>Shigellosis*</td>
</tr>
<tr>
<td>Campylobacter enteritis</td>
<td>3. Hepatitis C</td>
<td>Smallpox*</td>
</tr>
<tr>
<td>Chancroid</td>
<td></td>
<td>Streptococcal infections, Group A invasive*</td>
</tr>
<tr>
<td>Chickenpox (Varicella)</td>
<td></td>
<td>Streptococcal infections, Group B neonatal</td>
</tr>
<tr>
<td>Chlamydia trachomatis infections</td>
<td>Herpes (neonatal) and HIV removed</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Cholera*</td>
<td>Influenza</td>
<td>Tetanus</td>
</tr>
<tr>
<td>Clostridium difficile* associated disease (CDAD) outbreaks in public hospitals</td>
<td>Lassa Fever*</td>
<td>Lassa fever</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob Disease, all types</td>
<td>Legionellosis*</td>
<td>Tuberculosis, active and latent</td>
</tr>
<tr>
<td>Cryptosporidiosis*</td>
<td>Leprosy</td>
<td>Tularemia*</td>
</tr>
<tr>
<td>Cyclosporiasis*</td>
<td>Listeriosis*</td>
<td>Typhoid Fever*</td>
</tr>
<tr>
<td>Diphtheria*</td>
<td>Lyme Disease</td>
<td>Verotoxin-producing E. coli infection* indicator conditions, including Hemolytic Uremic Syndrome (HUS)*</td>
</tr>
<tr>
<td>Encephalitis*, including:</td>
<td></td>
<td></td>
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<tr>
<td>1. Primary, viral*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Post-infectious</td>
<td>Malaria</td>
<td></td>
</tr>
<tr>
<td>3. Vaccine-related</td>
<td>Measles*</td>
<td></td>
</tr>
<tr>
<td>4. Subacute sclerosing panencephalitis</td>
<td>Meningitis, acute*:</td>
<td>West Nile Fever*, including:</td>
</tr>
<tr>
<td>5. Unspecified</td>
<td>1. Bacterial*</td>
<td>1. West Nile fever*</td>
</tr>
<tr>
<td></td>
<td>2. Viral*</td>
<td>2. West Nile neurological manifestations*</td>
</tr>
<tr>
<td>Food poisoning, all causes*</td>
<td>3. Other*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meningococcal disease, invasive*</td>
<td>Yellow Fever*</td>
</tr>
<tr>
<td>Gastroenteritis, institutional outbreaks*</td>
<td></td>
<td>Yersiniosis</td>
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<tr>
<td>Giardiasis, except asymptomatic cases*</td>
<td>Mumps</td>
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<tr>
<td>Gonorrhea</td>
<td>Ophthalmia neonatorum</td>
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<tr>
<td></td>
<td>Paralytic shellfish poisoning</td>
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<tr>
<td></td>
<td>Paratyphoid fever*</td>
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<tr>
<td></td>
<td>Pertussis (whooping cough)</td>
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<td></td>
<td>Plague*</td>
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<tr>
<td></td>
<td>Pneumococcal disease, invasive</td>
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<td></td>
<td>Poliomyelitis, acute*</td>
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<td></td>
<td>Psittacosis/Optomisosis</td>
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</tbody>
</table>

**Other Reportable Conditions**

- in addition to reporting diseases, physicians have a legal responsibility to report certain conditions.
- The list below highlights some reportable conditions for Ontario, but is not exhaustive. See your jurisdiction’s regulatory body for the full list.

**Child Abuse – to local Children’s Aid Society (CAS)**
- all child abuse and neglect where reasonable grounds to suspect exist (including physical harm, emotional harm, sexual harm, and neglect)
- duty to report is ongoing: if additional reasonable grounds are suspect, a further report to CAS is necessary

**Unfit to Drive – to provincial Ministry of Transportation**
- all patients with a medical condition (e.g. dementia, untreated epilepsy) that may impede their driving ability
- if a physician does not report and the driver gets into an accident, the physician may be held liable

**Unfit to Fly – to federal Ministry of Transportation**
- all patients believed to be flight crew members or air traffic controller with a medical or optometric condition that is likely to constitute a hazard to aviation safety

**Gunshots Wounds – to local police service**
- all patients with a gunshot or stab wounds
- self-inflicted knife wounds are not reportable

References

BMAJ Updates Plus. Available from: http://plus.mcmaster.ca/evidenceupdates  
Canadian Institute for Health Information. Available from: http://www.cihi.ca.  
Clinical Research Database. Available from: http://www.crd.york.ac.uk/CRD.  
Health Protection and Promotion Act, R.S.O. 1990, c.H.7, amended to O Reg 559/91, amended to O Reg 48/07.  
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronyms</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric Assessment</td>
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</tr>
<tr>
<td>History</td>
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</tr>
<tr>
<td>Mental Status Exam</td>
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</tr>
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<td>Assessment and Plan</td>
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</tr>
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<td>Suicide</td>
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<tr>
<td>Psychotic Disorders</td>
<td>6</td>
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<tr>
<td>Differential Diagnosis of Psychosis</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Schizophréniform Disorder</td>
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<tr>
<td>Brief Psychotic Disorder</td>
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<tr>
<td>Schizoaffective Disorder</td>
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<tr>
<td>Delusional Disorder</td>
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<td>Mood Disorders</td>
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</tr>
<tr>
<td>Mood Episodes</td>
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<tr>
<td>Depressive Disorders</td>
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<td>Postpartum Mood Disorders</td>
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<tr>
<td>Bipolar Disorders</td>
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<tr>
<td>Anxiety Disorders</td>
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</tr>
<tr>
<td>Panic Disorder</td>
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<tr>
<td>Agoraphobia</td>
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<tr>
<td>Generalized Anxiety Disorder</td>
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<tr>
<td>Phobic Disorders</td>
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</tr>
<tr>
<td>Obsessive-Compulsive Disorder</td>
<td></td>
</tr>
<tr>
<td>Trauma- and Stressor-Related Disorders</td>
<td>17</td>
</tr>
<tr>
<td>Post-Traumatic Stress Disorder</td>
<td></td>
</tr>
<tr>
<td>Adjustment Disorder</td>
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<tr>
<td>Bereavement</td>
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<tr>
<td>Neurocognitive Disorders</td>
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<tr>
<td>Delirium</td>
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<tr>
<td>Major Neurocognitive Disorder (Dementia)</td>
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</tr>
<tr>
<td>Substance-Related and Addictive Disorders</td>
<td>21</td>
</tr>
<tr>
<td>Nicotine</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
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<tr>
<td>Opioids</td>
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<tr>
<td>Cocaine</td>
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<td>Amphetamines</td>
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<td>Cannabis</td>
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<td>Hallucinogens</td>
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<tr>
<td>“Club Drugs”</td>
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<tr>
<td>Somatic Symptom and Related Disorders</td>
<td>27</td>
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<tr>
<td>Somatic Symptom Disorder</td>
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<td>Illness Anxiety Disorder</td>
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<tr>
<td>Conversion Disorder (Functional Neurological Symptom Disorder)</td>
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<tr>
<td>Dissociative Disorders</td>
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<tr>
<td>Dissociative Identity Disorder</td>
<td></td>
</tr>
<tr>
<td>Dissociative Amnesia</td>
<td></td>
</tr>
<tr>
<td>Depersonalization/Derealization Disorder</td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>29</td>
</tr>
<tr>
<td>Sexuality and Gender</td>
<td>30</td>
</tr>
<tr>
<td>Gender Dysphoria</td>
<td></td>
</tr>
<tr>
<td>Paraphilic Disorders</td>
<td></td>
</tr>
<tr>
<td>Eating Disorders</td>
<td>30</td>
</tr>
<tr>
<td>Anorexia Nervosa</td>
<td></td>
</tr>
<tr>
<td>Bulimia Nervosa</td>
<td></td>
</tr>
<tr>
<td>Binge-Eating Disorder</td>
<td></td>
</tr>
<tr>
<td>Avoidant/Restrictive Food Intake Disorder</td>
<td></td>
</tr>
<tr>
<td>Personality Disorders</td>
<td>33</td>
</tr>
<tr>
<td>Child Psychiatry</td>
<td>35</td>
</tr>
<tr>
<td>Developmental Concepts</td>
<td></td>
</tr>
<tr>
<td>Mood Disorders</td>
<td></td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td></td>
</tr>
<tr>
<td>Neurodevelopmental Disorders</td>
<td>37</td>
</tr>
<tr>
<td>Autism Spectrum Disorder</td>
<td></td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td></td>
</tr>
<tr>
<td>Disruptive, Impulse Control, and Conduct Disorder</td>
<td>39</td>
</tr>
<tr>
<td>Oppositional Defiant Disorder</td>
<td></td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td></td>
</tr>
<tr>
<td>Intermittent Explosive Disorder</td>
<td></td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>40</td>
</tr>
<tr>
<td>Other Therapies</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>42</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td></td>
</tr>
<tr>
<td>Anxiolytics</td>
<td></td>
</tr>
<tr>
<td>Somatic Therapies</td>
<td>49</td>
</tr>
<tr>
<td>Electroconvulsive Therapy</td>
<td></td>
</tr>
<tr>
<td>Repetitive Transcranial Magnetic Stimulation (rTMS)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgical Treatments</td>
<td></td>
</tr>
<tr>
<td>Other Therapy Modalities</td>
<td></td>
</tr>
<tr>
<td>Canadian Legal Issues</td>
<td>50</td>
</tr>
<tr>
<td>Common Forms</td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td></td>
</tr>
<tr>
<td>Community Treatment Order (CTO)</td>
<td></td>
</tr>
<tr>
<td>Duty to Inform/Warn</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>52</td>
</tr>
</tbody>
</table>
Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tr>
<td>S-HT</td>
<td>serotonin</td>
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<tr>
<td>ACh</td>
<td>acetylcholine</td>
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<tr>
<td>ACT</td>
<td>assertive community treatment</td>
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<td>ADHD</td>
<td>attention deficit hyperactivity disorder</td>
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<td>AN</td>
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<td>ASD</td>
<td>autism spectrum disorder</td>
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<td>ASPD</td>
<td>antisocial personality disorder</td>
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<td>BNI</td>
<td>bulimia nervosa</td>
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<td>CBT</td>
<td>cognitive behavioural therapy</td>
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<tr>
<td>CD</td>
<td>conduct disorder</td>
</tr>
<tr>
<td>CRA</td>
<td>community reinforcement approach</td>
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<tr>
<td>CT</td>
<td>cognitive therapy</td>
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<tr>
<td>CTO</td>
<td>community treatment order</td>
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<tr>
<td>DA</td>
<td>dopamine</td>
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<td>DBT</td>
<td>dialectical behavioural therapy</td>
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<td>DZ</td>
<td>dizygotic</td>
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<td>electroconvulsive therapy</td>
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<td>EPS</td>
<td>extrapyramidal symptoms</td>
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<td>ERP</td>
<td>exposure to response prevention</td>
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<td>EtoH</td>
<td>ethanol/alcohol</td>
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<td>GAD</td>
<td>generalized anxiety disorder</td>
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<td>GMC</td>
<td>general medical condition</td>
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<td>IPT</td>
<td>interpositional therapy</td>
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<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
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<td>MDD</td>
<td>major depressive disorder</td>
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<td>MDE</td>
<td>major depressive episode</td>
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<td>MET</td>
<td>motivational enhancement therapy</td>
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<td>mental status examination</td>
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<td>MST</td>
<td>magnetic stimulation therapy</td>
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<td>NA</td>
<td>Narcoenic Anonymous</td>
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<td>NMS</td>
<td>neuroleptic malignant syndrome</td>
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<td>NOS</td>
<td>not otherwise specified</td>
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<tr>
<td>OCD</td>
<td>obsessive compulsive disorder</td>
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<td>ODD</td>
<td>oppositional defiant disorder</td>
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<td>PD</td>
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<td>pervasive developmental disorder</td>
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<td>repetitive transcranial magnetic stimulation</td>
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<td>SSAs</td>
<td>second generation antipsychotics</td>
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<td>SNRIs</td>
<td>serotonin and norepinephrine reuptake inhibitors</td>
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<td>serotonin syndrome</td>
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<tr>
<td>SSRIs</td>
<td>selective serotonin reuptake inhibitors</td>
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<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
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<tr>
<td>TD</td>
<td>tardive dyskinesia</td>
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</table>

Psychiatric Assessment

History

Identifying Data
- necessary: name, age, sex/gender, marital status, occupation/source of financial support, place/type of residency
- adjunct: makeup of household, education, ethnicity, nationality, immigration history (if applicable), religion, referral source, known or unknown to treatment team

Reliability of Patient as a Historian
- indicate if, and for what content; utilize collateral source (e.g. parent, teacher) if patient unable/unwilling to be interviewed

Chief Complaint
- in patient's own words, duration

History of Present Illness
- reason for seeking help (that day), current symptoms (onset, duration and course), stressors, supports, functional status, relevant associated symptoms (pertinent positives and negatives)
- current medication use, doses, and adherence
- safety screen: endangering self or others, dependents at home (e.g. children, pets), ability to drive safely, ability to care for self (e.g. eating, hygiene, taking medications)

Psychiatric Functional Inquiry
- mood: depression, mania
- anxiety: worries, panic attacks, phobias, history of trauma
- obsessive-compulsive: obsessions, compulsions
- psychosis: hallucinations, delusions
- risk assessment: suicidal ideation, plan, intent, history of attempts (see Suicide PS4)
- organic: EtoH/drug use or withdrawal, illness, dementia

Past Psychiatric History
- all previous psychiatric diagnoses, psychiatric contacts, treatments (pharmacological and non-pharmacological), and hospitalizations
- include past suicide attempts, substance use/abuse, and problems/encounters with the legal system

Past Medical/Surgical History
- all medical, surgical, neurological (e.g. head trauma, seizures), and psychosomatic illnesses
- current medications, allergies

Family Psychiatric/Medical History
- family members: ages, occupations, personalities, medical or genetic illnesses and treatments, relationships with parents/siblings
- family psychiatric history: any past or current psychiatric illnesses and hospitalizations, suicide, substance abuse

Past Personal/Developmental History (as relevant)
- prenatal and perinatal history (desired vs. unwanted pregnancy, maternal and fetal health, domestic violence, maternal substance use and exposures, complications of pregnancy/delivery)
- early childhood to age three (developmental milestones, activity/attention level, family stability, attachment figures)
- middle childhood to age 11 (school performance, peer relationships, fire-setting, stealing, incontinence)
- late childhood to adolescence (drugs/alcohol, legal problems, peer and family relationships)
- history of physical or sexual abuse
- adulthood (education, occupations, relationships)
- personality before current illness, recent changes in personality
- psychosexual history (puberty, first sexual encounter, romantic relationships, gender roles, sexual dysfunction)

Screening Questions for Major Psychiatric Disorders
- Have you ever been feeling down, depressed or hopeless?
- Do you feel anxious or worry about things?
- Have there been a time in your life where you have felt euphoric, extremely talkative, had a lot of energy, and a decreased need for sleep?
- Have you ever thought of harming yourself or committing suicide?

Psychiatric Functional Inquiry

MOAPS
Mood
Organic (e.g. substances and organic disease)
Anxiety
Psychosis
Safety

Always Remember to Ask About Abuse
See Family Medic ne, FM26
Mental Status Exam

General Appearance
- posture, gait, grooming, hygiene, manner of dress, body habitus, facial expression, chronological vs. apparent age, relaxed or in distress

Behaviour
- psychomotor activity (agitation, retardation), abnormal movements or lack thereof (tremors, akathisia, tardive dyskinesia, paralysis), attention level and eye contact, attitude toward examiner (ability to interact, level of cooperation)

Speech
- rate (e.g. pressured, slowed), rhythm/fluency, volume, tone, articulation, quantity, spontaneity

Mood and Affect
- mood: subjective emotional state (in patient's own words)
- affect: objective emotional state inferred from emotional responses to stimuli; described in terms of
  - quality ( euthymic, depressed, elevated, anxious, irritable)
  - range (full, restricted, flat, blunted)
  - stability (fixed, labile)
  - mood congruence (inferred by comparing the patient's subjective mood with their affect)
- appropriateness to thought content
- some clinicians use 0-10 scales when rating mood to help get a subjective norm for each patient that can help establish changes over time and with treatment

Thought Process/Form
- coherence (coherent, incoherent)
- logic (logical, illogical)
- stream
  - goal-directed: clearly answers questions in a linear, organized, logical fashion
  - circumstantial: speech is indirect and delayed in reaching its goal; eventually comes back to the point
  - tangential: speech is oblique or irrelevant; does not come back to the original point
  - loosening of associations/derailment: illogical shifting between topics
  - flight of ideas: quickly skipping from one idea to another where the ideas are marginally connected, usually associated with mania
  - word salad: jumble of words lacking meaning or logical coherence
- perseveration: repetition of the same verbal or motor response to stimuli
- echolalia: repetition of phrases or words spoken by someone else
- thought blocking: sudden cessation of flow of thought and speech
- clang associations: speech based on sound such as rhyming or punning
- neologism: use of novel words or of existing words in a novel fashion

Thought Content
- suicidal ideation/ homicidal ideation
- frequency and pervasiveness of thoughts, formulation of plan, means to plan, intent, active vs. passive, protective factors
- preoccupations, ruminations: reflections/thoughts at length, not fixed or false
- obsession: recurrent and persistent thought, impulse, or image which is intrusive or inappropriate and unwanted
  - cannot be stopped by logic or reason
  - causes marked anxiety and distress
  - common themes: contamination, orderliness, sexual, pathological doubt/worry/guilt
  - magical thinking: belief that thinking something will make it happen, normal in children and certain cultures
  - ideas of reference: similar to delusion of reference, but less fixed (the reality of the belief is questioned)
  - overvalued ideas: unusual/odd beliefs that are not of delusional proportions
  - first rank symptoms of schizophrenia: thought insertion/withdrawal/broadcasting
  - delusion: a fixed false belief that is out of keeping with a person's cultural or religious background and is firmly held despite incontrovertible proof to the contrary

Perception
- hallucination: sensory perception in the absence of external stimuli that is similar in quality to a true perception
  - auditory (most common), visual, gustatory, olfactory, tactile
- illusion: misperception of a real external stimulus (such as mistaking a coat on a rack as a person late at night)
- depersonalization: change in self-awareness such that the person feels unreal, distant, or detached from his or her body, and/or unable to feel emotion
- derealization: feeling that the world/outer environment is unreal
Cognition
- level of consciousness (alert, reduced, obtunded)
- orientation: time, place, person
- memory: immediate, recent, remote
- global evaluation of intellect (below average, average, above average, in keeping with person's education)
- intellectual functions: attention, concentration, calculation, abstraction (proverb interpretation, similarities test), language, communication
- MMSE/MOCA useful as standard screening assessments of cognition

Insight
- patient's ability to realize that he or she has a physical or mental illness and to understand its implications (none, limited, partial, full)

Judgment
- patient's ability to understand relationships between facts and draw conclusions that determine one's actions

Assessment and Plan

Historical Multiaxial Model
- since DSM-5, this model is no longer used for psychiatric diagnosis. Instead, relevant psychiatric and medical diagnoses are simply listed. Nevertheless, we offer it here as a possible framework for psychiatric patient assessment, as many physicians still employ it.

Multiaxial Assessment
- Axis I: differential diagnosis of DSM-5 clinical disorders
- Axis II: personality disorders, developmental disability
- Axis III: general medical conditions potentially relevant to understanding/management of the mental disorder
- Axis IV: psychosocial and environmental issues
- Axis V: Global Assessment of Functioning (GAF, 0 to 100) incorporating effects of axes I to IV

After History and MSE, the assessment and plan is recorded

Assessment/Problem Formulation
- identify predominant symptom cluster (mood, anxiety, psychosis organic) causing the most distress/interference, persist when other symptom categories not present (e.g. psychosis in the absence of mood symptoms)
- dominating symptoms will direct differential
- consider current issues as they relate to an individual's factors in three domains: biological, psychological, and social
- for each category: predisposing, precipitating, perpetuating, and protecting factors are considered

Approach to Management
- consider short-term and long-term, and three types: biological (e.g. pharmacotherapy), psychological (e.g. CBT), and social (e.g. support group)

Suicide

Importance
- must be screened for in every encounter; part of risk assessment along with violent/homicidal ideation

Approach
- ask every patient – e.g. "Have you had any thoughts of wanting to harm or kill yourself?"
- classify ideation
  - passive ideation: would rather not be alive but has no active plan for suicide
    - e.g. "I'd rather not wake up" or "I would not mind if a car hit me"
  - active ideation
    - e.g. "I think about killing myself"
- assess risk
  - plan: "Do you have a plan as to how you would end your life?"
  - intent: "Do you think you would actually carry out this plan?" "If not, why not?"
  - past attempts: highest risk if previous attempt in past year
    - ask about lethality, outcome, medical intervention
- assess suicidal ideation
  - onset and frequency of thoughts: "When did this start?" or "How often do you have these thoughts?"
  - control over suicidal ideation: "How do you cope when you have these thoughts?" "Could you call someone for help?"
  - intention: "Do you really want to end your life?" or "Do you wish to kill yourself?"
  - intended lethality: "What do you think would happen if you actually took those pills?"
  - access to means: "How will you get a gun?" or "Which bridge do you think you would go to?"
  - time and place: "Have you picked a date and place? Is it in an isolated location?"
  - provocative factors: "What makes you feel worse (e.g. being alone?)"
• protective factors: “What keeps you alive (e.g. friends, family, pets, faith, therapist)?”
• final arrangements: “Have you written a suicide note? Made a will? Given away your belongings?”
• practiced suicide or aborted attempts: “Have you ever put the gun to your head? Held the mediations in your hand? Stood at the bridge?”
• ambivalence: “I wonder if there is a part of you that wants to live, given that you came here for help?”

Assessment of Suicide Attempt
• setting (isolated vs. others present/chance of discovery)
• planned vs. impulsive attempt, triggers/stressors
• substance use/intoxication
• medical attention (brought in by another person vs. brought in by self to ED)
• time lag from suicide attempt to ED arrival
• expectation of lethality, dying
• reaction to survival (guilt/remorse vs. disappointment/self-blame)

Epidemiology
• attempted/completed = 20:1
• M:F = 1:4 for attempts, 3:1 for completed

Risk Factors
• epidemiologic factors
  • age: increases after age 14, second most common cause of death for ages 15-24, highest rates of completion in persons >65 yr
  • sex: male
  • race/ethnic background: white or Native Canadians
  • marital status: widowed/divorced
  • living situation: alone; no children <18 yr old in the household
  • other: stressful life events, access to firearms
• psychiatric disorders
  • mood disorders (15% lifetime risk in depression; higher in bipolar)
  • anxiety disorders (especially panic disorder)
  • schizophrenia (10-15% risk)
  • substance abuse (especially alcohol – 15% lifetime risk)
  • eating disorders (5% lifetime risk)
  • conduct disorder
  • personality disorders (borderline, antisocial)
• past history
  • prior suicide attempt
  • family history of suicide attempt/completion

Clinical Presentation
  symptoms associated with suicide
  • hopelessness
  • anhedonia
  • insomnia
  • severe anxiety
  • impaired concentration
  • psychomotor agitation
  • panic attacks

Management
• proper documentation of the clinical encounter and rationale for management is essential
• higher risk (hospitalization needs to be strongly considered)
  • patients with a plan and intention to act on the plan, access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder
  • do not leave patient alone; remove potentially dangerous objects from room
  • if patient refuses to be hospitalized, complete form for involuntary admission (Form 1)
• lower risk
  • patients who are not actively suicidal, with no plan or access to lethal means
  • discuss protective factors and supports in their life, remind them of what they live for; promote survival skills that helped them through previous suicide attempts
  • make a safety plan that could include an agreement that they will:
    • not harm themselves
    • avoid alcohol, drugs, and situations that may trigger suicidal thoughts
    • follow-up with you at a designated time
    • contact a health care worker, call a crisis line, or go to an emergency department if they feel unsafe or if their suicidal feelings return or intensify
• depression: consider hospitalization if symptoms severe or if psychotic features are present; otherwise outpatient treatment with good supports and SSRIs/SNRIs
• alcohol-related: usually resolves with abstinence for a few days; if not, suspect depression
• personality disorders: crisis intervention, may or may not hospitalize
• schizophrenia/psychosis: hospitalization might be necessary
• parasuicide/self-mutilation: long-term psychotherapy with brief crisis intervention when necessary
Psychotic Disorders

Definition
- characterized by a significant impairment in reality testing
- delusions or hallucinations (with/without insight into their pathological nature)
- behaving in a disorganized way so that it is reasonable to infer that reality testing is disturbed

Differential Diagnosis of Psychosis

Approach
- differentiate among psychotic disorders and distinguish them from other primary diagnoses with psychotic features
- consider symptoms, persistence, and time
- symptoms: what symptoms exist? The primary diagnosis needs full criteria to be met
  - mood: depressive episodes with psychotic features, manic episodes with psychotic features
  - psychotic: consider symptoms in Criterion A of schizophrenia, such as delusions, hallucinations, disorganized speech, grossly disorganized/catatonic behaviour, negative symptoms (i.e. diminished emotional expression or avolition)
- persistence: is there a time when certain symptom clusters are present without other clusters?
  - e.g. if there is a period of time with mood symptoms but not psychotic symptoms, consider mood disorder
  - e.g. if two weeks where psychotic symptoms persist in the absence of mood symptoms, consider schizoaffective disorder
- time: how long have the symptoms been present?

Table 1. Differentiating Psychotic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Psychotic Symptoms</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Brief Psychotic Disorder</td>
<td>≥1 positive symptoms of criterion A</td>
<td>&lt;1 mo</td>
</tr>
<tr>
<td>Schizophreniform Disorder</td>
<td>Criterion A</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Criterion A</td>
<td>&gt;6 mo</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>Criterion A + major mood episode, but ≥2 wk psychic without mood symptoms</td>
<td>&gt;1 mo</td>
</tr>
<tr>
<td>Delusional Disorder</td>
<td>Non-bizarre delusions, hallucinations</td>
<td>&gt;1 mo</td>
</tr>
<tr>
<td>2º to Subs ance Intoxication/ Withdrawal</td>
<td>Delusions or hallucinations During intoxication/withdrawal, not &gt;1 mo</td>
<td>without use</td>
</tr>
<tr>
<td>2º to Mood Disorder</td>
<td>Mood symptoms dominant + delusions/ hallucinations (mood congruent)</td>
<td>Psychosis may be present for the duration of the mood episode</td>
</tr>
</tbody>
</table>

Schizophrenia

DSM-5 Diagnostic Criteria for Schizophrenia

A. two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least one of these must be (1), (2), or (3)
1. delusions
2. hallucinations
3. disorganized speech (e.g. frequent derailment or incoherence)
4. grossly disorganized or catatonic behaviour
5. negative symptoms (i.e. diminished emotional expression or avolition)

B. decreased level of function: for a significant portion of time since onset, one or more major areas affected (e.g. work, interpersonal relations, self-care) is markedly decreased (or if childhood/adolescent onset, failure to achieve expected level)

C. at least 6 mo of continuous signs of the disturbance. Must include at least 1 mo of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms, during which, disturbance may manifest by only negative symptoms or by two or more Criterion A symptoms present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences)

D. rule out schizoaffective disorder and depressive or bipolar disorder with psychotic features because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness

E. rule out other causes: GMC, substances (e.g. drug of abuse, medication)

Disorganized Behaviours in Schizophrenia
- Catatonic stupor: fully conscious, but immobile, mute, and unresponsive
- Catatonic excitement: uncontrolled and aimless motor activity, maintaining bizarre positions for a long time
- Stereotypy: repeated but non-goal-directed movement (e.g. rocking)
- Mannerisms: goal-directed activities that are odd or out of context (e.g. grimacing)
- Echopraxia: imitates movements and gestures of others
- Automatic obedience: carries out simple commands in robot-like fashion
- Inappropriate affect, neglect of self-care, other odd behaviours (random shouting)
Epidemiology
- prevalence: 0.3-0.7%, M:F = 1:1
- mean age of onset: females late-20s; males early- to mid-20s
- suicide risk: 10% die by suicide, 30% attempt suicide

Etiology
- multifactorial: disorder is a result of interaction between both biological and environmental factors
  - genetic: 40% concordance in monozygotic (MZ) twins; 46% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected; vulnerable genes include Disrupted-in-Schizophrenia 1 (DISC1); neuregulin 1 (NRG 1); dystrobrevin binding protein (dysbindin (DTNBP1); catechol-O-methyltransferase (COMT); d-amino acid oxidase activator (DAOA); metabotropic glutamate receptor 3 (GRM3); and brain-derived neurotrophic factor (BDNF)
  - neurochemistry (’dopamine hypothesis’): excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis, while decreased dopamine in the prefrontal cortex may mediate negative and cognitive symptoms. GABA, glutamate, and ACh dysfunction are also thought to be involved
  - neuroanatomy: decreased frontal lobe function; asymmetric temporal/limbic function; decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytotoxicarchitectural abnormalities
  - neuroendocrinology: abnormal growth hormone, prolactin, cortisol, and ACTH
  - neuropsychology: global defects seen in attention, language, and memory suggest disrupted connectivity of neural networks
  - environmental: indirect evidence of cannabis use, geographical variance, winter season of birth obstetrical complications, and prenatal viral exposure

Pathophysiology
- neurodegenerative theory: natural history may be a rapid or gradual decline in function and ability to communicate
  - glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
  - neurodevelopmental theory: abnormal development of the brain from prenatal life
    - neurons fail to migrate correctly, make inappropriate connections, and apoptosis in later life

Comorbidity
- substance-related disorders
- anxiety disorders
- reduced life expectancy secondary to medical comorbidities (e.g. obesity, diabetes, metabolic syndrome, CV/pulmonary disease)

Management of Schizophrenia
- biological / somatic
  - acute treatment and maintenance: antipsychotics (haloperidol, risperidone, olanzapine, paliperidone; clozapine if refractory); often regimens of IM q2-4 wk used in severe cases to ensure adherence
  - adjunctive: ± mood stabilizers (for aggression/impulsiveness - lithium, valproate, carbamazepine) ± anxiolytics ± ECT
  - treat for at least 1-2 years after the first episode, at least 5 years after multiple episodes (relapse causes severe deterioration)
- psychosocial
  - psychotherapy (individual, family, group), supportive, CBT (see Table 14, PS41)
  - ACT (Assertive Community Treatment): mobile mental health teams that provide individualized treatment in the community and help patients with medication adherence, basic living skills, social support, job placements, resources
  - social skills training, employment programs, disability benefits
  - housing (group home, boarding home, transitional home)

Course and Prognosis
- majority of individuals display some type of prodromal phase
  - course is variable: some individuals have exacerbations and remissions while others remain chronically ill; accurate prediction of the long-term outcome is not possible
  - negative symptoms may be prominent early in the illness and may become more prominent and more disabling later on; positive symptoms appear and typically diminish with treatment
  - over time: 1/3 improve, 1/3 remain the same, 1/3 worsen

Good Prognostic Factors
- Acute onset
- Shorter duration of prodrome
- Female gender
- Good cognitive functioning
- Good premorbid functioning
- No family history
- Presence of affective symptoms
- Absence of structural brain abnormalities
- Good response to drugs
- Good support system
Psychotic Disorders

Schizophreniform Disorder

Diagnosis
Adopted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
• criteria A, D, and E of schizophrenia are met; an episode of the disorder lasts for at least 1 mo but less than 6 mo
• if the symptoms have extended past 6 mo the diagnosis becomes schizophrenia
• specifiers: with/without good prognostic features (e.g. acute onset, confusion, good premorbid functioning, absence of blunt/flat affect) with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis

Treatment
• similar to acute schizophrenia

Prognosis
• better than schizophrenia; begins and ends more abruptly; good pre and post-morbid function

Brief Psychotic Disorder

Diagnosis
Adopted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
• criteria A1-A4, D, and E of schizophrenia are met; an episode of the disorder lasts for at least 1 d but less than 1 mo with eventual full return to premorbid level of functioning
• specifiers: with/without marked stressors, with postpartum onset, with catatonia, current severity
• can occur after a stressful event or postpartum (see Postpartum Mood Disorders, PS12)

Treatment
• secure environment, antipsychotics, anxiolytics

Prognosis
• good, self-limiting, should return to pre-morbid function within 1 mo

Schizoaffective Disorder

DSM-5 Diagnostic Criteria for Schizoaffective Disorder
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. concurrent psychosis (criterion A of schizophrenia) and major mood episode - uninterrupted period of illness
B. delusions or hallucinations for 2 or more wk in the absence of a major mood episode during the lifetime duration of the illness
C. major mood episode symptoms are present for the majority of the total duration of the active and residual periods of the illness
D. the disturbance is not attributable to the effects of a substance or another medical condition
• specifiers: bipolar type, depressive type, with catatonia, type of episode, severity

Epidemiology
• one-third as prevalent as schizophrenia; schizoaffective disorder bipolar type more common in young adults, schizoaffective disorder depressive type more common in older adults
• depressive symptoms correlated with higher suicide risk

Treatment
• antipsychotics, mood stabilizers, antidepressants

Prognosis
• between that of schizophrenia and of mood disorder

Delusional Disorder

DSM-5 Diagnostic Criteria for Delusional Disorder
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. the presence of one (or more) delusions with a duration of 1 mo or longer
B. criterion A for schizophrenia has never been met
• Note: hallucinations, if present, are not prominent and are related to the delusional theme
C. apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behaviour is not obviously bizarre or odd
D. if manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder
• subtypes: erotomaniac, grandiose, jealous, persecutory, somatic, mixed, unspecified
• further specify: bizarre content, type of episode (e.g. first episode, multiple episode), severity
Treatment
• psychotherapy, antipsychotics, antidepressants

Prognosis
• chronic, unremitting course but high level of functioning; a portion will progress to schizophrenia

Mood Disorders

Definitions
• accurate diagnosis of a mood disorder requires a careful past medical and psychiatric history to detect past mood episodes and to rule out whether these episodes were secondary to substance use, a medical condition, a loss, etc
• mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration (e.g. major depressive, manic, mixed, hypomanic). DSM-5 Criteria for mood episodes are listed below
• types of mood disorders include
  - depressive (major depressive disorder, persistent depressive disorder)
  - bipolar (bipolar I/II disorder, cyclothymia)
  - secondary to general medical condition, substances, medications, other psychiatric issue

Medical Workup of Mood Disorder
• routine screening: physical exam, CBC, thyroid function test, extended electrolytes, urinalysis, drug screen, medications list
• additional screening: neurological consultation, chest X-ray, ECG, CT head

Mood Episodes

DSM-5 Diagnostic Criteria for Major Depressive Episode
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. ≥5 of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia)

Note: do not include symptoms that are clearly attributable to another medical condition
• depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
• markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
• significant and unintentional weight loss/weight gain, or decrease/increase in appetite nearly every day
• insomnia or hypersomnia nearly every day
• psychomotor agitation or retardation nearly every day
• fatigue or loss of energy nearly every day
• feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
• diminished ability to think or concentrate, or indecisiveness, nearly every day
• recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. the episode is not attributable to the direct physiological effects of a substance or a GMC

DSM-5 Criteria for Manic Episode
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood, and abnormally and persistently increased goal-directed activity or energy, lasting ≥1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary)

B. during the period of mood disturbance and increased energy or activity, ≥3 of the following symptoms have persisted (4 if the mood is only irritable) have been present to a significant degree and represent a noticeable change from usual behaviour
• inflated self-esteem or grandiosity
• decreased need for sleep (e.g. feels rested after only 3 h of sleep)
• more talkative than usual or pressure to keep talking
• flight of ideas or subjective experience that thoughts are racing
• distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
• increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
• excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained spending sprees, sexual indiscretions, or foolish business investments)

C. the mood disturbance is sufficiently severe to cause marked impairment in social/occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features

D. the episode is not attributable to the physiological effects of a substance or another medical condition
Note: A full manic episode that emerges during antidepressant treatment but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis. Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Hypomanic Episode
- criterion A and B of a manic episode is met, but duration is ≥4 days
- episode associated with an uncharacteristic change in functioning that is observable by others but not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features (if these are present the episode is, by definition, manic)

Mixed Features
- an episode specifier in bipolar or depression that indicates the presence of both depressive and manic symptoms concurrently, classified by the disorder and primary mood episode component (e.g. bipolar disorder, current episode manic, with mixed features)
- clinical importance due to increased suicide risk
- if found in patient diagnosed with major depression, high index of suspicion for bipolar disorder
- while meeting the full criteria for a major depressive episode, the patient has on most days ≥3 of criteria B for a manic episode
- while meeting the full criteria for a manic/hypomanic episode, the patient has on most days ≥3 of criteria A for a depressive episode (the following criterion A cannot count: psychomotor agitation, insomnia, difficulties concentrating, weight changes)

Depressive Disorders

MAJOR DEPRESSIVE DISORDER

DSM-5 Diagnostic Criteria for Major Depressive Disorder (MDD)
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. presence of a MDE
B. the MDE is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizoaffective disorder, delusional disorder, or psychotic disorder NOS
C. there has never been a manic episode or a hypomanic episode

Note: This exclusion does not apply if all of the manic-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of another medical condition

- specifiers: with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, seasonal pattern
- single vs. recurrent is an episode descriptor that carries prognostic significance. Recurrent is classified as the patient having two or more distinct MDE episodes; to be considered separate the patient must have gone 2 consecutive months without meeting criteria

Epidemiology
- lifetime prevalence: 12%
- peak prevalence age 15-25 yr (M:F = 1:2)

Etiology
- biological
  - genetic: 65-75% MZ twins; 14-19% DZ twins, 2-4 fold increased risk in first-degree relatives
  - neurotransmitter dysfunction: decreased activity of 5-HT, NE, and DA at neuronal synapse; changes in GABA and glutamate; various changes detectable by fMRI
  - neuroendocrine dysfunction: abnormal HPA axis activity
  - neuroanatomy and neurophysiology: decreased hippocampal volume, increased size of ventricles; decreased REM latency and slow-wave sleep; increased REM length
  - immunologic: increased pro-inflammatory cytokines IL-6 and TNF
  - secondary to medical condition, medication, substance use disorder
- psychosocial
  - psychodynamic (e.g. low self-esteem, unconscious aggression towards self or loved ones, disordered attachment)
  - cognitive (e.g. distorted schemata, Beck's cognitive triad: negative views of the self, the world, and the future)
  - environmental factors (e.g. job loss, bereavement, history of abuse or neglect, early life adversity)
  - comorbid psychiatric diagnoses (e.g. anxiety, substance abuse, developmental disability, dementia, eating disorder)

Risk Factors
- sex: F>M, 2:1
- family history: depression, alcohol abuse, suicide attempt or completion
- childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
- personality: neuroticism, insecure, dependent, obsessive
- recent stressors: illness, financial, legal, relational, academic
- lack of intimate, confiding relationships or social isolation
- low socioeconomic status

Antidepressants for Depression in Physical Medical Illness
Purpose: To evaluate whether antidepressants are clinically effective and acceptable for treatment of depression in patients who also have a physical illness.
Methods: Systematic review of RCTs comparing any antidepressant drug as defined by the British National Formulary with placebo or no treatment, in patients aged 16 years and over who have been formally diagnosed with depression by any criterion, and have a specified physical disorder. Main outcome measures were number of individuals demonstrating improvement or recovery by the end of the trial, and number completing treatment (as a proxy for treatment acceptability).
Results: Eighteen studies with 838 patients having varied physical illnesses were included. Patients treated with antidepressants were significantly more likely to improve than those given placebo (13 studies, OR 0.37, 95% CI 0.27-0.51) or no treatment (1 study, OR 3.45, 95% CI 1.33-9.30) (number needed to treat relative to placebo = 4.2, 3.2-6.4).
Most antidepressants were associated with a small but significant increase in dropouts (OR 1.36, 1.14-2.40; NNH 9.8, 5.4-42.9). Among two studies evaluating impact on function and quality of life, drug was found to be better than no treatment for HIV patients, and drug was not significantly different than placebo in lung disease patients. Tetracyclines appeared to be more effective than SSRI but also more likely to produce dropouts, based on non-randomized comparisons between trials.
Conclusion: Antidepressants cause improvements in depression in patients with various physical illnesses significantly more frequently than placebo or no treatment. Antidepressants were reasonably acceptable to patients. Tetracyclines may be more effective than SSRI but may also produce more dropouts. As such, antidepressants should at least be considered in those with comorbid physical illness and depression.
Depression in the Elderly

- affects about 15% of community residents >65 yr old; up to 50% in nursing homes
- high suicide risk due to social isolation, chronic medical illness, decreased independence
- suicide peak: males aged 80-90; females aged 50-65
- dysphoria may not be a reliable indicator of depression in those >85 yr
- often present with somatic complaints (e.g. changes in weight, sleep, energy) or anxiety symptoms
- may have prominent cognitive changes after onset of mood symptoms (dementia syndrome of depression)
- see Table 3, PS21, for a comparison of delirium and dementia

Treatment

- lifestyle: increased aerobic exercise, mindfulness-based stress reduction, zinc supplementation
- biological: SSRIs, SNRIs, other antidepressants, somatic therapies (see Pharmacotherapy, PS42, and Somatic Therapies, PS49)
  - 1st line pharmacotherapy: sertraline, escitalopram, venlafaxine, mirtazapine
  - for partial or non-response, can change class or add augmenting agent (bupropion, quetiapine-XR, aripiprazole, lithium)
  - typical response to antidepressant treatment: physical symptoms improve at 2 wk, mood/cognition by 4 wk; if no improvement after 4 wk at a therapeutic dosage, alter regimen
  - ECT: currently fastest and most effective treatment for MDD. Consider in severe, psychotic or treatment resistant cases
  - rTMS: early data support efficacy equivalent to ECT with good safety and tolerability
  - phototherapy: especially if seasonal component, shift work, sleep dysregulation
  - psychological
    - individual therapy (interpersonal, CBT), family therapy, group therapy
    - social: vocational rehabilitation, social skills training
    - experimental: magnetic seizure therapy, deep brain stimulation, vagal nerve stimulation, ketamine

Prognosis

- one year after diagnosis of MDD without treatment: 40% of individuals still have symptoms that are sufficiently severe to meet criteria for MDD, 20% continue to have some symptoms that no longer meet criteria for MDD, 40% have no mood disorder

PERSISTENT DEPRESSIVE DISORDER

DSM-5 Diagnostic Criteria for Persistent Depressive Disorder

Note: in DSM-IV-TR this was referred to as Dysthymia

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A. depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for ≥2 yr

B. presence, while depressed, of ≥2 of the following:
  - poor appetite or overeating
  - insomnia or hypersomnia
  - low energy or fatigue
  - low self-esteem
  - poor concentration or difficulty making decisions
  - feelings of hopelessness

C. during the 2 yr period (1 yr for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 mo at a time

D. criteria for a major depressive disorder may be continuously present for 2 yr

E. there has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder

F. the disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrrenia spectrum and other psychotic disorder

G. the symptoms are not due to the direct physiological effects of a substance or another medical condition

H. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Epidemiology

- lifetime prevalence: 2.3%; M=F

Treatment

- psychological
  - traditionally, psychotherapy was the principal treatment for persistent depressive disorder; recent evidence suggests some benefit, but generally inferior to pharmacological treatment. Combinations of the two may be most efficacious
  - biological
    - antidepressant therapy: SSRIs (e.g. sertraline, paroxetine), TCAs (e.g. imipramine) as an outpatient
Postpartum Mood Disorders

Postpartum “Blues”
- transient period of mild depression, mood instability, anxiety, decreased concentration; considered to be normal changes in response to fluctuating hormonal levels, the stress of childbirth, and the increased responsibilities of motherhood
- occurs in 50-80% of mothers; begins 2-4 d postpartum, usually lasts 48 h, can last up to 10 d
- does not require psychotropic medication
- usually mild or absent; feelings of inadequacy, anhedonia, thoughts of harming baby, suicidal thoughts

MAJOR DEPRESSIVE DISORDER WITH PERIPARTUM ONSET (POSTPARTUM DEPRESSION)

Clinical Presentation
- MDD with onset during pregnancy or within 4 wk following delivery
- typically lasts 2-6 mo; residual symptoms can last up to 1 yr
- may present with psychosis (rare, 0.2%), usually associated with mania, but also with MDE
- severe symptoms include extreme disinterest in baby, suicidal and infanticidal ideation

Epidemiology
- occurs in 10% of mothers, risk of recurrence 50%

Risk Factors
- previous history of a mood disorder (postpartum or otherwise), family history of mood disorder
- psychosocial factors: stressful life events, unemployment, marital conflict, lack of social support, unwanted pregnancy, colicky or sick infant

Treatment
- psychotherapy (CBT or IPT)
- short-term safety of maternal SSRIs for breastfeeding infants established; long-term effects unknown
- if depression severe or psychotic symptoms present, consider ECT

Prognosis
- impact on child development: increased risk of cognitive delay, insecure attachment, behavioural disorders
- treatment of mother improves outcome for child at 8 mo through increased mother-child interaction

Bipolar Disorders

BIPOLAR I / BIPOLAR II DISORDER

Definition
- Bipolar I Disorder
  - disorder in which at least one manic episode has occurred
  - if manic symptoms lead to hospitalization, or if there are psychotic symptoms, the diagnosis is BP I
  - commonly accompanied by at least 1 MDE but not required for diagnosis
  - time spent in mood episodes: 53% asymptomatic, 32% depressed, 9% cycling/mixed, 6% hypo/manic
- Bipolar II Disorder
  - disorder in which there is at least 1 MDE, 1 hypomanic and no manic episodes
  - while hypomania is less severe than mania, Bipolar II is not a “milder” form of Bipolar I
  - time spent in mood episodes: 46% asymptomatic, 50% depressed, 1% cycling/mixed, 2% hypo/manic
- Bipolar II is often missed due to the severity and chronicity of depressive episodes and low rates of spontaneous reporting and recognition of hypomanic episodes

Classification
- classification of bipolar disorder involves describing the disorder (I or II) and the current or most recent mood episode as either manic, hypomanic, or depressed
- specifiers: with anxious distress, depressed with mixed features, hypo/manic with mixed features, melancholic features, atypical features, mood-congruent or -incongruent psychotic features, catatonia, peripartum onset, seasonal pattern, rapid cycling (4+ mood episodes in 1 yr)

Epidemiology
- lifetime prevalence: 1% BPI, 1.1% BPII, 2.4% Subthreshold BPD; M:F = 1:1
- age of onset: teens to 20s usually MDE first, manic episode 6-10 years after average age of first manic episode 32 yr

Risk Factors
- genetic: 60-65% of bipolar patients have family history of major mood disorders, especially bipolar disorders
- clinical features of MDE history favouring bipolar over unipolar diagnosis: early age of onset (<25 yr), increased number of MDEs, psychotic symptoms, postpartum onset, anxiety disorders (especially separat on, panic), antidepressant failure due to early “poop out” or hypomanic symptoms, early impulsivity and aggression, substance abuse, cyclothymic temperament

Selective Serotonin Reuptake Inhibitors in Pregnancy and Infant Outcomes

Paediatr Child Health 2011;16:562-563
Canadian Pediatric Society (CPS) clinical practice guideline recommendations: It is important to treat depression in pregnancy. There is no evidence that SSRIs increase the risk of major malformations. There is conflicting evidence concerning the association of paroxetine and cardiac malformations. SSRIs are not contraindicated while breast-feeding.

Bipolar II is quite often missed and many patients are symptomatic for up to a decade before accurate diagnosis and treatment

Patients with bipolar disorder are at higher risk for suicide when they switch from mania to depression, especially as they become aware of consequences of their behaviour during the manic episode
Treatment
- **lifestyle:** psychoeducation regarding cycling nature of illness, ensure regular check ins, develop early warning system, “emergency plan” for manic episodes, promote stable routine (sleep, meals, exercise)
- **biological:** lithium, anticonvulsants, antipsychotics, ECT (if refractory); monotherapy with antidepressants should be avoided
  - mood stabilizers vary in their ability to “treat” (reduce symptoms acutely) or “stabilize” (prevent relapse and recurrence) manic and depressive symptoms; multi-agent therapy is common
  - treating mania: lithium, valproate, carbamazepine (2nd line), SGA, ECT, benzodiazepines (for acute agitation)
  - preventing mania: same as above but usually at lower dosages, minus benzodiazepines
  - treating depression: lithium, lurisdione, quetiapine, lamotrigine, antidepressants (only with mood stabilizer), ECT
  - preventing depression: same as above plus aripiprazole, valproate (note: quetiapine first line in treating bipolar II depression)
  - mixed episode or rapid cycling: multi-agent therapy, lithium or valproate + SGA (lurisdione, aripiprazole, olanzapine)
- **psychological:** supportive psychotherapy, CBT, IPT or interpersonal social rhythm therapy, family therapy
- **social:** vocational rehabilitation, consider leave of absence from school/work, assess capacity to manage finances, drug and ETOH cessation, sleep hygiene, social skills training, education and recruitment of family members

Course and Prognosis
- high suicide rate (15% mortality from suicide), especially in mixed states
- BP I and II are chronic conditions with a relapsing course featuring alternating manic and depressive episodes; depressive symptoms tend to occur more frequently and last longer than manic episodes
- can achieve high level of functioning between episodes
- may switch rapidly between depression and mania without any period of euthymia in between
- high recurrence rate for mania – 90% will have a subsequent episode in the next 5 yr
- long term follow-up of BP I – 15% well, 45% well with relapses, 30% partial remission, 10% chronically ill

**CYCLOTHYMIA**
Adapted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

**Diagnosis**
- presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for full hypomanic episode or MDE) for ≥2 yr; never without symptoms for ≥2 mo
- never have met criteria for MDE, manic or hypomanic episodes
  - symptoms not better explained by any psychotic disorder (including schizoaffective, schizophrenia, schizoaffectiveform, delusional disorder, or other specified/unspecified)
  - symptoms are not due to the direct physiological effects of a substance or GMC
- symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

**Treatment**
similar to Bipolar I: mood stabilizer ± psychotherapy, avoid antidepressant monotherapy, treat any comorbid substance use disorder

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**Anxiety Disorders**

**Definition**
- anxiety is a universal human characteristic involving tension, apprehension, or even terror which serves as an adaptive mechanism to warn about an external threat
- manifestations of anxiety are a result of the activation of the sympathetic nervous system and can be described through P:
  - **physiology:** main brain structure involved is the amygdala (fear conditioning); neurotransmitters involved include 5-HT, cholecystokinin, epinephrine, norepinephrine, DA
  - **psychology:** one’s perception of a given situation is distorted which causes one to believe it is threatening in some way
  - **behaviour:** once feeling threatened, one responds by escaping or facing the situation, thereby causing a disruption in daily functioning
- anxiety becomes pathological when:
  - fear is greatly out of proportion to risk/severity of threat
  - response continues beyond existence of threat or becomes generalized to other similar or dissimilar situations
  - social or occupational functioning is impaired
  - often comorbid with substance use and depression

---

**Lithium** is among few agents with proven efficacy in preventing suicide attempts and completions

**Monotherapy with antidepressants should be avoided in patients with bipolar depression as patients can switch from depression into mania**

**The 4 L's or Bipolar Depression**
Lithium, Lamotrigine, Lurasidone, SeroqueL

**A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-Term Change**
*J Clin Psychiatry* 2006;67:277-286

**Purpose:** To evaluate long-term change with cognitive therapy plus emotive techniques for the treatment of bipolar disorder.

**Methods:** Blinded RCT including patients with DSM-IV bipolar I or II disorder allocated to either a 6 mo trial of cognitive therapy (CT) with emotive techniques or treatment as usual. Both groups received mood stabilizers. Main outcomes were relapse rates, dysfunctional attitudes, psychosocial functioning, hopelessness, self-control, and medication adherence. Patients were assessed by independent raters blinded to treatment group.

**Results:** At 6 mo, CT patients experienced fewer depressive symptoms and fewer dysfunctional attitudes. There was a non-significant (p=0.06) trend to greater time to depressive relapse. At 12 mo follow-up, CT patients had lower Young Mania Rating scores and improved behavioral self-control. At 18 mo, CT patients reported less severity of illness.

**Conclusions:** CT appears to provide benefits in the 12 mo after completion of therapy.
Differential Diagnosis

Table 2. Differential Diagnosis of Anxiety Disorders

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Post-MI, arrhythmia, congestive heart failure, pulmonary embolus, mitral valve prolapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Asthma, COPD, pneumonia, hyperventilation</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hyperthyroidism, pheochromocytoma, hypoglycemia, hyperadrenalism, hyperparathyroidism</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Vitamin B12 deficiency, porphyria</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neoplasm, vestibular dysfunction, encephalitis</td>
</tr>
<tr>
<td>Substance-Induced</td>
<td>Intoxication (caffeine, amphetamines, cocaine, thyroid preparations, OTC for colds/decongestants), withdrawal (benzodiazepines, alcohol)</td>
</tr>
<tr>
<td>Other Psychiatric Disorders</td>
<td>Psychotic disorders, mood disorders, personality disorders (OCPD), somatoform disorders</td>
</tr>
</tbody>
</table>

Medical Workup of Anxiety Disorder
- routine screening: physical exam, CBC, thyroid function test, electrolytes, urinalysis, urine drug screening
- additional screening: neurological consultation, chest X-ray ECG, CT head

Panic Disorder

DSM-5 Diagnostic Criteria for Panic Disorder

A. recurrent unexpected panic attacks - a panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur
- palpitations, pounding heart, or accelerated heart rate
- sweating
- trembling or shaking
- sensations of shortness of breath or smothering
- feelings of choking
- chest pain or discomfort
- nausea or abdominal distress
- feeling dizzy, unsteady, light-headed, or faint
- chills or heat sensations
- paresthesias (numbness or tingling sensations)
- derealization (feelings of unreality) or depersonalization (being detached from oneself)
- fear of losing control or “going crazy”
- fear of dying

B. 1 mo (or more) of “anxiety about panic attacks” - at least one of the attacks has been followed by one or both of the following:
- persistent concern or worry about additional panic attacks or their consequences
- a significant maladaptive change in behaviour related to the attacks

C. the disturbance is not attributable to the physiological effects of a substance or another medical condition

D. the disturbance is not better explained by another mental disorder

Epidemiology
- prevalence: 2-5% (one of the top five most common reasons to see a family doctor); M:F = 1:2-3
- onset: average early-mid 20s, familial pattern

Treatment
- psychological
  - CBT: interoceptive exposure (eliciting symptoms of a panic attack and learning to tolerate the symptoms without coping strategies); cognitive restructuring (addressing underlying beliefs regarding the panic attacks), relaxation techniques (visualization, box-breathing)
- pharmacological
  - SSRIs: fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline
  - SNRI: venlafaxine
  - with SSRIs/SNRIs, start with low doses, titrate up slowly
  - anxiety disorders often require treatment at higher doses for a longer period of time than depression (i.e. full response may take up to 12 wk)
  - treat for up to 1 year after symptoms resolve to avoid relapse
  - to prevent non-compliance due to physical side effects, explain symptoms to expect prior to initiation of therapy
  - other antidepressants (mirtazapine, MAOIs)
  - consider avoiding buproprion or TCAs due to stimulating effects (exacerbate anxious symptoms)
  - benzodiazepines (short-term, low dose, regular schedule, long half-life, avoid prn usage)

Starting Medication for Anxiety
- start low, go slow, aim high and explain symptoms to expect prior to initiation of therapy to prevent non-compliance due to physical side effects

Prognosis
- 6-10 yr post-treatment: 30% well, 40-50% improved, 20-30% no change or worse
- clinical course: chronic, but episodic with psychosocial stressors
Agoraphobia

DSM-5 Diagnostic Criteria for Agoraphobia
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. marked fear or anxiety about two (or more) of the following five situations:
   - using public transportation
   - being in open spaces
   - being in enclosed places
   - standing in line or being in a crowd
   - being outside of the home alone
B. the individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms
C. the agoraphobic situations almost always provoke fear or anxiety
D. the agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety
E. the fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context
F. the fear, anxiety, or avoidance is persistent, typically lasting ≥6 mo
G. the fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
H. if another medical condition is present, the fear, anxiety, or avoidance is clearly excessive
I. the fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder and are not related exclusively to obsessions, perceived defects or flaws in physical appearance, reminders of traumatic events, or fear of separation

Note: agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned

Treatment
- as per panic disorder

Generalized Anxiety Disorder

DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder
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A. excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance)
B. the individual finds it difficult to control the worry
C. the anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 mo)
   1. restlessness or feeling keyed up or on edge
   2. being easily fatigued
   3. difficulty concentrating or mind going blank
   4. irritability
   5. muscle tension
   6. sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D. the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition
F. the disturbance is not better explained by another mental disorder

Epidemiology
- 1 yr prevalence: 3-8%; M:F = 1:2
- if considering only those receiving inpatient treatment, ratio is 1:1
- most commonly presents in early adulthood

Treatment
- lifestyle: caffeine and EtOH avoidance, sleep hygiene
- psychological: CBT including relaxation techniques, mindfulness
- biological
   - SSRIs and SNRIs are 1st line (paroxetine, escitalopram, sertraline, venlafaxine XL)
   - 2nd line: buspirone (tid dosing), bupropion (caution due to stimulating effects),
   - add-on benzodiazepines (short-term, low dose, regular schedule, long half-life, avoid prn usage)
   - β-blockers not recommended

Prognosis
- chronically anxious adults become less so with age
- depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress
- difficult to treat
**Phobic Disorders**

Adopted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013 American Psychiatric Association

**Specific Phobia**
- definition: marked and persistent (>6 mo) fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
- lifetime prevalence 12-16%; M:F ratio variable
- types: animal/insect, environment (heights, storms), blood/injection/injury, situational (airplane, closed spaces), other (loud noise, clowns)

**Social Phobia (Social Anxiety Disorder)**
- definition: marked and persistent (>6 mo) fear of social or performance situations in which one is exposed to unfamiliar people or to possible scrutiny by others; fearing he/she will act in a way that may be humiliating or embarrassing (e.g. public speaking, initiating or maintaining conversation, dating, eating in public)
- 12 mo prevalence rate may be as high as 7%; M:F ratio approximately equal

**Diagnostic Criteria for Phobic Disorders**
- exposure to stimulus almost invariably provokes an immediate anxiety response; may present as a panic attack
- person recognizes fear as excessive or unreasonable
- situations are avoided or endured with anxiety/distress
- significant interference with daily routine, occupational/social functioning, and/or marked distress

**Treatment**
- psychological
  - cognitive behaviour therapy (focusing on both in vivo and virtual exposure therapy, gradually facing feared situations)
  - behavioural therapy is more efficacious than medication
- biological
  - SSRIs/SNRIs (e.g. fluoxetine, paroxetine, sertraline, venlafaxine), MAOIs
  - β-blockers or benzodiazepines in acute situations (e.g. public speaking)

**Prognosis**
- chronic

**Obsessive-Compulsive Disorder**

**DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder**
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A. presence of obsessions, compulsions, or both
- obsessions are defined by (1) and (2)
  1. recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and cause marked anxiety or distress in most individuals
  2. the individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e. by performing a compulsion; see below)
- compulsions are defined by (1) and (2)
  1. repetitive behaviours (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly
  2. behaviours mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive

B. the obsessions or compulsions are time-consuming (e.g. take >1 h/d) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. the obsessive-compulsive symptoms are not attributable to the physiological effects of a substance or another medical condition

D. the disturbance is not better explained by the symptoms of another mental disorder

**Epidemiology**
- 12 mo prevalence 1.1-1.8%; females affected at slightly higher rates than males
- rate of OCD in first-degree relatives is higher than in the general population

**Treatment**
- CBT: exposure with response prevention (ERP) – involves exposure to feared situations with the addition of preventing the compulsive behaviours; cognitive strategies include challenging underlying beliefs
- pharmacotherapy: SSRIs/SNRIs (12-16 week trials, higher doses vs. depression), clomipramine; adjunctive antipsychotics (risperidone)

**Prognosis**
- tends to be refractory and chronic
### DSM-5 Diagnostic Criteria for Post-Traumatic Stress Disorder


A. exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
   1. directly experiencing the traumatic event(s)
   2. witnessing, in person, the event(s) as it occurred to others
   3. learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental
   4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g. first responders collecting human remains: police officers repeatedly exposed to details of child abuse)

B. presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred
   1. recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)
   2. recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s)
   3. dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring
   4. intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
   5. marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)

C. persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following
   1. avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)
   2. avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)

D. negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following
   1. inability to remember an important aspect of the traumatic event(s)
   2. persistent and exaggerated negative beliefs or expectations about oneself, others, or the world
   3. persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others
   4. persistent negative emotional state (e.g. fear, horror, anger, guilt, or shame)
   5. markedly diminished interest or participation in significant activities
   6. feelings of detachment or estrangement from others
   7. persistent inability to experience positive emotions

E. marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following
   1. irritable behaviour and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects
   2. reckless or self-destructive behaviour
   3. hypervigilance
   4. exaggerated startle response
   5. problems with concentration
   6. sleep disturbance (e.g. difficulty falling or staying asleep or restless sleep)

F. duration of the disturbance (criteria B, C, D, and E) is more than 1 mo

G. the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

H. the disturbance is not attributable to the physiological effects of a substance or another medical condition

### Epidemiology

- prevalence of 7% in general population
- men's trauma is most commonly combat experience/physical assault; women's trauma is usually physical or sexual assault

### Treatment

- psychotherapy, CBT
  - ensure safety and stabilize: emotional regulation techniques (e.g. breathing, relaxation)
  - once coping mechanisms established, can explore/mourn trauma - challenge dysfunctional beliefs, etc.
  - reconnect and integrate - exposure therapy, etc.
• biological
  ■ SSRIs (e.g. paroxetine, sertraline)
  ■ prazosin (for treating disturbing dreams and nightmares)
  ■ benzodiazepines (for acute anxiety)
  ■ adjunctive atypical antipsychotics (risperidone, olanzapine)
• eye movement desensitization and reprocessing (EMDR): an experimental method of reprocessing memories of distressing events by recounting them while using a form of dual attention stimulation such as eye movements, bilateral sound, or bilateral tactile stimulation (its use is controversial because of limited evidence)

Complications
• substance abuse, relationship difficulties, depression, impaired social and occupational functioning disorders, personality disorders

Adjustment Disorder

Definition
• a diagnosis encompassing patients who have difficulty coping with a stressful life event or situation and develop acute, often transient, emotional or behavioural symptoms that resemble less severe versions of other psychiatric conditions

DSM 5 Diagnostic Criteria for Adjustment Disorder
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A. the development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 mo of the onset of the stressor(s)
B. these symptoms or behaviours are clinically significant as evidenced by either of the following:
  ■ marked distress that is in excess of what would be expected from exposure to the stressor
  ■ significant impairment in social or occupational (academic) functioning
C. the stress-related disturbance does not meet criteria for another mental disorder and is not merely an exacerbation of a pre-existing mental disorder
D. the symptoms do not represent normal bereavement
E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 mo
  ■ specifiers: with depressed mood, with anxiety, with mixed anxiety/depression, with conduct disturbance, with mixed disturbance of conduct/emotions unspecified

Classification
• types of stressors
  ■ single (e.g. termination of romantic relationship)
  ■ multiple (e.g. marked business difficulties and marital problems)
  ■ recurrent (e.g. seasonal business crises)
  ■ continuous (e.g. living in a crime-ridden neighbourhood)
  ■ developmental events (e.g. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)

Epidemiology
• F:M 2:1, prevalence 2-8% of the population

Treatment
• brief psychotherapy individual or group (particularly useful for patients dealing with unique and specific medical issues; e.g. colostomy or renal dialysis groups), crisis intervention
• biological
  ■ benzodiazepines may be used for those with significant anxiety symptoms (short-term, low-dose, regular schedule)

Bereavement

Clinical Presentation
• bereavement is a normal psychological and emotional reaction to a significant loss, also called grief or mourning
• length and characteristics of “normal” bereavement are variable between individuals/cultures
• normal response: protest → searching and acute anguish → despair and detachment → reorganization
• presence of the following symptoms may indicate abnormal grief/presence of MDD
  ■ guilt about things other than actions taken or not taken by the survivor at the time of death
  ■ thoughts of death other than the survivor feeling that they would be better off dead or should have died with the deceased person; morbid preoccupation with worthlessness
  ■ marked psychomotor retardation; prolonged and marked functional impairment
  ■ hallucinatory experiences other than thinking that the survivor hears the voice of or transiently sees the image of the deceased person
  ■ dysphoria that is pervasive and independent of thoughts or triggers of the deceased, absence of mood reactivity

Risk Factors for Poor Bereavement Outcome
• Poor social supports
• Unanticipated death or lack of preparation for death
• Highly dependent relationship with deceased
• High initial distress
• Other concurrent stresses and losses
• Death of a child
• Pre-existing psychiatric disorders, especially depression and separation anxiety
Neurocognitive Disorders

Delirium

- see Neurology, N20 and Geriatric Medicine, G4

DSM-5 Diagnostic Criteria for Delirium

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A. attention and awareness: disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)

B. acute and fluctuating: disturbance develops over short period of time (usually hours to days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day

C. cognitive changes: an additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)

D. not better explained: disturbances in criteria A and C are not better explained by another neurocognitive disorder (pre-existing, established, or evolving) and do not occur in the context of a severely reduced level of arousal (e.g. coma)

E. direct physiological cause: evidence that disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or medication), toxin, or is due to multiple etiologies

Note: delirium can be described as HYPERactive, HYPOfactive, or MIXED presentation. While patients with hyperactive delirium may demonstrate features of restlessness and agitation, as well as experience hallucinations and delusions, those with hypoactive delirium present with lethargy, sedation and respond slowly to questioning

Clinical Presentation and Assessment

- common symptoms
  - distractibility, disorientation (time, place, rarely person)
  - misinterpretations, illusions, hallucinations
  - speech/language disturbances (dysarthria, dysnomia)
  - affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
  - shifts in psychomotor activity (groping/picking at clothes, attempts to get out of bed when unsafe, sudden movements, sluggishness, lethargy)
  - impairment in sleep duration and/or architecture (e.g. sleep-wake reversal)
  - Folstein Mini Mental Status Exam or Montreal Cognitive Assessment are helpful to assess baseline of altered mental state (i.e. score will improve as symptoms resolve)

Risk Factors

- most common precipitating factors include: polypharmacy (particularly involving psychoactive drugs such as anticholinergics), infection, dehydration, immobility, malnutrition, and use of bladder catheters
- other factors include:
  - hospitalization (incidence 10-56%), frail and surgical patients are at the greatest risk
  - previous delirium
  - nursing home residents (incidence 60%)
  - old age (especially males)
  - severe illness (e.g. cancer, AIDS)
  - recent anesthesia or surgery
  - brain vulnerability: substance abuse, past psychiatric illness, pre-existing neurologic or neurocognitive disorder

Investigations

- standard: CBC and differential, electrolytes (including Ca, Mg and PO₄), glucose, BUN, Cr, TSH/T4, LFTs, vit B₆, folate, albumin; urinalysis, urine C+S
- as indicated: ECG (to assess QT interval when considering treatment with an antipsychotic agent), CXR, CT head, toxicology/heavy metal screen, VDRL, HIV, LP blood cultures, EEG (typically abnormal - generalized slowing [most common] or fast activity, can also be used to rule out underlying seizures or post-ictal states as etiology)

Treatment

- support and watchful waiting should be first line, as well as education and normalization of the grief process
- screen for increased alcohol, cigarette and drug use
- normal grief should not be treated with antidepressant or anxiolytic medication, as it is important to allow the person to experience the whole mourning process to achieve resolution
- psychosocial: for those needing additional support, complex grief/bereavement, or significant MDD, grief therapy (individual or group) is indicated
- pharmacotherapy: if MDD present, past history of mood disorders, severe or autonomous symptoms

Neurocognitive Disorders

Etiology of Delirium

- old age
- nursing home residents (incidence 60%)
- hospitalization (incidence 10-56%)
- frail and surgical patients
- hyperactive or hypoactive

Bereavement is associated with a significant increase in morbidity and mortality acutely following the loss, with effects seen up to 1 yr after.

Loneliness is the most common symptom that continues to persist in normal bereavement and may last several years.

Confusion Assessment Method (CAM) for Diagnosis of Delirium

Highly sensitive and specific method to diagnosis delirium
- Part 1: an assessment instrument that screens for overall cognitive impairment
- Part 2: includes four features found best able to distinguish delirium from other cognitive impairments

Need (1) + (2) = (3 or 4)
(1) Acute onset and fluctuating course
(2) Inattention
(3) Disorganized thinking
(4) Altered level of consciousness - hyperactive or hypoactive

Visual hallucinations are organic until proven otherwise

Etiology of Delirium

I WATCH DEATH
- Infectious (encephalitis, meningitis, UTI, pneumonia)
- Withdrawal (alcohol, barbiturates, benzodiazepines)
- Acute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
- Trauma (head injury, post-operative)
- CNS pathology (stroke, hemorhage, tumour, seizure disorder, Parkinson’s)
- Hypoxia (anemia, cardiac failure, pulmonary embolus)
- Deficiencies (vitamin B₁₂, folic acid, thiamine)
- Endocrinopathies (thyroid, glucose, parathyroid, adrenal)
- Acute vascular (shock, vasculitis, hypertensive encephalopathy)
- Toxins: substance use sedatives, opioids (especially morphine), anesthetics, anticholinergics anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
- Heavy metals (arsenic, lead, mercury)
indications for CT head: focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, history of cancer

MRI may be useful to exclude acute or subacute stroke and multifocal inflammatory lesions in patients with delirium of unknown cause and negative head CT

Management
- identify and manage underlying cause
- identify and treat underlying cause immediately
- stop all non-essential medications
- maintain nutrition, hydration, electrolyte balance and monitor vitals
- optimize the environment
  - environment: quiet, well-lit, near window for cues regarding time of day
  - optimize hearing and vision
  - room near nursing station for closer observation; constant care if patient jumping out of bed, pulling out lines
  - family member present for reassurance and re-orientation
- frequent orientation - calendar, clock, reminders
- pharmacotherapy
  - low dose, high potency antipsychotics: haloperidol has the most evidence; reasonable alternatives include risperidone, olanzapine (more sedating, less QT prolongation), quetiapine (if EPS), aripiprazole (may shorten QTc)
  - benzodiazepines only to be used in alcohol/substance withdrawal delirium; otherwise, can worsen delirium (antipsychotics will not be useful in substance withdrawal delirium)
- try to minimize anticholinergic side effects
- physical restraints to maintain safety only if necessary (last resort)

Prognosis
- up to 50% 1 yr mortality rate after episode of delirium

Major Neurocognitive Disorder (Dementia)

see Neurology: N21

DSM-5 Diagnostic Criteria for Major Neurocognitive Disorder
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A. evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  1. concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function;
  and
  2. substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment

B. cognitive deficits interfere with independence in everyday activities (i.e. at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)
- Note: if deficits do not interfere as in B, and impairments are mild-moderate as in A, this is considered "mild neurocognitive disorder"; see Neurology: N21

C. cognitive deficits do not occur exclusively in the context of a delirium

D. cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia)

E. in the case of neurodegenerative dementias such as Alzheimer's Disease, disturbances should be of insidious onset and progressive

Specify whether due to:

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Normal pressure hydrocephalus</th>
<th>Substance/Medication use</th>
<th>HIV infection</th>
<th>Prion disease</th>
<th>Parkinson's disease</th>
<th>Huntington's disease</th>
<th>Another medical condition</th>
<th>Multiple etiologies</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Normal pressure hydrocephalus</td>
<td>Substance/Medication use</td>
<td>HIV infection</td>
<td>Prion disease</td>
<td>Parkinson's disease</td>
<td>Huntington's disease</td>
<td>Another medical condition</td>
<td>Multiple etiologies</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Frontotemporal lobar degeneration</td>
<td>Normal pressure hydrocephalus</td>
<td>Substance/Medication use</td>
<td>HIV infection</td>
<td>Prion disease</td>
<td>Parkinson's disease</td>
<td>Huntington's disease</td>
<td>Another medical condition</td>
<td>Multiple etiologies</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Lewy body disease</td>
<td>Normal pressure hydrocephalus</td>
<td>Substance/Medication use</td>
<td>HIV infection</td>
<td>Prion disease</td>
<td>Parkinson's disease</td>
<td>Huntington's disease</td>
<td>Another medical condition</td>
<td>Multiple etiologies</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Normal pressure hydrocephalus</td>
<td>Substance/Medication use</td>
<td>HIV infection</td>
<td>Prion disease</td>
<td>Parkinson's disease</td>
<td>Huntington's disease</td>
<td>Another medical condition</td>
<td>Multiple etiologies</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>Normal pressure hydrocephalus</td>
<td>Substance/Medication use</td>
<td>HIV infection</td>
<td>Prion disease</td>
<td>Parkinson's disease</td>
<td>Huntington's disease</td>
<td>Another medical condition</td>
<td>Multiple etiologies</td>
<td>Unspecified</td>
</tr>
</tbody>
</table>

Epidemiology
- prevalence increases with age: 5% in patients >65 yr of age; 35-50% in patients >85 yr of age
- pre-test probability of dementia in an older person with reported memory loss is estimated to be 60%
- prevalence is increased in people with Down's syndrome and head trauma
- Alzheimer's disease comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia neurocognitive disorder – see Neurology: N23)
- average duration of illness from onset of symptoms to death is 8-10 yr

Subtypes
- with or without behavioural disturbance (e.g. wandering, agitation)
- early-onset: age of onset <65 yr
- late-onset: age of onset >65 yr
Investigations (rule out reversible causes)
- standard: see Delirium, PS19
- as indicated: VDRL, HIV, SPECT, CT head in dementia
- indications for CT head: same as for delirium, plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 mo), dementia of relatively short duration (<2 yr), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/seizures)

Management
- see Neurology, N20 for further management
- treat underlying medical problems and prevent others
- provide orientation cues for patient (e.g. clock, calendar)
- provide education and support for patient and family (e.g. day programs, respite care, support groups, home care)
- consider long-term care plan (nursing home) and power of attorney/living will
- inform Ministry of Transportation about patient's inability to drive safely
- consider pharmacological therapy
  - cholinesterase inhibitors (e.g. donepezil [Aricept®], rivastigmine, galantamine) for mild to severe disease
  - NMDA receptor antagonist (e.g. memantine) for moderate to severe disease
  - low-dose neuroleptics (e.g. risperidone, quetiapine), antidepressants or trazodone if behavioural or emotional symptoms prominent – start low and go slow
  - reassess pharmacological therapy every 3 mo

Table 3. Comparison of Dementia, Delirium, and Pseudodementia of Depression

<table>
<thead>
<tr>
<th></th>
<th>Dementia/Major Neurocognitive Disorder</th>
<th>Delirium</th>
<th>Pseudodementia of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual/step-wise decline</td>
<td>Acute (hours to days)</td>
<td>Subacute</td>
</tr>
<tr>
<td>Duration</td>
<td>Months-years</td>
<td>Days-weeks</td>
<td>Variable</td>
</tr>
<tr>
<td>Natural History</td>
<td>Progressive</td>
<td>Fluctuating, reversible</td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td>Usually irreversible</td>
<td>High morbidity/mortality in the elderly</td>
<td>Usually reversible</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Normal</td>
<td>Fluctuating (over 24 h)</td>
<td>Normal</td>
</tr>
<tr>
<td>Attention</td>
<td>Not initially affected</td>
<td>Decreased (wandering, easy distraction)</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Orientation</td>
<td>Intact initially</td>
<td>Impaired (usually to time and place), fluctuates</td>
<td>Intact</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Disinhibition, impairment in ADL/IADL, personality change, loss of social graces</td>
<td>Severe agitation/retardation</td>
<td>Importuning, self-harm/ suicide</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
<td>Slowing</td>
</tr>
<tr>
<td>Sleep Wake Cycle</td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep wake cycle</td>
<td>Early morning awakening</td>
</tr>
<tr>
<td>Mood and Affect</td>
<td>Labile but not usually anxious</td>
<td>Anxious, irritable, fluctuating</td>
<td>Depressed, stable</td>
</tr>
<tr>
<td>Cognition</td>
<td>Decreased executive functioning, paucity of thought</td>
<td>Fluctuating preceded by mood changes</td>
<td>Fluctuating</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
<td>Recent, More likely to complain.</td>
</tr>
<tr>
<td>Language</td>
<td>Agnosia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia)</td>
<td>Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes</td>
<td>Not affected</td>
</tr>
<tr>
<td>Delusions</td>
<td>Compensatory</td>
<td>Nightmarish and poorly formed</td>
<td>Nihilistic, somatic</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Variable</td>
<td>Visual common</td>
<td>Less common, auditory predominates</td>
</tr>
<tr>
<td>Quality of Hallucinations</td>
<td>Vacuous/bland</td>
<td>Frightening/bizarre</td>
<td>Self-deprecatory</td>
</tr>
<tr>
<td>Medical Status</td>
<td>Variable</td>
<td>Acute illness, drug toxicity</td>
<td>Rule out systemic illness, medications</td>
</tr>
</tbody>
</table>

Overview
- a neurobiological disorder involving compulsive drug seeking and drug taking, despite adverse consequences, with loss of control over drug use (think issues with the “3 Cs”: compulsive, consequences, control)
- dependence is the hallmark of substance use disorders and comes in the following forms:
  - behavioural: substance-seeking activities and pathological use patterns
  - physical: physiologic withdrawal effects without use
  - psychological: continuous or intermittent cravings for the substance to avoid dysphoria or attain drug state
- abuse: drug use that deviates from the approved social or medical pattern, usually causing impairment or disruption to function in self or others
- these disorders are usually chronic with a relapsing and remitting course

Epidemiology
- 47% of those with substance abuse have mental health problems
- 29% of those with a mental health disorder have a substance use disorder
- 47% of those with schizophrenia and 25% of those with an anxiety disorder have a substance use disorder
Etiology
- almost all drugs (and activities) of abuse increase dopamine in the nucleus accumbens, an action that contributes to their euphoric properties and, with repeated use, to their ability to change signalling pathways in the brain's reward system
- substance use disorders arise from multifactorial interactions between genes (personality, neurobiology) and environment (low socioeconomic status, substance-using peers, abuse history, chronic stress)

Diagnosis
- substance use disorders are measured on a continuum from mild to severe based on the number of criteria met within 12 mo
  - mild: 2-3
  - moderate: 4-5
  - severe: 6 or more
- each specific substance is addressed as a separate use disorder and diagnosed utilizing the same overarching criteria (e.g. a single patient may have moderate alcohol use disorder, and a mild stimulant use disorder)
- testing for illicit drugs is most commonly done on urine or blood samples; Serum toxicology screen is needed to assess alcohol level
- criteria for substance use disorders (PEC WITH MCAT)
  - use despite Physical or psychological problem (e.g. alcoholic liver disease or cocaine related nasal problems)
  - failures in important External roles at work/school/home
  - Craving or a strong desire to use substance
  - Withdrawal
  - continued use despite Interpersonal problems
  - Tolerance, needing to use more substance to get same effect
  - use in physically Hazardous situations
  - More substance used or for longer period than intended
  - unsuccessful attempts to Cut down
  - Activities given up due to substance
  - excessive Time spent on using or finding substance

Classification of Substances

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intoxication</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressants</td>
<td>Alcohol, opioids, barbiturates, benzodiazepines, GHB</td>
<td>Euphoria, slurred speech, disinhibition, confusion, poor coordination, coma (severe)</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amphetamines, methylphenidate, MDMA, cocaine</td>
<td>Euphoria, mania, psychomotor agitation, anxiety, psychosis (especially paranoia), insomnia, cardiovascular complications (stroke, MI, arrhythmias), seizure</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>LSD, mescaline, psilocybin, PCP, ketamine, ibogaine, salvia</td>
<td>Distortion of sensory stimuli and enhancement of feelings, psychosis (+++ visual hallucinations), delirium, anxiety (panic), poor coordination</td>
</tr>
</tbody>
</table>

General Approach to Assessment
- ask about socially accepted substances (e.g. nicotine, alcohol) before asking about use of marijuana, misuse of prescription medicines, and about illicit drugs
- obtaining history from family members may be helpful

General Approach to Treatment
- approach must be appropriate to the patient's current state of change (see Population Health and Epidemiology, Health Promotion Strategies, PH6, for Prochaska’s Stages of Change Model)
- patients will only change when the pain of change appears less than the pain of staying the same
- provider can help by providing psychoeducation (emphasize neurobiologic model of addiction), motivation, and hope
- principles of motivational interviewing (see Psychotherapy, PS40)
  - non-judgmental stance
  - space for patient to talk and reflect
  - offer accurate empathic reflections back to patient to help frame issue
  - encourage and offer referral to evidence based services
  - social: 12-step programs (alcoholics anonymous, narcotics anonymous), family education and support
  - psychological therapy: addiction counselling, motivational enhancement therapy (MET), CBT, contingency management, group therapy, family therapy, marital counselling
  - medical management (differs depending on substance): acute detoxification, pharmacologic agents to aid maintenance
  - harm reduction whenever possible: safe-sex practices, avoid driving while intoxicated, avoid substances with child care, safe needle practices/exchange, pill-testing kits, reducing tobacco use
  - comorbid psychiatric conditions: many will resolve with successful treatment of the substance use disorder but patients who meet full criteria for another disorder should be treated for that disorder with psychological and pharmacologic therapies

Questions to Characterize Substance Use and Risk Assessment
- When was the last time you used?
- How long can you go without using?
- By what route (oral ingestion, insufflation, smoking, IV) do you usually use?
- Are there any triggers that you know will cause you to use?
- How has your substance use affected your work, school, relationships?
- Substances can be very expensive, how do you support your drug use?
- Have you experienced medical or legal consequences of your use?
- Any previous attempts to cut down or quit, and did you experience any withdrawal symptoms?
Nicotine

- see Family Medicine, FM11

Alcohol

- see Family Medicine, FM12 and Emergency Medicine, ER54

History

- CAGE: validated screening questionnaire
  - C ever felt the need to Cut down on drinking?
  - A ever felt Annoyed at criticism of your drinking?
  - G ever feel Guilty about your drinking?
  - E ever need a drink first thing in morning (Eye opener)?
    - for men, a score of ≥2 is a positive screen; for women, a score of ≥1 is a positive screen
    - if positive CAGE, then assess further to distinguish between problem drinking and alcohol use disorder

<table>
<thead>
<tr>
<th>Table 4. Canada’s Low-Risk Alcohol Drinking Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Drinking</td>
</tr>
<tr>
<td>Men: 3 or less/d (≤15/wk)</td>
</tr>
<tr>
<td>Women: 2 or less/d (≤10/wk)</td>
</tr>
<tr>
<td>Elderly: 1 or less/d</td>
</tr>
</tbody>
</table>

Alcohol Intoxication

- legal limit for impaired driving is 10.6 mmol/L (50 mg/dL) reached by 2-3 drinks/h for men and 1-2 drinks/h for women
- coma can occur with >60 mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)

Alcohol Withdrawal

- occurs within 12-48 h after prolonged heavy drinking and can be life-threatening
- alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced:
  - stage 1 (onset 12-18 h after last drink): “the shakes” tremor, sweating, agitation, anorexia, cramps, diaphoresis, sleep disturbance
  - stage 2 (onset 7-48 h): alcohol withdrawal seizures, usually tonic-clonic, non-focal and brief
  - stage 3 (onset 48 h): visual, auditory, olfactory or tactile hallucinations
  - stage 4 (onset 3-5 d): delirium tremens, confusion, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (fever, tachycardia, HTN)
- course: almost completely reversible in young; elderly often left with cognitive deficits
- mortality rate 20% if untreated

Management of Alcohol Withdrawal

- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
  - areas of assessment include:
    - physical (5): nausea and vomiting, tremor, agitation, paroxysmal sweats, headache/fullness in head
    - psychological/cognitive (2): anxiety, orientation/clouding of sensorium
    - perceptual (3): tactile disturbances, auditory disturbances, visual disturbances
  - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67
  - mild <10, moderate 10-20, severe >20

<table>
<thead>
<tr>
<th>Table 5. CIWA-A Scale Treatment Protocol for Alcohol Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Protocol</td>
</tr>
<tr>
<td>Diazepam 20 mg PO q1-2h pm until CIWA-A &lt;10 points</td>
</tr>
<tr>
<td>Observe 1-2 h after last dose and reassess on CIWA-A scale</td>
</tr>
<tr>
<td>Thiamine 100 mg IM then 100 mg PO OD for 3 d</td>
</tr>
<tr>
<td>Supportive care (hydration and nutrition)</td>
</tr>
<tr>
<td>History of Withdrawal Seizures</td>
</tr>
<tr>
<td>Diazepam 20 mg PO q1h for minimum of three doses regardless of subsequent CIWA scores</td>
</tr>
<tr>
<td>If age &gt;65 or patient has severe liver disease, severe asthma or respiratory failure</td>
</tr>
<tr>
<td>Use a short acting benzodiazepine</td>
</tr>
<tr>
<td>Lorazepam PO/SL/IM 1-4 mg q1-2h</td>
</tr>
<tr>
<td>If Hallucinations are present</td>
</tr>
<tr>
<td>Haloperidol 2-5 mg IM/PO q1-4h – max 5 doses/d or atypical antipsychotics (olanzapine, risperidone)</td>
</tr>
<tr>
<td>Diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold)</td>
</tr>
<tr>
<td>Admit to Hospital if</td>
</tr>
<tr>
<td>Still in withdrawal after &gt;80 mg of diazepam</td>
</tr>
<tr>
<td>Delirium tremens, recurrent arrhythmias, or multiple seizures</td>
</tr>
<tr>
<td>Medically ill or unsafe to discharge home</td>
</tr>
</tbody>
</table>

Delirium Tremens (alcohol withdrawal delirium)

- Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)
- Hand tremor
- Insomnia
- Psychomotor agitation
- Anxiety
- Nausea or vomiting
- Tonic-clonic seizures
- Visual/tactile/auditory hallucinations
- Persecutory delusions

Confabulations: the fabrication of imaginary experiences to compensate for memory loss

Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)

A “Standard Drink”

| Spirit (40%): 1.5 oz. or 43 mL |
| Table Wine (12%): 5 oz. or 142 mL |
| Fortified Wine (18%): 3 oz. or 85 mL |
| Regular Beer (5%): 12 oz. or 341 mL |
| OR |
| 1 pint of beer = 1.5 SD |
| 1 bottle of wine = 5 SD |
| 1 “mickey” = 8 SD (375 ml) |
| "26-e-" = 17 SD (750 ml) |
| "40 oz. = 27 SD |

A few books recommended:
- booksfree.com
- booksfree.com
Treatment of Opioid Use Disorder

- **Wernicke-Korsakoff Syndrome**
  - alcohol-induced amnestic disorders due to thiamine deficiency
  - necrotic lesions: mammillary bodies, thalamus, brainstem
  - Wernicke's encephalopathy (acute and reversible): triad of oculomotor dysfunction such as nystagmus (CN VI palsy), gait ataxia, and confusion
  - Korsakoff's syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and confabulations; cannot occur during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal
  - management
    - Wernicke's: thiamine 100 mg PO OD x 1-2 wk
    - Korsakoff's: thiamine 100 mg PO bid/tid x 3-12 mo

- **Treatment of Alcohol Use Disorder**

  - **see General Approach to Treatment, PS4**
  - **pharmacological**
    - naltrexone (Revia®): opioid antagonist, shown to be successful in reducing the "high" associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges
    - disulfiram (Antabuse®): prevents oxidation of alcohol (blocks acetaldehyde dehydrogenase); with alcohol consumption, acetaldehyde accumulates to cause a toxic reaction (vomiting, tachycardia, death); if patient relapses, must wait 48 h before restarting Antabuse®; prescribed only when treatment goal is abstinence. RCT evidence is generally poor or negative
    - acamprosate (Campral®): NMDA glutamate receptor antagonist; useful in maintaining abstinence and decreasing cravings

- **Opioids**

  - types of opioids: heroin, morphine, oxycodone, Tylenol #3® (codeine), hydromorphone, fentanyl
  - major risks associated with the use of contaminated needles: increased risk of hepatitis B and C, bacterial endocarditis, HIV/AIDS

- **Acute Intoxication**

  - direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), and respiratory depression

- **Toxic Reaction**

  - typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
  - management
    - ABCs
    - IV glucose
    - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
    - treatment: intubation and mechanical ventilation, ± naloxone drip, until patient alert without naloxone (up to >48 h with long-acting opioids)
  - caution with longer half-life; may need to observe for toxic reaction for at least 24 h

- **Withdrawal**

  - symptoms: depression, insomnia, drug-craving, myalgias, nausea, chills, autonomic instability (lacrimation, rhinorrhea, piloerection)
  - onset: 6-12 h; duration: 5-10 d
  - complications: loss of tolerance (overdose on relapse), miscarriage, premature labour
  - management: long-acting oral opioids (methadone, buprenorphine), α-adrenergic agonists (clonidine)

- **Treatment of Opioid Use Disorder**

  - long term treatment may include withdrawal maintenance treatment with methadone (opioid agonist) or buprenorphine (mixed agonist-antagonist)
  - Suboxone® formulation includes naloxone in addition to buprenorphine, in an effort to prevent injection of the drug. When naloxone is injected, it will precipitate opiate withdrawal and block the opiate effect of buprenorphine; however, it will not have this antagonist action when taken sublingually

- **Cocaine**

  - street names: blow, C, coke, crack, flake, freebase, rock, snow
  - alkaloid extracted from leaves of the coca plant; blocks presynaptic uptake of serotonin (causing euphoria), dopamine (linked to its addictive effect), norepinephrine and epinephrine (causing vasoconstriction, HTN)
  - sodium channel blockade - cocaine slows or blocks nerve conduction and acts as a local anesthetic by altering recovery of neuronal Na+ channels. It has a similar effect on cardiac Na+ channels and in overdose can manifest on ECG as prolongation of the QRS complex
  - self-administered by inhalation (90% bioavailability), insufflation (e.g. intranasal; 80% bioavailability), or intravenous route
Substance-Related and Addictive Disorders

- onset and duration of action: onset within seconds if inhaled, lasting 15-30 min; onset in 3-5 min if insufflated, blood levels peak at 10-20 min with effects beginning to fade after 45-60 min. Cocaine has a biologic half life of 1 h, thus repeated self-administration is common among users to maintain an effect

Intoxication
- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (e.g. tachycardia, mydriasis, sweating)
- prolonged use may result in paranoia and psychosis

Overdose
- medical emergency: HTN, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias
- treatment with IV diazepam to control seizures
- beta-blockers (incl. labetalol or propranolol) are not recommended because of risk from unopposed alpha-adrenergic stimulation

Withdrawal
- initial “crash” (1-48 h): increased sleep, increased appetite
- withdrawal (1-10 wk): dysphoric mood plus fatigue, irritability, vivid unpleasant dreams, insomnia or hypersomnia, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management

Treatment of Cocaine Use Disorder
- see General Approach to Treatment, PS4
- no pharmacologic agents have widespread evidence or acceptance of use

Complications
- cardiovascular: arrhythmias, MI, CVA, ruptured AAA, chest pain (accounts for 40% of all cocaine-related ED visits)
- neurologic: seizures
- psychiatric: psychosis, paranoia, delirium, suicidal ideation
- other: nasal septal deterioration, acute/chronic lung injury “crack lung”, possible increased risk of connective tissue disease

Amphetamines
- includes prescription medications for ADHD such as Ritalin® and Adderall®
- intoxication characterized by euphoria, improved concentration, sympathetic and behavioural hyperactivity and at high doses can mimic psychotic mania, can eventually cause coma
- chronic use can produce a paranoid psychosis which can resemble schizophrenia with agitation, paranoia, delusions and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- treatment of amphetamine induced psychosis: antipsychotics for acute presentation, benzodiazepines for agitation, β-blockers for tachycardia, hypertension

Cannabis
- cannabis (marijuana) is the most commonly used recreational drug
- psychoactive substance: delta-9-tetrahydrocannabinol (Δ9-THC)
- general clinical manifestations: intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, altered sensorium, increased appetite, and muscle relaxation
- neuropsychiatric effects:
  - altered mood, perception and thought content: increased sense of well-being, euphoria/laughter
  - impaired cognitive and psychomotor performance: reduced reaction time, impaired attention, concentration and short-term memory.
  - It may also impair motor coordination required to complete complex tasks requiring divided attention. Notably, psychomotor impairments may interfere with one’s ability to operate heavy machinery such as automobiles
-inhaled marijuana: onset of psychoactive effects occurs rapidly with peak effects felt 15-30 min after intake and lasting up to 4 h
- acute exacerbation in patients with asthma may be a complication with inhalation
- ingested marijuana: following oral ingestion, psychotrophic effects set in with a delay of 30-90 min, reach their maximum after 2-3 h and last for about 4-12 h, depending on dose (Grottenhrenen, 2003, pharmacokinetics and pharmacodynamics of cannabinoids)
- high doses can cause depersonalization, paranoia, anxiety and may trigger psychosis and schizophrenia if predisposed
- chronic use is associated with tolerance and an apathetic, amotivational state, and increases risk of later manic episodes
- assessment: standard urine drug screens
- treatment of cannabis use disorder: see General Approach to Treatment, PS4
- cessation following heavy use produces a significant withdrawal syndrome: irritability, anxiety, insomnia, decreased food intake
Hallucinogens

- Types of hallucinogens by primary action:
  - 5-HT2A agonists: LSD, mescaline (peyote), psilocybin mushrooms, DMT (ayahuasca)
  - NMDA antagonists: PCP, ketamine
  - K-opioid agonists: salvinorin A, ibogaine
- 5-HT2A agonists are most commonly used; intoxication characterized by tachycardia, HTN, mydriasis, tremor, hyperpyrexia, and a variety of perceptual, mood and cognitive changes (rarely, if ever, deadly; treat with diazepam symptomatically)
- Psychological effects of high doses: depersonalization, derealization, paranoia, and anxiety (panic with agoraphobia)
- Tolerance develops rapidly (hours-days) to most hallucinogens so physical dependency is virtually impossible, although psychological dependency and problematic usage patterns can still occur
- No specific withdrawal syndrome characterized
- Management of acute intoxication
- Support, reassurance, diminished stimulation; benzodiazepines or high potency antipsychotics seldom required (if used, use small doses), minimize use of restraints
- Long term adverse effects: controversial role in triggering psychiatric disorders, particularly mood or psychosis, thought to be chiefly in genetic with other risk factors
- Hallucinogen Persisting Perception Disorder: DSM-5 diagnosis characterized by long lasting, spontaneous, intermittent recurrences of visual perceptual changes reminiscent of those experienced with hallucinogen exposure

"Club Drugs"

Table 6. The Mechanism and Effects of Common "Club Drugs"

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA (&quot;Ecstasy&quot;, &quot;X&quot;, &quot;E&quot;, &quot;M&quot;, &quot;Molly&quot;)</td>
<td>Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and stimulant</td>
<td>Enhanced sensorium; feelings of well-being, empathy</td>
<td>Sweating, tachycardia fatigue, muscle spasms (especially jaw clenching), ataxia, hyperpyrexia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death</td>
</tr>
<tr>
<td>Gamma Hydroxybutyrate (GHB, &quot;G&quot;, &quot;Liquid Ecstasy&quot;)</td>
<td>Biphasic dopamine response (inhibition then release) and releases opiate-like substance</td>
<td>Euphoric effects, increased aggression, impaired judgment</td>
<td>Sweating, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, severe withdrawal from abrupt cessation of high doses: tremor, seizures, psychosis</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol® &quot;Roofies&quot;, &quot;Rope&quot;, &quot;The Forget Pill&quot;)</td>
<td>Potent benzodiazepine rapid oral absorption</td>
<td>Sedation, psychomotor impairment, amnestic effects, decreased sexual inhibition</td>
<td>CNS depression with EtOH</td>
</tr>
<tr>
<td>Ketamine (&quot;Special K&quot;, &quot;K-Kkat&quot;)</td>
<td>NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics and by veterinarians</td>
<td>&quot;Dissociative&quot; state, profound amnesia/ analgesia, hallucinations and sympathomimetic effects</td>
<td>Psychological distress, accidents due to intensity of experience and lack of bodily control. In overdose: decreased LOC, respiratory depression, catatonia</td>
</tr>
<tr>
<td>Methamphetamine (&quot;speed&quot;, &quot;meth&quot;, &quot;chalk&quot;, &quot;ice&quot;, &quot;crystal&quot;)</td>
<td>Amphetamine stimulant, induces noradrenaline, dopamine, and serotonin release</td>
<td>Rush begins in min, effects last 6-8 h, increased activity, decreased appetite, general sense of well-being, tolerance occurs quickly, users often binge and crash</td>
<td>Short-term use: high agitation, rage, violent behaviour, occasionally hyperthermia and convulsions. Long-term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (especially formication), delusions mood disturbance, suicidal and homicidal thoughts, stroke. May be contaminated with lead, and IV users may present with acute lead poisoning</td>
</tr>
<tr>
<td>Phencyclidine (&quot;PCP&quot;, &quot;angel dust&quot;)</td>
<td>Not understood, used by veterinarians to immobilize large animals</td>
<td>Amnestic, euphoric, hallucinatory state</td>
<td>Horizontal/vertical myostagmus, myoclonus, ataxia, autonomic instability (treat with diazepam IV), prolonged agitation psychosis (treat with haloperidol); high risk for suicide; violence towards others. High dose can cause coma</td>
</tr>
</tbody>
</table>

Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review

The Lancet 2007;370:319-328

Purpose: To review the evidence for cannabis use and occurrence of psychotic or affective mental health outcomes.

Study Characteristics: A meta-analysis of 35 population-based longitudinal studies, or case-control studies nested within longitudinal designs.

Results: There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio = 1.41, 95% CI 1.20-1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently (2.09, 95% CI 1.54-2.84). Findings for depression, suicidal thoughts, and anxiety outcomes were less consistent. In both cases (psychotic and affective outcomes), a substantial confounding effect was present.

Conclusions: The findings are consistent with the view that cannabis increases risk of psychotic outcomes independent of transient intoxication effects, though evidence is less strong for affective outcomes. Although cannabis use and the development of psychosis are strongly associated, it is difficult to determine causality and it is possible that the association results from confounding factors or bias. The authors did conclude that there is sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

Date Rape Drugs

- GHB
- Flunitrazepam (Rohypnol®)
- Ketamine

Emerging Medical Uses of Hallucinogens

Many hallucinogens are currently under investigation for therapeutic benefit; LSD & Psilocybin for end of life anxiety, MDMA for PTSD. Ketamine for rapid treatment of depression, ibogaine derivatives for addiction.
Somatic Symptom and Related Disorders

General Characteristics
• physical signs and symptoms lacking objective medical support in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance
• cause significant distress or impairment in functioning
• symptoms are produced unconsciously and are not the result of malingering or factitious disorder, which are disorders of voluntary presentation of symptoms (or intentionally inducing, e.g. injecting feces) for secondary gain
• primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict with no external incentive
• secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (e.g. work)

Management of Somatic Symptom and Related Disorders
• brief, regular scheduled visits with GP to facilitate therapeutic relationship and help patient feel cared for
• limit number of physicians involved in care, minimize medical investigations; coordinate necessary investigations
• emphasis on what the patient can change and control; the psychosocial coping skills, not their physical symptoms (functional recovery > explanation of symptoms)
• do not tell patient it is “all in their head,” emphasize these disorders are real entities or functional in nature
• psychotherapy: CBT, mindfulness interventions, biofeedback, conflict resolution
• minimize psychotropic drugs: anxioleptics in short-term only, antidepressants for comorbid depression and anxiety

Somatic Symptom Disorder

DSM-5 Diagnostic Criteria for Somatic Symptom Disorder
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. one or more somatic symptoms that are distressing or result in significant disruption of daily life
B. excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns as manifested by at least one of the following
  1. disproportionate and persistent thoughts about the seriousness of one's symptoms
  2. persistently high level of anxiety about health or symptoms
  3. excessive time and energy devoted to these symptoms or health concerns
C. although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 mo)
• somatic symptom disorder with predominant pain (previously pain disorder) for those whose somatic symptom is primarily pain
• patients have physical symptoms and believe these symptoms represent the manifestation of a serious illness
• persistent belief despite negative medical investigations and may develop different symptoms over time
• lifetime prevalence may be around 5-7% in the general adult population
• females tend to report more somatic symptoms than males do, cultural factors may influence sex ratio
• complications: anxiety and depression commonly comorbid (up to 80%), unnecessary medications or surgery
• often a misdiagnosis for an insidious illness so rule out all organic illnesses (e.g. multiple sclerosis)

Illness Anxiety Disorder
• preoccupation with fear of having, or the idea that one has, a serious disease, to the point of causing significant impairment
• convictions persist despite negative investigations and medical reassurance
• somatic symptoms are mild or not present
• there is a high level of anxiety about health and the individual is easily alarmed about personal health status
• person engages in maladaptive behaviour such as excessive physical checking or total healthcare avoidance
• duration is ≥6 mo; onset in 3rd-4th decade of life
• a new diagnostic entity so epidemiology is not well known; however, it is likely less common than SSD
• possible role for SSRIs due to generally high level of anxiety
**Conversion Disorder (Functional Neurological Symptom Disorder)**

- one or more symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or GMC (e.g. impaired coordination, local paralysis, double vision, seizures, or convulsions)
- does not need to be preceded by a psychological event as per previous DSM criteria, however this is still worth exploring as many patients will present after such an event or related to a medical diagnosis in a first-degree relative
- 2-5/100,000 in general population; 5% of referrals to neurology clinics
- more common in rural populations and in individuals with little medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 mo)
- incompatible findings detected from specific neurological testing can help differentiate between functional and neurological origin (e.g. Hoover's sign, dermatome testing)

<table>
<thead>
<tr>
<th>Table 7. Differential of Somatic Symptom and Related Disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>Somatic Symptom Disorder</strong></td>
</tr>
<tr>
<td>Somatic Symptoms</td>
</tr>
<tr>
<td>Symptoms Produced</td>
</tr>
<tr>
<td>Physical Findings</td>
</tr>
</tbody>
</table>

**Dissociative Disorders**

**Definition**
- severe dissociation resulting in breakdown of integrated functions of consciousness and perception of self
- differential diagnosis: PTSD, acute stress disorder, borderline personality disorder, somatic symptom disorder, substance abuse, GMC (various neurologic disorders including complex/partial seizures, migraine, Cotard syndrome)

**Dissociative Identity Disorder**

disruption of identity characterized by two or more distinct personality states or an experience of possession
- can manifest as sudden alterations in sense of self and agency (ego-dystonic emotions, behaviours, speech)
- features recurrent episodes of amnesia (declarative or procedural)

**Dissociative Amnesia**

- inability to recall important autobiographical information, usually of a traumatic or stressful nature, that is inconsistent with normal forgetting and not attributable to a psychiatric disorder or medical illness
- localized/selective amnesia: failure to recall all/some events during a prescribed period of time
- generalized amnesia: (more rare) complete loss of memory for one’s life history, ± procedural knowledge, ± semantic knowledge. Usually sudden onset. Often presents with perplexity, disorientation, aimless wandering

**Depersonalization/Derealization Disorder**

- persistent or recurrent episodes of one or both of:
  - depersonalization: experiences of detachment from oneself, feelings of unreality, or being an outside observer to one’s thoughts, feelings, speech, and actions (can feature distortions in perception including time, as well as emotional and physical numbing)
  - derealization: experiences of unreality or detachment with respect to the surroundings (e.g. feeling as if in a dream, or that the world is not real, external visual world is foggy or distorted)
- transient (seconds-hours) experiences of this nature are quite common in the general population
- episodes can range from hours-years, patients are often quite distressed and verbalize concern of “going crazy”

**Fugue**

Purposeful travel or bewildered wandering while in amnesic state

**La belle indifférence**

An inappropriately cavalier patient attitude in the face of serious symptoms; classically associated with conversion disorder
Sleep Disorders

for more information regarding normal sleep cycles and the illnesses described, see Neurology, Sleep Disorders, N46

Overview

• adequate sleep is essential to normal functioning; deprivation can lead to cognitive impairment and increased mortality
• circadian rhythms help regulate mood and cognitive performance
• neurotransmitters commonly implicated in psychiatric illnesses also regulate sleep
  ▪ acetylcholine activity and decreased activity of monoamine neurotransmitters is associated with greater REM sleep
  ▪ decreased adrenergic and cholinergic activity are associated with NREM sleep
• depression is associated with decreased Δ (deep, slow-wave) sleep, decreased REM latency, and increased REM density
• criteria
  ▪ must cause significant distress or impairment in normal functioning
  ▪ not due to a GMC or medications/drugs (unless specified)

Management

• pharmacological treatments are illness-specific
  ▪ non-benzodiazepines preferable (e.g. trazodone, zopiclone, quetiapine), but benzodiazepines a short term option
  ▪ medication should not be prescribed without having first made a diagnosis and considering major psychiatric illnesses (major depression and alcohol use disorders are common etiologies)
• sleep hygiene is a simple, effective, but often underutilized method for addressing sleep disturbances; recommendations include
  ▪ waking up and going to bed at same time every day, including on weekends
  ▪ avoiding long periods of wakefulness in bed
  ▪ not using bed for non-sleep activities (reading, TV, work)
  ▪ avoiding napping
  ▪ discontinuing or reducing consumption of alcohol, caffeine, drugs
  ▪ exercising at least 3-4x per week (but not in the evening, if this interferes with sleep)
• Cognitive Behavioural Therapy for insomnia (CBTi)

Table 8. Major DSM-5 Sleep-Wake Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Uncategorized)</td>
<td>Insomnia disorder</td>
<td>Difficulty sleeping</td>
</tr>
<tr>
<td></td>
<td>Hypersomnia disorder</td>
<td>Feeling sleep throughout the day</td>
</tr>
<tr>
<td></td>
<td>Narcolepsy</td>
<td>Recurrent attacks of irrepressible need to sleep</td>
</tr>
<tr>
<td></td>
<td>Circadian rhythm sleep-wake disorders</td>
<td>Insomnia or excessive sleepiness due to misalignment or alteration in endogenous circadian rhythm</td>
</tr>
<tr>
<td></td>
<td>Restless legs syndrome</td>
<td>Uncomfortable, frequent urge to move legs at night</td>
</tr>
<tr>
<td></td>
<td>Substance/medication-induced sleep disorder</td>
<td>Disturbance in sleep (insomnia or daytime sleepiness) caused by substance/medication intoxication or withdrawal</td>
</tr>
<tr>
<td>Breathing-related sleep disorders</td>
<td>Obstructive sleep apnea hypopnea</td>
<td>Breathing issues due to obstruction</td>
</tr>
<tr>
<td></td>
<td>Central sleep apnea</td>
<td>Breathing issues due to aberrant brain signaling</td>
</tr>
<tr>
<td></td>
<td>Sleep-related hypoventilation</td>
<td>Breathing issues due to decreased responsiveness to carbon dioxide levels</td>
</tr>
<tr>
<td>Parasomnias</td>
<td>Non-rapid eye movement sleep arousal disorders</td>
<td>Incomplete awakening from sleep, complex motor behaviour without conscious awareness; amnesia regarding episodes; includes symptoms of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sleepwalking: rising from bed and walking about, blank face, unresponsive, awakened with difficulty</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sleep terrors: recurrent episodes of abrupt terror arousals from sleep, usually beginning with a panicky scream, intense fear and autonomic arousal, relative unresponsiveness to comfort during episodes</td>
</tr>
<tr>
<td></td>
<td>Nightmare disorder</td>
<td>Repeated extended, extremely dysphoric, often very vivid, well-remembered dreams that usually involve significant threats; rapid orientation and alertness on awakening with autonomic arousal</td>
</tr>
<tr>
<td></td>
<td>Rapid eye movement sleep behaviour disorder</td>
<td>Arousal during sleep, associated with vocalization and/or complex motor behaviours; can cause violent injuries; rapid orientation and alertness on awakening</td>
</tr>
</tbody>
</table>
Sexuality and Gender

Gender Dysphoria

Definition
- the distress that may coincide with conflict between one's experienced/expressed gender and one's assigned gender

Typical Presentation
- strong and persistent cross-gender identification
- desire to be rid of primary/secondary sex characteristics and to gain the primary/secondary sex characteristics of their identified gender
- repeated stated desire or insistence that one is of the opposite sex
- intense desire to participate in the stereotypical games and pastimes of the opposite sex
- strong preference for playmates of the opposite sex
- significant distress or impairment in functioning and persistent discomfort with his or her sex or gender role

Treatment
- psychotherapy
- hormonal therapy
- sexual reassignment surgery

Paraphilic Disorders

Definition
- intense and persistent sexual interest that is not sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners
- paraphilic disorder: paraphilia that causes distress or functional impairment to the individual, or a paraphilia whose realization entails personal harm, or risk of harm to others
- subtypes: voyeuristic, exhibitionistic, frotteuristic, sexual masochism, sexual sadism, pedophilic, fetidistic, transvestic, other specified paraphilic disorder, unspecified paraphilic disorder
- rarely self referred; come to medical attention through interpersonal or legal conflict
- person usually has more than one paraphilia; 5% of paraphilias attributed to women
- typical presentation: begins in childhood or early adolescence; increasing in complexity and stability with age
- chronic, decreases with advancing age but may increase with stress

Treatment
- anti-androgen drugs
- behaviour modification
- psychotherapy

SEXUAL DYSFUNCTION
- see Gynecology, GY33 and Urology, U34

Eating Disorders

Definition
- eating disorders are characterized by a persistent disturbance of eating that impairs psychosocial functioning or health
- disorders include: anorexia nervosa, avoidant/restrictive food intake disorder, binge eating disorder, bulimia nervosa, pica and rumination disorder.

Epidemiology
- anorexia nervosa (AN): 1% of adolescent and young adult females; onset 13-20 yr old
- bulimia nervosa (BN): 2-4% of adolescent and young adult females; onset 16-18 yr old
- F:M=10:1; mortality 5-10%

Etiology
- multifactorial: psychological, sociological, and biological associations
- individual: perfectionism, lack of control in other life areas, history of sexual abuse
- personality: obsessive-compulsive, histrionic, borderline
- familial: maintenance of weight equilibrium and control in dysfunctional family
• cultural factors: prevalent in industrialized societies, idealization of thinness in the media
• genetic factors
  • AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs versus concordance in 1 of 14 dizygotic pairs
  • BN: higher familial incidence of affective disorders than the general population

Risk Factors
• physical factors: obesity, chronic medical illness (e.g. DM)
• psychological factors: individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance abuse), history of sexual abuse (especially for BN), homosexual males, competitive athletes, concurrent associated mental illness (depression, OCD, anxiety disorder [especially panic and agoraphobia], substance abuse [specifically for BN])

Anorexia Nervosa

DSM-5 Diagnostic Criteria for Anorexia Nervosa
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A. intake and weight: restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected
B. fear or behaviour: intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though at a significantly low weight
C. perception: disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation or persistent lack of recognition of the seriousness of the current low body weight
• specifiers: partial remission, full remission, severity based on BMI (mild = BMI >17 kg/m², moderate = BMI 16-16.99 kg/m², severe = BMI 15-15.99 kg/m², extreme = BMI <15 kg/m²), type (restricting = during last 3 mo no episodes of binge-eating or purging vs. binge-eating/purging type = in last 3 mo have participated in recurrent episodes of binge-eating/purging)

Management
• psychotherapy: individual, group, family (gold standard): address food and body perception, coping mechanisms health effects
• medications of little value
• outpatient and inpatient programs are available
• inpatient hospitalization for treatment of eating disorders is rarely on an acute basis (unless there is a concurrent psychiatric reason for emergent admission e.g. suicide risk)
• criteria to admit to medical ward for hospitalization: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry, or if actively suicidal
• agree on target body weight on admission and reassure this weight will not be surpassed
• monitor for complications of AN (see Table 9, PS33)
• monitor for refeeding syndrome
  • potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
  • complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium, and death
  • prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, and close monitoring of electrolytes and cardiac status

Prognosis
• early intervention much more effective (adolescent onset has much better prognosis than adult onset)
• 1 in 10 adolescents continue to have anorexia nervosa as adults
• with treatment, 70% resume a weight of at least 85% of expected levels and about 50% resume normal menstrual function
• eating peculiarities and associated psychiatric symptoms are common and persistent
• long-term mortality: 10-20% of patients hospitalized will die in next 10-30 yr (secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion committing suicide)

Bulimia Nervosa

DSM-5 Diagnostic Criteria for Bulimia Nervosa
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. recurrent episodes of binge-eating: an episode of binge-eating is characterized by both of the following
• eating, in a discrete period of time, an amount of food that is definitely larger than what most individuals would eat during a similar period of time and under similar circumstances
• a sense of lack of control over eating during the episode
B. recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise
C. the binge-eating and inappropriate compensatory behaviours both occur, on average, at least once a week for 3 mo
D. self-evaluation is unduly influenced by body shape and weight
E. the disturbance does not occur exclusively during episodes of AN
   • specifiers: partial remission, full remission, severity (measured in # of inappropriate compensatory behaviours/wk: mild = 1-3, moderate = 4-7, severe = 8-13, extreme = 14+)

Associated Features
• fatigue and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
• tooth decay
• swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention
• reddened knuckles, Russell’s sign (knuckle callus from self-induced vomiting)
• trouble concentrating
• weight fluctuation over time

Management
• admission for significant electrolyte abnormalities
• biological: treatment of starvation effects, SSRIs (fluoxetine most evidence) as adjunct
• psychological: develop trusting relationship with therapist to explore personal etiology and triggers, CBT, family therapy, recognition of health risks
• social: challenge destructive societal views of women, use of hospital environment to provide external patterning for normative eating behaviour

Prognosis
• relapsing/remitting disease
• good prognostic factors: onset before age 15, achieving a healthy weight within 2 yr of treatment
• poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance
• 60% good treatment outcome, 30% intermediate outcome, 10% poor outcome

Binge-Eating Disorder

Definition
• recurrent episodes of binge-eating (as defined by criteria A of BN) that are associated with eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts when not physically hungry, eating alone because embarrassed by how much one is eating, feeling disgusted with self/depressed, very guilty afterwards at least once/wk x 3 mo
• not associated with any compensatory behaviours
• dieting usually follows binge-eating (vs. BN where dysfunctional dieting typically precedes binge-eating)
• associated with health consequences (e.g. increased risk of weight gain, obesity)

Epidemiology
• F:M = 2:1
• begins in adolescence or young-adulthood

Treatment
• CBT

Avoidant/Restrictive Food Intake Disorder

Definition
• eating/feeding disturbance to the extent of persistent failure to meet appropriate nutritional and/or energy needs, resulting in significant weight loss/growth failure and nutritional deficiencies. Patients experience disturbances in psychosocial functioning and may become dependent on enteral feeding/oral nutritional supplementation
• does not occur during an episode of AN or BN
• no evidence of distress in the way in which one’s body weight or shape is experienced

Risk Factors
• temperament (e.g. anxiety disorders), environment (e.g. familial anxiety), genetic (e.g. history of GI conditions)
• begins in infancy and can persist into adulthood

Treatment
• psychoeducation
• behaviour modification
• psychotherapy
Table 9. Physiologic Complications of Eating Disorders

<table>
<thead>
<tr>
<th>System</th>
<th>Starvation/Restriction</th>
<th>Binge-Purge</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Low BP, low HR, significant orthostatic changes ± syncopal episodes, low temperature, vitamin deficiencies</td>
<td>Russell’s sign (knuckle callus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parotid gland enlargement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perioral skin irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pericardial and palatal petechiae</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of dental enamel and caries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic alkalosis secondary to hypokalemia and loss of acid</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Primary or secondary amenorrhea, decreased T&lt;sub&gt;3&lt;/sub&gt;/T&lt;sub&gt;4&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Seizure (decreased Ca&lt;sup&gt;2+&lt;/sup&gt;, Mg&lt;sup&gt;2+&lt;/sup&gt;, PO&lt;sub&gt;4&lt;/sub&gt;&lt;sup&gt;3-&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Dry skin, lanugo hair, hair loss or thinning, brittle nails, yellow skin from high carotene</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Constipation, GERD, delayed gastric emptying</td>
<td>Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear</td>
</tr>
<tr>
<td>CVS</td>
<td>Anhydremias, CHF</td>
<td>Anhydremias, cardiomypathy (from use of ipecac), sudden cardiac death (decreased K&lt;sup&gt;-&lt;/sup&gt;)</td>
</tr>
<tr>
<td>MSK</td>
<td>Osteoporosis secondary to hypogonadism</td>
<td>Muscle wasting</td>
</tr>
<tr>
<td>Renal</td>
<td>Pre-renal failure (hypovolemia), renal calculi</td>
<td>Renal failure (electrolyte disturbances)</td>
</tr>
<tr>
<td>Extremities</td>
<td>Pedal edema (decreased albumin)</td>
<td>Pedal edema (decreased albumin)</td>
</tr>
<tr>
<td>Lab Values</td>
<td>Starvation: decreased RBCs, decreased WBCs, decreased LH, decreased FSH, decreased estrogen, decreased testosterone, increased growth hormone, increased cholesterol Dehydration: increased BUN</td>
<td>Vomiting: decreased Na&lt;sup&gt;+&lt;/sup&gt;, decreased K&lt;sup&gt;-&lt;/sup&gt;, decreased Cl&lt;sup&gt;-&lt;/sup&gt;, decreased H&lt;sup&gt;+&lt;/sup&gt;, increased amylase; hypokalemia with metabolic alkalosis Laxatives: decreased Na&lt;sup&gt;+&lt;/sup&gt;, decreased K&lt;sup&gt;-&lt;/sup&gt;, decreased Cl&lt;sup&gt;-&lt;/sup&gt;, increased H&lt;sup&gt;+&lt;/sup&gt;; metabolic acidosis</td>
</tr>
</tbody>
</table>

Personality Disorders

- in the literature, personality and its disorders are better understood using a trait-based dimensional approach (e.g. 5 major traits such as extraversion, agreeableness, conscientiousness, neuroticism, and openness to experiences rated on a continuum of dysfunctional effects) rather than discrete categories; however, the discrete categories still remain in the current DSM and will be referenced here.

General Information

- an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual’s culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- pattern is stable and well established by adolescence or early adulthood (vs. a sudden onset)
- associated with many complications, such as depression, suicide, violence, brief psychotic episodes, multiple drug use, and treatment resistance
- relationship building and establishing boundaries are important; focus should be placed on validating, finding things to be truly empathetic about, and speaking to the patient’s strengths.
- mainstay of treatment is psychotherapy, add pharmacotherapy to treat associated psychiatric disorders (i.e. depression, anxiety, substance abuse)

Classification

- personality disorders are divided into three clusters (A, B and C), with shared features among disorders within each
# Table 10. Description and Diagnosis of Personality Disorders

## Cluster A: "Mad" Personality Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Diagnosis Requires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid Personality Disorder (0.5-3%)</td>
<td>Pervasive distrust and suspiciousness of others, interpret motives as malevolent</td>
<td>5+ of: IMPULSIVE</td>
</tr>
<tr>
<td></td>
<td>Blame problems on others and seem angry and hostile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suggestive that others are exploiting or deceiving them</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unforgiving (bears grudges)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spousal infidelity suspected without justification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perceive attacks on character, counterattacks quickly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confiding in others is feared</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Threats interpreted in benign remarks</td>
<td></td>
</tr>
</tbody>
</table>

| Schizotypal Personality Disorder (3-5.6%) | Pattern of eccentric behaviours; peculiar thought patterns | 5+ of: ME PECULIAR |
| | Diagnosis requires | |
| | 1. Magical thinking | |
| | 2. Experiences unusual perceptions (including body illusions) | |
| | 3. Paranoid ideation | |
| | 4. Eccentric behaviour or appearance | |
| | 5. Constricted or inappropriate affect | |
| | 6. Unusual thinking/speech (e.g. vague, stereotyped) | |
| | 7. Lacks close friends | |
| | 8. Ideas of reference | |
| | 9. Anxiety in social situations | |
| | (Note: Rule out psychotic/pervasive developmental disorders - this is not part of the criteria) | |

## Cluster B: "Bad" Personality Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Diagnosis Requires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline Personality Disorder (2-4%)</td>
<td>Unstable moods and behaviour, feel alone in the world, problems with self-image. History of repeated suicide attempts, self-harm behaviours. Inpatients commonly report history of sexual abuse. Tends to fizzle out as patients age. DBT is the principal treatment (see Psychotherapy, PS40)</td>
<td>5+ of: IMPULSIVE</td>
</tr>
<tr>
<td></td>
<td><strong>10% suicide rate</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Impulsive (min. 2 self-damaging ways, e.g. sex/drugs/spending)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Mood/affect instability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Paranoid or dissociation under stress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Unstable self-image</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Labile intense relationships</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Suicidal gestures / self-harm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Inappropriate anger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. Avoiding abandonment (real or imagined, frantic efforts to)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9. Emptiness (feelings of)</td>
<td></td>
</tr>
</tbody>
</table>

| Narcissistic Personality Disorder (2%) | Sense of superiority, needs constant admiration, lacks empathy, but with fragile sense of self. Consider themselves "special" and will exploit others for personal gain. | 5+ of: GRANDIOSE |
| | Diagnosis requires | |
| | 1. Grandiose | |
| | 2. Requires excessive admiration | |
| | 3. Arrogant | |
| | 4. Needs to be special (and associate with other specials) | |
| | 5. Dreams of success, power, beauty, love | |
| | 6. Interpersonally exploitative | |
| | 7. Others (lacks empathy, unable to recognize feelings/needs of) | |
| | 8. Sense of entitlement | |
| | 9. Envious (or believes others are envious) | |

| Antisocial Personality Disorder (M: 3%, F: 1%) | Lack of remorse for actions, manipulative and deceitful, often violate the law. May appear charming on first impression. Pattern of disregard for others and violation of others’ rights must be present before age 15; however, for the diagnosis of ASPD patients must be at least 18. Strong association with Conduct Disorder, history of trauma/abuse common. (see Child Psychiatry) | 3+ of: CORRUPT |
| | Diagnosis requires | |
| | 1. Cannot conform to law | |
| | 2. Obligations ignored (irresponsible) | |
| | 3. Reckless disregard for safety | |
| | 4. Remorseless | |
| | 5. Underhanded (deceitful) | |
| | 6. Planning insufficient (impulsive) | |
| | 7. Temper (irritable and aggressive) | |

| Histrionic Personality Disorder (1.3-3%) | Attention-seeking behaviour and excessively emotional. Are dramatic, flamboyant, and extroverted. Cannot form meaningful relationships. Often sexually inappropriate | 5+ of: ACTRESSS |
| | Diagnosis requires | |
| | 1. Appearance used to attract attention | |
| | 2. Centre of attention (else uncomfortable) | |
| | 3. Theatrical | |
| | 4. Relationships (believed to be more intimate than they are) | |
| | 5. Easily influenced | |
| | 6. Seductive behaviour | |
| | 7. Shallow expression of emotions (which rapidly shift) | |
| | 8. Speech (impressionistic and vague) | |
Table 10. Description and Diagnosis of Personality Disorders (continued)

<table>
<thead>
<tr>
<th>Cluster C “Sad” Personality Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients seem anxious, fearful</td>
</tr>
<tr>
<td>• Familial association with anxiety disorder</td>
</tr>
<tr>
<td>• Common defense mechanisms: isolation, avoidance, hypochondriasis</td>
</tr>
</tbody>
</table>

**Avoidant Personality Disorder (0.5-1.5%)**
Timid and socially awkward with a pervasive sense of inadequacy and fear of criticism. Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited. Diagnosis requires 4+ of: CRINGES
1. Criticism or rejection preoccupies thoughts in social situations
2. Restraint in relationships due to fear of being shamed
3. Inhibited in new relationships due to fear of inadequacy
4. Needs to be sure of being liked before engaging socially
5. Gets around occupational activities requiring interpersonal contact
6. Embarrassment prevents new activity or taking risks
7. Self-viewed as unappealing or inferior

**Dependent Personality Disorder (1.6-6.7%)**
Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviours. Difficulty making everyday decisions. Useful to set regulated treatment schedule (regular, brief visits) and being firm about in between issues. Encourage patient to do more for themselves, engage in own problem-solving. Diagnosis requires 5 of: RELIANCE
1. Reassurance required for everyday decisions
2. Expressing disagreement difficult
3. Life responsibilities assumed by others
4. Initiating projects difficult (because no confidence)
5. Alone (feels helpless and uncomfortable when alone)
6. Nurture (goes to excessive lengths to obtain)
7. Companionship sought urgently
8. Exaggerated fears of being left to care for self

**Obsessive-Compulsive Personality Disorder (3-10%)**
Preoccupation with orderliness, perfectionism, and mental and interpersonal control. Is inflexible, closed-off, and inefficient. Diagnosis requires 4+ of: SCRIMPER
1. Stubborn
2. Cannot discard worthless objects
3. Rule/detail obsessed (to point of activity lost)
4. Inflexible in matters of morality, ethics, values
5. Misery
6. Perfectionistic
7. Excludes leisure due to devotion to work
8. Reluctant to delegate to others

Table 11. Key Differences Among Schizoid, Schizotypal, and Schizophrenia

<table>
<thead>
<tr>
<th>Schizoid</th>
<th>Schizotypal</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thought Form</td>
<td>Organized</td>
<td>Organized, but vague and circumstantial</td>
</tr>
<tr>
<td>Thought Content</td>
<td>No psychosis</td>
<td>No psychosis, may have ideas of reference, paranoid ideation, odd beliefs and magical thinking</td>
</tr>
<tr>
<td>Relationships</td>
<td>Solitary, NO desire for social relationships</td>
<td>Lacks close relationships, INTERESTED in relationships but socially inept</td>
</tr>
</tbody>
</table>

**Child Psychiatry**

**Developmental Concepts**

- **temperament**: a child’s innate psycho-physiological and behavioural characteristics (e.g. emotionality, activity, and sociability); spectrum from “difficult” to “slow-to-warm-up” to “easy temperament”
- **parental fit**: the congruence between parenting style (authoritative, permissive) and child temperament
- **attachment**: special relationship between child and primary caretaker(s); develops during first year, the caretaker’s attachment style is the best predictor of their child’s attachment style, refer to Table 12
- **separation anxiety** (normal between 10-18 mo): where separation from attachment figure results in distress

Table 12. Attachment Models

<table>
<thead>
<tr>
<th>Parent/Caregiver</th>
<th>Attachment Type</th>
<th>Features in Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loving, consistently available, sensitive, and responsive</td>
<td>Secure</td>
<td>Freely explores and engages strangers well (as long as mother in close proximity), upset with caregiver’s departure, happy with return</td>
</tr>
<tr>
<td>Rejecting, unavailable psychologically, insensitive responses</td>
<td>Insecure (avoidant)</td>
<td>Ignores caregiver, shows little emotion with arrival or departure, little exploration</td>
</tr>
<tr>
<td>Inconsistent, insensitive responses, role reversal</td>
<td>Insecure (ambivalent/resistant)</td>
<td>Clingy but inconsolable, often displays anger or helplessness, little exploration</td>
</tr>
<tr>
<td>Frightening, dissociated, sexualized, or atypical</td>
<td>Disorganized</td>
<td>Simultaneous approach/avoidance and stress related straining behaviour</td>
</tr>
<tr>
<td>Often history of trauma or loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tips for the Child Interview**

- Use language the child will understand (i.e. don’t ask about feeling of worthlessness, ask about whether they feel like they’re a bad kid)
- Children in some cultures are taught to be quiet and avoid eye contact with adults who are authority figures (do not mistake with depression)
- Use developmentally-appropriate questions (i.e. don’t ask about lack of interest in activities, ask children whether they feel bored)
Mood Disorders

MAJOR DEPRESSIVE DISORDER

Epidemiology
pre-pubertal 1-2% (no gender differences); post-pubertal 4-18% (F:M = 2:1)

Clinical Presentation
• see Mood Disorders, PS9
• only difference in diagnostic criteria is that irritable mood may replace depressed mood
• physical factors: insomnia (children), hypersomnia (adolescents), somatic complaints, substance abuse, decreased hygiene
• psychological factors: irritability, boredom, anhedonia, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation, listlessness
• comorbid diagnoses: anxiety, ADHD, ODD, conduct disorder, and eating disorders

Treatment
• majority never seek treatment
• individual (CBT, IPT), family therapy and education, modified school program
• SSRIs: strongest evidence for fluoxetine. Escitalopram and sertraline would be second line medications of choice
• close follow-up for adolescents starting SSRIs to monitor for increased suicidal ideation or behavior
• ECT: only in adolescents who have severe illness, psychotic features, catatonic features, persistently suicidal
• internet based psychotherapy, light therapy, self-help books

Prognosis
• prolonged episodes, up to 1-2 yr
• adolescent onset predicts chronic mood disorder; up to 2/3 will have another depressive episode within 5 yr
• complications: negative impact on family and peer relationships, school failure significantly increased risk of suicide attempt (10%) or completion (however, suicide risk low for pre-pubertal children), substance abuse

DISRUPTIVE MOOD DYSREGULATION DISORDER

Clinical Presentation
• severe, developmentally inappropriate, recurrent verbal or behavioral temper outbursts at least 3x per wk
• mood is predominantly irritable or angry in between outbursts, as observable by others
• these symptoms occur before 10 yr, have been occurring for 12 mo, with no more than 3 consecutive mo free from symptoms
• high rates of comorbidities; ADHD, ODD, anxiety disorders, depressive disorders

BIPOLAR DISORDER

Clinical Presentation
• see Bipolar Disorder, PS12
• mixed presentation and psychotic symptoms (hallucinations and delusions) more common in adolescent population than adult population
• unipolar depression may be an early sign of adult bipolar disorder
• ~30% of psychotic depressed adolescents receive a bipolar diagnosis within 2 yr of presentation
• associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family pharmaco logically-induced mania

Treatment
• pharmacotherapy: mood stabilizers and/or antipsychotics
• psychotherapy: CBT, Family Focused Therapy

Anxiety Disorders

• lifetime prevalence 10-20%; F:M = 2:1

Clinical Presentation
• children and adolescents rarely vocalize their anxiety but instead exhibit behavioral manifestations
• school problems, recurrent physical symptoms (abdominal pain, headaches) especially in mornings, social and relationship problems, social withdrawal and isolation, family conflict, difficulty with sleep initiation, temper tantrums, irritability and mood symptoms, alcohol and drug use in adolescent

Differential Diagnosis
• depressive disorders, ODD, truancy
• clinical judgment important to differentiate developmentally normal from pathological anxiety
• for school avoidance, differentiate fear of general performance and humiliation. Consider anxiety about separation, and rule out bullying and school refusal due to learning disorder
Course and Prognosis
- better prognosis with later age of onset, lower co-morbidities, early initiation of treatment, ability to maintain school attendance and peer relationships, absence of social anxiety disorder
- with treatment, up to 80% of children will not meet criteria for their anxiety disorder at 3 yr follow-up, but up to 30% will meet criteria for another psychiatric disorder

Treatment
- similar principles for most childhood anxiety disorders due to overlapping symptomatology and frequent comorbidity
- family psychotherapy, predictive and supportive environment
- CBT: child and parental education, relaxation techniques (e.g. deep breathing), exposure/desensitization, recognizing and correcting anxious thoughts
- pharmacotherapy: SSRIs (e.g. fluoxetine), benzodiazepines (alprazolam, clonazepam) have evidence – use with caution due to addictive and abuse potential as well as disinhibiting effect, especially in neurodevelopmental delay, fluvoxamine and sertraline also have good evidence, particularly for OCD

SEPARATION ANXIETY DISORDER
- excessive and developmentally inappropriate anxiety on real, threatened, or imagined separation from primary caregiver or home, with physical or emotional distress for at least 4 wk (e.g. worries of something happening to parent or themselves if separated)
- school refusal (75%) and comorbid major depression common (2/3)
- persistent worry, refusal to sleep alone, clinging, nightmares involving separation, somatic symptoms

SOCIAL ANXIETY DISORDER (SOCIAL PHOBIA)
- anxiety, fear, and/or avoidance provoked by situations where child feels under the scrutiny of others
- must distinguish shy child, child with issues functioning socially (e.g. autism), and child with social anxiety
- diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning, or if markedly distressed. Must occur in settings with peers, not just adults
- features: temper tantrums, freezing, clinging behaviour, mutism, excessively timid, stays on periphery, refuses to be involved in group play
- significant implication for future quality of life if untreated; lower levels of satisfaction in leisure activities, higher rates of school dropout, poor workplace performance, increased rates of remaining single

SELECTIVE MUTISM
- consistent failure to speak in specific social situations where speaking is expected, despite speaking in other situations
- the disturbance interferes with educational or occupational achievement or with social communication

GENERALIZED ANXIETY DISORDER
- diagnostic criteria same as adults (see Generalized Anxiety Disorder, PS15)
  note: only 1 item is required in children for Criteria C
- often redo tasks, show dissatisfaction with their work, and tend to be perfectionistic
- often fearful in multiple settings and expect more negative outcomes when faced with academic or social challenges, and require reassurance and support to take on new tasks

SPECIFIC PHOBIA
- common phobias in childhood: fear of heights, small animals, doctors, dentists, darkness, loud noises, thunder, and lightning

Neurodevelopmental Disorders

Autism Spectrum Disorder

Diagnosis
- persistent deficits in social communication and interaction, manifested in three areas:
  - social-emotional reciprocity: ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation, to reduced sharing of interests, emotions, or affect, to failure to initiate or respond to social interactions
  - nonverbal communicative behaviours, ranging, for example, from poorly integrated verbal and nonverbal communication, to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to a total lack of facial expressions and nonverbal communication
  - developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts, to difficulties in sharing imaginative play or in making friends, to absence of interest in peers
- restricted, repetitive patterns of behaviour, interests, or activities Manifested by two or more of the following:
  - stereotyped or repetitive motor movements, insistence on sameness, highly restricted fixed interests, hyper-/hypo-reactivity to sensory input
  - symptoms must be present in early developmental period

Attachment type can be assessed in infants 10-18 mo of age using the Strange Situation test, in which the child is stressed by the caregiver being removed from the situation and the stranger staying. Attachment style is measured by the child’s behaviour during the reunion with the caregiver

Attachment problems may present as a child who is difficult to soothe, has difficulty sleeping, problems feeding, tantrums, or behavioural problems

The shy child is quiet and reluctant to participate but slowly ‘warms up’

Fluoxetine, Cognitive-Behavioural Therapy and Their Combination for Adolescents with Depression: Treatment for Adolescents with Depression Study (TADS) Randomized C controlled Trial

Purpose: To evaluate effectiveness of fluoxetine alone, cognitive behavioural therapy (CBT) alone, CBT with fluoxetine and placebo among adolescents with major depressive disorder (MDD)

Methods: Randomized controlled trial at 13 US academic and community clinics between spring 2000-summer 2003, including patients aged 12-17 with a primary DSM-IV diagnosis of MDD assigned to one of the aforementioned four treatment arms.

The primary outcome was the Children’s Depression Rating Scale-Revised (CDRS-R) total score.

Results: Fluoxetine with CBT had a statistically significant CDRS-R score as compared to placebo (p=0.001) with a 71% response rate. This combination was greater than fluoxetine alone (p=0.03), and CBT alone (p=0.01). Fluoxetine alone was greater than CBT alone (p=0.01).

Conclusion: Combination of fluoxetine with CBT offered the most favourable benefit-risk tradeoff for adolescents with MDD

Newer Generation Antidepressants for Depressive Disorders in Children and Adolescents

Cochrane Database Syst Rev 2012;11:CD004851

Purpose: To determine the efficacy and adverse outcomes of newer generation antidepressants versus placebo for child and adolescent depressive disorders

Methods: Meta-analysis of RCTs, crossover trials and cluster trials with children and adolescents aged 6 to 18 years and a diagnosis of depressive disorder, assigned to antidepressants or placebo.

Depression severity score was the main outcome measure.

Results: Nineteen trials involving 3,335 participants were included. Children treated with an antidepressant had lower depression severity score and higher rates of response/ remission. Children on antidepressants were also found to be at increased risk (58%) of suicide-related outcome (RR 1.58; 95% CI 1.02-2.45).

Conclusion: In children and adolescents, antidepressants are effective at treating depression, yet may cause a higher chance of suicide-related outcomes.
Neurodevelopmental Disorders

- symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
- not better explained by intellectual disability or global developmental delay
- specifiers
  - current severity: requiring very substantial support, requiring substantial support, requiring support
  - ± language impairment, ± intellectual impairment
  - associated with known medical or genetic condition or environmental factors (i.e. Rett's disorder)

Differential Diagnosis
- developmental disability, childhood schizophrenia, social phobia, OCD, communication disorder, non-verbal learning disorder, ADHD, abuse, hearing or visual impairment, seizure disorder, motor impairment

Management
- hearing and vision test to rule out impairment
- psychological testing to assess intellectual functioning and learning
- chromosomal analysis to rule out abnormalities (e.g. Trisomy 21, Fragile X syndrome)
- rule out psychotic disorders, social problems, depression, anxiety abuse

Treatment
- team-based: school, psychologist, occupational therapist, physiotherapist, speech and language therapy, pediatrics, psychiatry
- psychosocial: family education and support, school programming, behaviour management, social skills training
- treat concomitant disorders such as ADHD, tics, OCD, anxiety, depression, and seizure disorder
- pharmacotherapy: atypical antipsychotics (for irritability, aggression, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated inattention and hyperactivity)

Prognosis
- variable, but improves with early intervention
- better if IQ >60 and able to communicate

Attention Deficit Hyperactivity Disorder

- prevalence: 5-12% of school-aged children; M:F = 4:1, although girls may be under-diagnosed
- girls tend to have inattentive/distractible symptoms; boys have impulsive/hyperactive symptoms

Etiology
- genetic: 75% heritability, dopamine candidate genes DAT1, DRD4
- neurobiology: decreased catecholamine transmission, low prefrontal cortex (PFC) activity, increased beta activity on EEG
- cognitive: developmental disability, poor inhibitory control, and other errors of executive function

Diagnosis
- differential: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (fetal alcohol syndrome, Fragile X), lead poisoning, history of head injury, traumatic life events (abuse)
- diagnosis requires: onset before age 12, persistent symptoms >6 mo, symptoms present in at least two settings (i.e. home, school, work), interferes with academic, family, and social functioning, and is divided into 3 subtypes
  - combined type: ≥6 symptoms of inattention and ≥6 symptoms of hyperactivity-impulsivity
  - predominantly inattentive type: ≥6 symptoms of inattention
  - predominantly hyperactive-impulsive type: ≥6 symptoms of hyperactivity-impulsivity
- for older adolescents (>17 yr) or adults, 5 symptoms required
- does not occur exclusively during the course of another psychiatric disorder

Table 13. Core Symptoms of ADHD (DSM-5)

<table>
<thead>
<tr>
<th>Inattention</th>
<th>Hyperactivity</th>
<th>Impulsivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careless mistakes</td>
<td>Fidgets, squirms in seat</td>
<td>Blurs out answers before questions completed</td>
</tr>
<tr>
<td>Cannot sustain attention in tasks or play</td>
<td>Leaves seat when expected to remain seated</td>
<td>Difficulty awaiting turn</td>
</tr>
<tr>
<td>Does not listen when spoken to directly</td>
<td>Runs and climbs excessively</td>
<td>Interrupts/intrudes on others</td>
</tr>
<tr>
<td>Fails to complete tasks</td>
<td>Cannot play quietly</td>
<td></td>
</tr>
<tr>
<td>Disorganized</td>
<td>“On the go”, driven by a motor</td>
<td></td>
</tr>
<tr>
<td>Avoids, dislikes tasks that require sustained mental effort</td>
<td>Talks excessively</td>
<td></td>
</tr>
<tr>
<td>Loses things necessary for tasks or activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distractible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forgetful</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Observe child for “ATTENTION” features
- Annoy[ing]
- Tempor[atural]
- Energetic
- Noisy
- Task incomplet[ion]
- Inattentive
- Oppos[itional]
- Negativ[ism]

Treatment with stimulant medications of ADHD in childhood does not increase the likelihood of substance abuse later in life, contrary to the concerns of many parents and health care providers
**Features**
- difficult to differentiate from highly variable normative behaviour before age 4, but often identified upon school entry
- rule out developmental delay, sensory impairments, genetic syndromes, encephalopathies, or toxins (alcohol lead)
- increased risk of substance abuse, depression, anxiety, academic failure, poor social skills, comorbid CD and/or ODD, adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics

**Treatment**
- non-pharmacological: parent management, anger control strategies, positive reinforcement, social skills training, individual/family therapy, behaviour therapy, tutors, classroom intervention, exercise routines, extracurricular activities, omega-3 fatty acids
- pharmacological: first line: stimulants (methylphenidate, amphetamine salts); second line: atomoxetine; third line/adjunct: nonstimulants (α-agonists; clonidine, guanfacine, NDRI; buproprion)
- for comorbid symptoms: antidepressants, antipsychotics

**Prognosis**
- 70-80% continue into adolescence, but hyperactive symptoms usually abate
- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable

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**Disruptive, Impulse Control, and Conduct Disorder**

**Oppositional Defiant Disorder**
- prevalence: 2-16%, M:F after puberty

**Diagnosis**
- pattern of negativistic/hostile and defiant behaviour for ≥6 mo with ≥4 of:
  - angry/irritable mood: easily loses temper, touchy or easily annoyed, often angry and resentful
  - argumentative/defiant: argues with adults/authority figure, defies requests/rules, deliberately annoys, blames others for their own mistakes or misbehaviour
  - vindictive: spiteful or vindictive twice in past 6 mo
  - behaviour causes significant impairment in social, academic, or occupational functioning
  - behaviours do not occur exclusively during the course of a psychotic or mood disorder
  - criteria not met for conduct disorder (CD); if ≥18 yr, criteria not met for ASPD
  - may progress to CD, differentiated by an absence of destructive or physically aggressive behaviour
  - features that typically differentiate ODD from transient developmental stage: onset <8 yr, chronic duration (>6 mo), frequent intrusive behaviour
  - impact of ODD: poor school performance, few friends, strained parent/child relationships, risk of later mood disorders

**Treatment**
- parent: management training, psychoeducation and family therapy to reduce punitive parenting and parent-child conflict
- behavioural therapy: to teach, practice, and reinforce prosocial behaviour
- social: school/day-care interventions
- pharmacotherapy for comorbid disorders

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**Conduct Disorder**
- prevalence: 1.5-3.4% (M:F = 4:12:1)

**Etiology**
- parental/familial factors: parental psychopathology (e.g. ASPD, substance abuse), child-rearing practices (e.g. child abuse, discipline), low socioeconomic status (SES), family violence
- child factors: difficult temperament, ODD, learning problems, neurobiology
Diagnosis
• differential: ADHD, depression, head injury, substance abuse
• diagnosis: use multiple sources (Achenbach Child Behavioural Checklist, Teacher’s Report Form)
  • pattern of behaviour that violates rights of others and age appropriate social norms with ≥3 criteria noted in past 12 mo and ≥1 in past 6 mo
  • aggression to people and animals: bullying, initiating physical fights, use of weapons, forced sex cruel to people and/or animals, stealing while confronting a person (e.g. armed robbery)
  • destruction of property: arson, deliberately destroying others’ property
  • deceitfulness or theft: breaking and entering, conning others, stealing nontrivial items without confrontation
  • violation of rules: out all night before age 13, often truant from school before age 13, runaway ≥2 times at least overnight or for long periods of time
  • disturbance causes clinically significant impairment in social, academic, or occupational functioning
  • if ≥18 yr, criteria not met for ASPD

• diagnostic types
  • childhood onset: at least one criterion prior to age 10
  • poor prognosis: associated with ODD, aggressiveness, impulsiveness
  • adolescent onset: absence of any criteria until age 10
  • better prognosis; least aggressive, gang-related delinquency
  • mild, moderate, severe

Treatment
• early intervention necessary and more effective; long-term follow-up required
• psychosocial: parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training
• pharmacotherapy: for comorbid disorders

Prognosis
• poor prognostic indicators include early-age onset, high frequency, variety of behaviours, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance abuse
• 50% of CD children become adult ASPD

Intermittent Explosive Disorder

Diagnosis
• recurrent behavioural outbursts representing a failure to control aggressive impulses in children >6 yr, manifested as either
  • verbal or physical aggression that does not damage others or property, occurring 2+ times per wk for 3 mo
  • 3 outbursts involving physical damage to another person, animal or piece of property in the last 12 mo
  • outbursts are out of proportion to triggers or provocation, are not premeditated, and not for primary gain
  • outbursts cause clinically significant impairment in social, academic, or occupational functioning

See Pediatrics
• Child Abuse, P14
• Chronic Abdominal Pain, P39
• Developmental Delay, P22
• Intellectual Disability, P22
• Learning Disabilities, P24
• Sleep Disturbances, P12

See Neurology
• Tic Disorders, N33
• Tourette’s Syndrome, N34

Psychotherapy
• treatment in which a person with mental or physical difficulties aims to achieve symptomatic relief through talks with another person
• psychotherapy is delivered by a specially trained social worker, nurse, psychologist, psychiatrist, counsellor or general practitioner
• various types of therapy exist because of diverse theories of human psychology and mental illness etiology

Common Factors of Psychotherapy
• good evidence that effective psychotherapy creates observable changes in brain circuitry and connectivity, similar to those observed with successful pharmacologic and other treatment modalities
• studies suggest that up to 30-70% of therapy outcome is due to common factors with only 10-40% from specific factors
• common factors are: warmth (unconditional positive regard), accurate empathy, genuineness, goodness of fit
## Table 14. Summary of Psychotherapeutic Modalities

<table>
<thead>
<tr>
<th>Type</th>
<th>Indications</th>
<th>Approach, Technique and Theory</th>
<th>Ideal Candidates</th>
<th>Duration</th>
</tr>
</thead>
</table>
| **Psychoanalytic/Psychodynamic**      | Psychoneuroses; anxiety, obsessional thinking, compulsive or conversion disorders, sexual dysfunction, depressive states | Theory: Exploration of meaning of early experiences and how they affect emotions and patterns of behaviour  
(Recollection (remembering), repetition (reliving with the analyst), working through (gaining insight))  
Techniques: free association, dream interpretation, transference analysis | Psychologically minded, highly motivated, wish to understand selves and not just relieve symptoms  
Able to withstand difficult emotions without fleeing or self-destructive acts  
High level of function | Time intensive:  
Classically: 4-5 times/wk for 3-7 yr  
Psychodynamically oriented therapy: 2-3 times/wk for fewer years |
| **Supportive**                        | Adjustment disorders, psychosomatic disorders, severe psychotic or personality disorders | Ameliorate symptoms through behavioural or environmental restructuring to aid adaptation and facilitate coping  
Help patients feel safe, secure, and encouraged | Individuals in crisis or with severe symptoms in acute or chronic settings  
Low insight, low motivation, “weak” ego systems | Variable (single session to years, though often short intermittent) |
| **Interpersonal**                     | Mood disorders                                                               | Focuses on how interpersonal relationships impact symptoms  
4 key problem areas addressed: grief and loss, role transitions, conflict, interpersonal deficits  
Break the interpersonal cycle: depression, self-esteem, social withdrawal | Individuals with depression or bipolar disorder with some insight and difficult social functioning  
Absence of severe psychotic process, personality disorder, or comorbid substance abuse | 12-20 wk |
| **Behavioural**                       | Most mental health disorders benefit from specific application of behavioural therapy (e.g., behavioural activation for depression; exposure therapy for phobias; contingency management for anorexia nervosa and substance use disorder) | Systematic Desensitization: mastering anxiety-provoking situations by approaching them gradually and in a relaxed state that limits anxiety  
Flooding: confronting feared stimulus for prolonged periods until it is no longer frightening  
Positive Reinforcement: strengthening behaviour and causing it to occur more frequently by rewarding it  
Negative Reinforcement: causing behaviour to occur more frequently by removing a noxious stimulus when desired behaviour occurs  
Extinction: causing a behaviour to diminish by not rewarding it  
Punishment (aversion therapy): causing a behaviour to diminish by applying a noxious stimulus | Individuals with motivation to change and specific symptoms that are amenable to change  
Global areas of dysfunction such as personality disorder are difficult to treat with behavioural therapy | Usually short term (weeks-months) |
| **Cognitive Therapy**                 | Depression, anxiety, panic disorder, personality disorders, and somatoform disorders | Moods/emotions are influenced by one’s thoughts and psychiatric disturbances are often caused by habitual errors in thinking  
Therapy helps patient make explicit their inaccurate automatic thoughts and correct assumptions with a more balanced perspective  
Uses thought records (often charts with column headings including “situation,” “feeling,” “thought,” “cognitive distortion”) to help monitor thoughts, the situations they occur in, and the feelings they might provoke due to their underlying cognitive errors | Motivated patients who will comply with homework, openness to changing core beliefs | First course - usually 15-25 wk  
Maintenance therapy can be carried over years |
| **Cognitive Behavioural Therapy**     | Most mental health disorders including: mood anxiety, OCD, personality, eating, substance use, psychotic disorders | Combines theory and method from Cognitive and Behavioural therapies to teach the patient to change connections between thinking patterns, habitual behaviours, and mood/anxiety problems | Individuals with motivation to change and are able to participate in homework | Typically 6-18 wk, 1 hr sessions  
Maintenance sessions can be added over time |
| **Dialectical Behavioural Therapy**   | Borderline Personality Disorder | Therapy that combines CBT techniques with Buddhist Zen mindfulness practices and dialectical philosophy  
Focuses on 4 types of skills: mindfulness, emotion regulation, interpersonal effectiveness, and distress tolerance  
Involves 4 components: individual therapy, group skills training, phone consultations, and a consultation team | Patients with severe problems of emotional dysregulation, impulsivity, and self-harm  
Patients with borderline personality disorder or borderline personality trait | Typically 1 yr |
| **Motivational Interviewing**         | Substance use disorders | Spirit of MI (CAPE): Compassion, Acceptance, Partnership, Evocation  
Principles of MI (RULE): Resist “righting reflex”, Understand client and their reasons for change, Listen, Empower by conveying hope and supporting autonomy  
Techniques of MI (OARS): Open-ended questions, Affirmations to validate client, Reflections (the skill of accurate empathy), Summaries to help client organize self | Patients with problematic substance use, maladaptive behaviour patterns (therapy disengagement, medication noncompliance, poor health habits) | Brief interventions (efficacy with as little as 15 min, single sessions), better result with more sessions  
Addiction is a chronic condition, often need boosters over time |
| **Motivational Enhancement Therapy (MET)** | Techniques can be applied to facilitate behavioural change in most psychological problems | | | MET = 4 sessions |
Other Therapies

- group psychotherapy
  - aims to promote self-understanding, acceptance, social skills
- family therapy
  - family system considered more influential than individual, especially for children

Mindfulness-Based Cognitive Therapy (MBCT)/stress reduction (MBSR)

- derived from Buddhist meditative and philosophical practices; aims to help people attend to thoughts, behaviours, and emotions in the moment and non-judgmentally using guided breathing exercises. Emerging evidence for treating adjustment disorder, MDD, anxiety, pain disorders, insomnia, substance relapse prevention
- narrative psychotherapy
  - an integrative approach that attempts to understand the patient’s experience as a whole
  - hypnosis
  - mixed evidence for treatment of pain, phobias, anxiety, and smoking cessation

Pharmacotherapy

Antipsychotics

- “antipsychotics” and “neuroleptics” are terms used interchangeably
- overall mechanism of action: block, to varying degrees, dopamine activity in target brain pathways
- indications: for managing agitation, sleep, psychosis and mania reduction, mood stabilizing - used in schizophrenia and other psychotic disorders, mood disorders with or without psychosis, violent behaviour, autism, Tourette’s, somatoform disorders, dementia, OCD
- onset: immediate calming effect and decrease in agitation; thought disorder responds in 2-4 wk
- rational use
  - no reason to combine antipsychotics
  - choosing an antipsychotic
    - all antipsychotics are equally effective, except for clozapine (considered to be most effective in treatment-refractory psychosis)
    - atypical antipsychotics (SGA) are as effective as typical (first generation) antipsychotics but are thought to have better side effect profiles
    - choose a drug that the patient has responded to in the past or that was used successfully in a family member
- route: PO, short-acting or long-acting depot IM injections, sublingual
- if no response in 4-6 wk, switch drugs; if response, titrate dose
- duration: minimum 6 mo, usually for life

Long-Acting Preparations

- antipsychotics formulated in oil for IM injection
- received on an outpatient basis
- indications: individuals with schizophrenia or other chronic psychosis who relapse because of non-adherence
- dosing: start at low dosages, then titrate every 2-4 wk to maximize safety and minimize side effects
- should be exposed to oral form prior to first injection
- side effects: risk of EPS, parkinsonism, increased risk of NMS

Canadian Guidelines for the Treatment of Acute Psychosis in the Emergency Setting

- haloperidol 5 mg IM ± lorazepam 2 mg IM
- loxapine 25 mg ± lorazepam 2 mg IM
- olanzapine 2.5-10 mg (PO, IM, quick dissolve)
- risperidone 2 mg (M-tab, liquid)

<table>
<thead>
<tr>
<th>Dopamine Pathways Affected by Antipsychotics</th>
<th>Pathway</th>
<th>Effects</th>
<th>Associated Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesolimbic</td>
<td>Emotion</td>
<td>HIG dopaminergic activity</td>
<td>Pathways</td>
</tr>
<tr>
<td></td>
<td>origination, reward</td>
<td>cause positive symptoms of schizophrenia, violent behaviour, autism, Tourette’s, somatoform disorders, dementia, OCD</td>
<td></td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Cognition, executive</td>
<td>LOW dopaminergic activity</td>
<td>Pathways</td>
</tr>
<tr>
<td></td>
<td>function</td>
<td>cause negative symptoms of schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Nigrostriatal</td>
<td>Movement</td>
<td>LOW dopaminergic activity</td>
<td>Pathways</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cause EPS</td>
<td></td>
</tr>
<tr>
<td>Tubero-infundibular</td>
<td>Prolectin</td>
<td>LOW dopaminergic activity</td>
<td>Pathways</td>
</tr>
<tr>
<td></td>
<td>hormone release</td>
<td>cause hyperprolactinemia</td>
<td></td>
</tr>
</tbody>
</table>

Two Year Randomized Controlled Trial and Follow-Up Of Dialectical Behaviour Therapy (DBT) vs. Treatment by Experts for Suicidal Behaviours and Borderline Personality Disorder

**Purpose**: To determine how DBT compares with non-behavioural psychotherapy.

**Methods**: RCT involving 1 year of DBT or of non-behavioural therapy, followed by 1-year follow-up period. Women with recent suicidal and self-injurious behaviours meeting DSM criteria and matched to various demographic data were included. Primary outcome was trimester assessments of suicidal behaviour, emergency services use and general psychological well-being.

**Results**: Patients receiving DBT were half as likely to attempt suicide, required less hospitalization for suicidal ideation, had fewer medical risks for suicide attempts, were less likely to drop out of therapy, and had few emergency room visits for suicidal ideation.

**Conclusions**: DBT is effective in reducing suicidal behaviour in patients with borderline personality disorder.
### Table 15. Common Antipsychotic Agents

<table>
<thead>
<tr>
<th>Typical (in order of potency from high to low)</th>
<th>Starting Dose</th>
<th>Maintenance</th>
<th>Maximum</th>
<th>Relative Potency (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>2-5 mg IM q4-8h 0.5-5 mg PO b/id 0.2 mg/kg/d PO</td>
<td>Based on clinical effect</td>
<td>20 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Fluphenazine enanthate (Mediten®, Modecate® for IM formulation)</td>
<td>2.5-10 mg/d PO</td>
<td>1-5 mg PO qhs 25 mg IM/SC q1-2wk</td>
<td>20 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Zuclopenthixol HCI (Clopoxol®)</td>
<td>20-30 mg/d PO</td>
<td>20-40 mg/d PO</td>
<td>100 mg/d PO</td>
<td>4</td>
</tr>
<tr>
<td>Zuclopenthixol acetate (Acuphase®)</td>
<td>50-150 mg IM q48-72h</td>
<td>100 mg IM q1-4wk 150-300 mg IM q2wk</td>
<td>400 mg IM (q2wk)</td>
<td>6</td>
</tr>
<tr>
<td>Perphenazine (Trilafon®)</td>
<td>8-16 mg PO b/id</td>
<td>4-8 mg PO t/qid</td>
<td>64 mg/d PO</td>
<td>10</td>
</tr>
<tr>
<td>Loxapine HCI (Loxatane®)</td>
<td>10 mg PO tid 12.5-50 mg IM q4-6h</td>
<td>60 100 mg/d PO</td>
<td>250 mg/d PO</td>
<td>10</td>
</tr>
<tr>
<td>Chlorpromazine (Largactil®)</td>
<td>10-25 mg PO b/t/qid</td>
<td>400 mg/d PO</td>
<td>1000 mg/d PO</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 16. Commonly Used Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Atypicals (in order of potency from high to low)</th>
<th>Starting Dose</th>
<th>Maintenance</th>
<th>Maximum</th>
<th>Relative Potency (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone (Risperdal®, Risperdal Consta® for IM long acting preparation, Risperdal M-Tab for melting form – placed on tongue)</td>
<td>1-2 mg OD/bid</td>
<td>4-8 mg/d PO 25 mg IM q2wk</td>
<td>8 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Paliperidone (Invega®)</td>
<td>3 mg/d PO</td>
<td>3-12 mg/d PO</td>
<td>12 mg/d PO</td>
<td>4</td>
</tr>
<tr>
<td>Olanzapine (ZYPREXA®, Zyprexa Zydis® for melting form – placed on tongue, Zyprexa Intramuscular®)</td>
<td>5 mg/d PO</td>
<td>10-20 mg/d PO</td>
<td>30 mg/d PO</td>
<td>5</td>
</tr>
<tr>
<td>Aserpine (Saphr s®)</td>
<td>5 mg SL bid</td>
<td>5-10 mg S bid</td>
<td>10 mg bid</td>
<td>5</td>
</tr>
<tr>
<td>Ziprasidone (Zify®)</td>
<td>20 mg bid PO</td>
<td>40-80 mg bid PO</td>
<td>160 mg/d PO</td>
<td>6</td>
</tr>
<tr>
<td>Aripiprazole (Abilify®)</td>
<td>10-15 mg/d PO</td>
<td>10-15 mg/d PO</td>
<td>30 mg/d PO</td>
<td>7.5</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®, Seroquel XR® for extended release)</td>
<td>25 mg PO bid</td>
<td>400-800 mg/d PO</td>
<td>800 mg/d PO</td>
<td>75</td>
</tr>
<tr>
<td>Clozapine (Clozaril®)</td>
<td>25 mg PO bid</td>
<td>300-600 mg/d PO</td>
<td>600 mg/d PO</td>
<td>100</td>
</tr>
</tbody>
</table>

### Advantages
- Lower incidence of EPS than typical antipsychotics at lower doses (<8 mg)
- Associated with less weight gain compared to clozapine and olanzapine
- Better overall efficacy compared to haloperidol
- Well tolerated
- Low incidence of EPS and TD
- Mood stabilizing
- Most effective for treatment-resistant schizophrenia
- Does not worsen tardive symptoms; may treat them
- Approximately 50% of patients benefit, especially paranoid patients and those with onset after 20 yr
- Less weight gain and risk of metabolic syndrome compared to olanzapine
- A lower incidence of EPS compared to haloperidol

### Disadvantages
- SE: insomnia, agitation, EPS, H/A, anxiety, prolactin, postural hypotension, constipation, dizziness, weight gain
- Highest risk of EPS among atypicals (still lower than high-potency typicals)
- SE: mild sedation, insomnia, dizziness, minimal anticholinergic, early AST and ALT elevation, restlessness
- High risk of metabolic effects (weight gain, DM, hyperlipidemia)
- SE: H/A, sedation, dizziness, constipation
- Most sedating of first line atypicals
- SE: drowsiness/sedation, hyperactivation, tachycardia, myocarditis, cardiomyopathy, dizziness, EPS, NAMS
- 1% agranulocytosis

### Comments
- Quick dissolve (Zydis®) used commonly in ER setting for better compliance
- IM form available
- Quick dissolve formulation (Zydos®) used commonly in ER setting for better compliance
- Weekly blood counts for 6 mo, then q2wk
- Do not use with drugs which may cause bone marrow suppression due to risk of agranulocytosis

### Note
- Risk of weight gain: Clozapine > Olanzapine > Quetiapine > Risperidone

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**Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia**


**Purpose:** To compare perphenazine with several newer drugs (olanzapine, quetiapine, risperidone, ziprasidone) in patients with chronic schizophrenia.

**Methods:** Randomized, double-blind, active-control trial with median follow-up of 56 mo, involving patients with a diagnosis of schizophrenia (as per DSM-IV criteria) and able to take antipsychotic medications (as determined by study doctors). Patients were assigned to receive 1-4 capsules daily of olanzapine (20.1 mg), quetiapine (643.4 mg), risperidone (6.9 mg), perphenazine (30.8 mg), or ziprasidone (112.8 mg), with dosage at the discretion of the study doctor. Main outcome was discontinuation of treatment for any cause.

**Results:** 1,432 patients were included. The olanzapine group had statistically significant lower rate of discontinuation for any cause (H4%) from all others (quetiapine – 82%, risperidone – 81%, perphenazine – 79%, ziprasidone – 98%). There were no significant differences in time until discontinuation due to intolerable side effects; however, olanzapine was associated with a significantly higher rate of metabolic side effects.

**Conclusion:** The majority of patients in each group discontinued treatment due to inefficacy and intolerable side effects; for other reasons. Olanzapine was most effective in terms of lowest rates of discontinuation. Efficacy of conventional antipsychotic agent perphenazine was similar to quetiapine, risperidone and olanzapine.

**Anticholinergic Effects**

- Red as a beet
- Hot as a hare
- Dry as a bone
- Blined as a bat
- Mad as a hatter

**Note:** high potency antipsychotics (e.g. haloperidol) have low doses, while low potency antipsychotics (e.g. chlorpromazine) have high doses
Anticholinergic Agents

- benztropine (Cogentin®) 2 mg PO, IM, or IV OD (1-6 mg)
- amantadine (Symmetrel®) 100 mg PO bid (100-400 mg)
- diphenhydramine (Benadryl®) 25-50 mg PO/IM qid
- do not always prescribe with neuroleptics
- give anticholinergic agents only if at high risk for acute EPS or if acute EPS develops
- do not give these for tardive syndromes because they worsen the condition

Antidepressants

- onset of effect
  - relief of neurovegetative/physical symptoms: 1-3 wk
  - relief of emotional/cognitive symptoms: 2-6 wk
- taper TCAs slowly (over weeks-months) because they can cause withdrawal reactions
- tapering of any antidepressant is usually required and is based on the medication’s half-life and the patient’s individual sensitivity (e.g. fluoxetine does not require a slow taper due to long half life)

Table 17. Side Effects of Antipsychotics

<table>
<thead>
<tr>
<th>System</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic Blockade</td>
<td>Dry mouth, urinary retention, constipation, blurred vision, toxic-confusional states</td>
</tr>
<tr>
<td>α-adrenergic Blockade</td>
<td>Orthostatic hypotension, impotence, failure to ejaculate</td>
</tr>
<tr>
<td>Dopaminergic Blockade</td>
<td>Extrapyramidal syndromes, galactorrhea, amenorrhea, impotence, weight gain</td>
</tr>
<tr>
<td>Anti-histamine</td>
<td>Sedation</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Agranulocytosis (clozapine)</td>
</tr>
<tr>
<td>Hypersensitivity Reactions</td>
<td>Liver dysfunction, blood dyscrasias, skin rashes, neuroleptic malignant syndrome, altered temperature regulation (hyperthermia or hyperthermia)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Metabolic syndrome</td>
</tr>
</tbody>
</table>

Neuroleptic Malignant Syndrome

- psychiatric emergency
  - due to massive dopamine blockade; increased incidence with high potency and depot neuroleptics
- risk factors
  - medication factors: sudden increase in dosage, starting a new drug
  - patient factors: medical illness, dehydration, exhaustion, poor nutrition, external heat load, male, young adults
- clinical presentation
  - mental status changes (usually occur first), fever, autonomic reactivity, rigidity
  - develops over 24-72 h
  - labs: increased creatine phosphokinase, leukocytosis, myoglobinuria
- treatment: supportive - discontinue drug, hydration, cooling blankets, dantrolene (hydrantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)
- mortality: 5%

Extrapyramidal Symptoms

- incidence related to increased dose and potency
- acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)

Table 18. Extrapyramidal Symptoms

<table>
<thead>
<tr>
<th>Onset</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: within 5 d Tardive: &gt;90 d</td>
<td>Acute: benztropine or diphenhydramine</td>
</tr>
<tr>
<td>Acute: within 10 d Tardive: &gt;90 d</td>
<td>Acute: lorazepam, propranolol, diphenhydramine; reduce or change neuroleptic to lower potency</td>
</tr>
<tr>
<td>Acute: within 30 d Tardive: &gt;90 d</td>
<td>Acute: benzotripe (or ben diazepine if side effects); reduce or change neuroleptic to lower potency</td>
</tr>
<tr>
<td>Purposeless, constant movements, involving facial and mouth musculature, or less commonly – the limbs</td>
<td>Tardive: no good treatment; may try clozapine; discontinue drug or reduce dose</td>
</tr>
</tbody>
</table>

Metabolic and Cardiovascular Adverse Effects Associated with Antipsychotic Drugs

- important side effect of antipsychotics
- consider getting ECG prior to initiating new medication and to monitor side effects
- typical: chlorpromazine and haloperidol warrant cardiac monitoring
- Atypicals: ziprasidone has the highest risk among atypicals, clozapine also warrant monitoring

Selective Serotonin Reuptake Inhibitors (SSRIs) vs. Other Antidepressants for Depression

**Conclusion**: There is no clinically significant difference in effectiveness of SSRIs vs. TCAs. The standardized effect size for SSRIs and related drugs was that of 0.035 (95% CI -0.006 to 0.076; p< 0.001).

**Methods**: Systematic review of RCTs comparing the efficacy of SSRIs with other kinds of antidepressants (e.g., tricyclic antidepressants (TCAs)) for management of depressive disorders.

**Results**: Ninety-eight trials were included, with 5,044 patients treated with an SSRI or related drug, and 4,510 with an alternate antidepressant. The outcome measures assessed were measures of depression severity.

**Conclusions**: There is no clinically significant difference in effectiveness of SSRIs vs. TCAs. Treatment decisions should consider relative patient acceptability, toxicity, and cost.
must be vigilant over the first 2 wk of therapy; neurovegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be particularly at risk for suicidal behaviour during this time; in children/adolescents, paroxetine and venlafaxine may increase restlessness and suicide ideation, so are generally not prescribed)

- treatment of bipolar depression
  - patients with bipolar disorder should only be treated with an antidepressant if combined with a mood stabilizer or antipsychotic; monotherapy with antidepressants is not advisable as the depression can turn into mania

### Table 19. Common Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Daily Starting Dose (mg)</th>
<th>Therapeutic Dose (mg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>fluoxetine (Prozac®)</td>
<td>20</td>
<td>20-80</td>
<td>Useful for anxiety states, OCD, eating disorders, seasonal depression, typical and atypical depression</td>
</tr>
<tr>
<td></td>
<td>fluvoxamine (Luxox®)</td>
<td>50-100</td>
<td>150-300</td>
<td>All SSRIIs have similar effectiveness but consider side effect profiles and half-lives</td>
</tr>
<tr>
<td></td>
<td>paroxetine (Paxil®)</td>
<td>10</td>
<td>20-60</td>
<td>Citalopram, and escitalopram have the fewest drug-interactions and are sleep-wake neutral</td>
</tr>
<tr>
<td></td>
<td>sertraline (Zoloft®)</td>
<td>50</td>
<td>50-200</td>
<td>Sertraline is the safest SSRI in pregnancy and breastfeeding</td>
</tr>
<tr>
<td></td>
<td>citalopram (Celexa®)</td>
<td>20</td>
<td>20-40</td>
<td>Fluoxetine and paroxetine are the most activating drugs (recommend taking in the AM)</td>
</tr>
<tr>
<td></td>
<td>escitalopram (Cipralex®)</td>
<td>10</td>
<td>10-20</td>
<td>Fluoxetine does not require a taper due to long half-life and is the most used in children as it has most evidence</td>
</tr>
<tr>
<td></td>
<td>duloxetine (Cymbalta®)</td>
<td></td>
<td></td>
<td>Fluvoxamine is sedating (should be taken in PM)</td>
</tr>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor®)</td>
<td>37.5-75</td>
<td>75-225</td>
<td>Useful for depression, anxiety disorders</td>
</tr>
<tr>
<td></td>
<td>Desvenlafaxine (Pristiq®)</td>
<td>50</td>
<td>50-100</td>
<td>Useful for depression, seasonal depression</td>
</tr>
<tr>
<td></td>
<td>duloxetine (Cymbalta®)</td>
<td>30</td>
<td>30-60</td>
<td>Causes less sexual dysfunction (may reverse effects of SSRIIs/SNRIs), weight gain, and sedation</td>
</tr>
<tr>
<td></td>
<td>sertraline (Zoloft®)</td>
<td>10</td>
<td>50-100</td>
<td>Increased risk of seizures at higher doses</td>
</tr>
<tr>
<td></td>
<td>tranylcypromine (Parnate®)</td>
<td>30</td>
<td>10-60</td>
<td>Contraindicated with history of seizure, stroke brain tumour, brain injury, closed head injury</td>
</tr>
<tr>
<td>MAOI</td>
<td>phenelzine (Nardil®)</td>
<td>45</td>
<td>60-90</td>
<td>Useful for moderate/severe depression that does not respond to SSRI, atypical depression</td>
</tr>
<tr>
<td></td>
<td>tranylcypromine (Parnate®)</td>
<td>30</td>
<td>10-60</td>
<td>Important to specify formulation, as available in IR, SR, XL (longest)</td>
</tr>
<tr>
<td>MAOI</td>
<td>moclobemide (Manerix®)</td>
<td>300</td>
<td>300-600</td>
<td>Useful for depression unresponsive to other therapies</td>
</tr>
<tr>
<td>NASSA</td>
<td>mirtazapine (Remeron®)</td>
<td>15</td>
<td>15-45</td>
<td>Useful in depression with prominent features of insomnia, agitation, or cachexia</td>
</tr>
<tr>
<td>NDRI</td>
<td>bupropion (Wellbutrin®)</td>
<td>100</td>
<td>300-450</td>
<td>Useful as mood stabilizer or in combination with an antidepressant</td>
</tr>
</tbody>
</table>

MAOI = monoamine oxidase inhibitors; NASSA = noradrenergic and specific serotonin antagonists; NDRI = norepinephrine and dopamine reuptake inhibitors; RIMA = reversible inhibition of MAO-A; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants

### Treatment Approach for Depression

- optimization: ensuring adequate drug doses for the individual
- augmentation: the addition of a medication that is not considered an antidepressant to an antidepressant regimen (e.g. thyroid hormone, lithium, atypical antipsychotics (specifically: olanzapine, risperidone, aripiprazole))
- combination: the addition of another antidepressant to an existing treatment regimen (e.g. the addition of bupropion to an SSRI or SNRI)
- substitute: change in the primary antidepressant (within or outside a class)
- note: it is important to fully treat depression symptoms in order to decrease relapse rates and severity
<table>
<thead>
<tr>
<th>Table 20. Features of Commonly Used Antidepressant Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI</strong></td>
</tr>
<tr>
<td><strong>Examples</strong></td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
</tr>
<tr>
<td><strong>Risk in Overdose</strong></td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
</tr>
</tbody>
</table>

**Serotonin Syndrome**
- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as SSRI+MAOI, SSRI+tryptophan, MAOI+meperidine, MAOI+tryptophan
- rare but potentially life-threatening adverse reaction to SSRIs, especially when switching from an SSRI to an MAOI
- symptoms include nausea, diarrhea, palpitations, chills, restlessness, confusion, and lethargy but can progress to myoclonus, hyperthermia, rigor and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS

**Discontinuation Syndrome**
- caused by the abrupt cessation of an antidepressant; most commonly with paroxetine, fluvoxamine, and venlafaxine (drugs with shortest half-lives)
- symptoms usually begin within 1-3 d and include: anxiety, insomnia, irritability, mood lability, nausea/vomiting, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy, and myalgia
- treatment: symptoms may last between 1-3 wk, but can be relieved within 24 h by restarting antidepressant therapy at the same dose the patient was taking and initiating a slow taper over several weeks
- consider using a drug with a longer half-life such as fluoxetine
Mood Stabilizers

General Prescribing Information
- examples: lithium, lamotrigine, divalproex, carbamazepine
- used in conjunction with atypical antipsychotics for managing episodes of bipolar disorder - depression, mania, stabilization
- vary in their ability to "treat" (reduce symptoms acutely) or "stabilize" (prevent relapse and recurrence)
- manic and depressive symptoms; multi-agent therapy is common
- before initiating, get baseline: CBC, ECG (if patient >45 yr old or cardiovascular risk), urinalysis, BUN, Cr, electrolytes, TSH
- before initiating lithium: screen for pregnancy, thyroid disease, seizure disorder, neurological, renal, cardiovascular diseases
- full effects not for 2-4 wk; thus may need acute coverage with benzodiazepines or antipsychotics

Specific Prescribing Information
- detailed pharmacological guidelines available online from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)
- for clinical information for treating bipolar disorder (see Mood Disorders, PS9)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Lithium</th>
<th>Lamotrigine (Lamictal®)</th>
<th>Divalproex (Epival®)</th>
<th>Carbamazepine (Tegretol®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>1st line</td>
<td>1st line</td>
<td>2nd line</td>
<td></td>
</tr>
<tr>
<td>Acute mania (monotherapy or with adjunct SGA)</td>
<td>Bipolar I depression (monotherapy)</td>
<td>Acute mania (monotherapy or with adjunct SGA)</td>
<td>Acute mania (monotherapy)</td>
<td></td>
</tr>
<tr>
<td>Bipolar I depression (monotherapy or in combination with SSRI, divalproex, or bupropion)</td>
<td>Bipolar disorder maintenance (limited efficacy in preventing mania, more effective when combined with lithium)</td>
<td>Bipolar I depression (combination with SSRI or lithium)</td>
<td>Bipolar disorder maintenance (monotherapy or with adjunct SGA)</td>
<td></td>
</tr>
<tr>
<td>Bipolar I disorder maintenance (monotherapy or with adjunct SGA)</td>
<td>Other uses</td>
<td>Bipolar II depression</td>
<td>Other uses</td>
<td></td>
</tr>
<tr>
<td>MDE and OCD</td>
<td>Other uses</td>
<td>Other uses</td>
<td>Other uses</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td></td>
<td></td>
<td>Rapid cycling bipolar disorder</td>
<td></td>
</tr>
<tr>
<td>Chronic aggression antisocial behaviour</td>
<td></td>
<td></td>
<td>Mixed phase/dysphoric mania</td>
<td></td>
</tr>
<tr>
<td>Recurrent depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mode of Action
- Unknown
- Therapeutic response within 7-14 d
- May inhibit 5-HT3 receptors
- May potentiate DA activity

Dosage
- Adult: 600-1500 mg/d
- Geriatric: 150-600 mg/d
- Usually daily dosing
- Starting: 12.5-15 mg/d
- Daily dose: 100-200 mg/d
- Dose adjusted in patients taking other anticonvulsants
- Note: very slow titration due to risk of Stevens-Johnson Syndrome

Therapeutic Level
- Adult: 0.8-1.0 mmol/L (1.0-1.25 mmol/L for acute mania)
- Geriatric: 0.5-0.8 mmol/L
- Therapeutic plasma level not established
- Dosing based on therapeutic response
- 17-50 mmol/L
- Therapeutic levels are for seizure prophylaxis
- 350-700 µmol/L

Monitoring
- Monitor serum levels until therapeutic (always wait 12 h after dose)
- Then monitor b.i.w. or monthly until a steady state is reached, then q2mo
- Monitor thyroid function q6mo, creatinine q6mo, urinalysis q1yr
- Monitor for suicidality, particularly when initiating treatment
- LFTs weekly x 1 mo, then monthly, due to risk of liver dysfunction
- Watch for signs of liver dysfunction: nausea, edema, malaise
- Monitor levels to confirm adherence
- Weekly blood counts for first month, due to risk of agranulocytosis
- Watch for signs of blood dyscrasias: fever, rash, sore throat, easy bruising

Side Effects
- GI: N/V, diarrhea, stomach pain
- GU: polyuria, polydipsia, GN, renal failure, nephrogenic DI
- CNS: fine tremor, lethargy, fatigue, headache
- Hematologic: reversible leukocytosis
- Other: teratogenic (Estbeen’s anomaly), weight gain, edema, paresthesia, hypothyroidism, hair thinning, muscle weakness, ECG changes
- GI: liver dysfunction, N/V, diarrhea, nausea, edema, malaise
- Glutamatergic: reversible drug because of risk of Stevens-Johnson syndrome, increased lamotrigine levels = increased risk of rash
- Anxiety

Interactions
- NSAIDs decrease clearance
- OCP
- OCP
Lithium Toxicity
- clinical diagnosis as toxicity can occur at therapeutic levels
- common causes: overdose, sodium/fluid loss, concurrent medical illness
- clinical presentation
  - GI: severe nausea/vomiting and diarrhea
  - cerebellar: ataxia, slurred speech, lack of coordination
  - cerebral: drowsiness, myoclonus, tremor, upper motor neuron signs, seizures, delirium, coma
- management
  - discontinue lithium for several doses and begin again at a lower dose when lithium level has fallen to a non-toxic range
  - serum lithium levels, BUN, electrolytes
  - saline infusion
  - hemodialysis if lithium >2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 h, or deterioration

Anxiolytics
- anxiolytics mask or alleviate symptoms; they do not cure them
- indications
  - short-term treatment of transient forms of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, organic brain syndrome (acute agitation in delirium), EPS and akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders
- relative contraindications
  - major depression (except as an adjunct to other treatment), history of drug/alcohol abuse, caution in pregnancy/breastfeeding
- mechanism of action
  - benzodiazepines: potentiate binding of GABA to its receptors; results in decreased neuronal activity
  - buspirone: partial agonist of 5-HT1A receptors

Benzodiazepines
- should be used for limited periods (weeks-months) to avoid dependence
- all benzodiazepines are sedating; be wary with use in the elderly
- have similar efficacy, so choice depends on half-life, metabolites and route of administration, OD or bid
- taper slowly over weeks-months because they can cause withdrawal reactions
  - low dose withdrawal: tachycardia, HTN, panic, insomnia, anxiety, impaired memory and concentration, perceptual disturbances
  - high dose withdrawal: hyperpyrexia, seizures, psychosis, death
- avoid alcohol because of potentiation of CNS depression; caution with drinking and driving/machinery use
- side effects
  - CNS: drowsiness, cognitive impairment, reduced motor coordination, memory impairment
  - physical dependence, tolerance
- withdrawal
  - symptoms: anxiety, insomnia, autonomic hyperactivity (less common)
  - onset: 1-2 d (short-acting), 2-4 d (long-acting)
  - duration: weeks-months
  - complications with above 50 mg diazepam/day: seizures, delirium, arrhythmias, psychosis
  - management: taper with long-acting benzodiazepine
  - similar to but less severe than alcohol withdrawal; can be fatal
- overdose
  - commonly used drug in overdose
  - overdose is rarely fatal
  - benzodiazepines are more dangerous and may cause death when combined with alcohol, other CNS depressants or TCAs

Benzodiazepine Antagonist – Flumazenil (Anexate®)
- use for suspected benzodiazepine overdose
- specific antagonist at the benzodiazepine receptor site
Table 22. Common Anxiolytics

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dose Range (mg/d)</th>
<th>t1/2 (h)</th>
<th>Appropriate Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>clonazepam (Rivotril®)</td>
<td>0.25-4</td>
<td>18-50</td>
<td>Akathisia, generalized anxiety, seizure prevention, panic disorder</td>
</tr>
<tr>
<td></td>
<td>diazepam (Valium®)</td>
<td>2-40</td>
<td>30-100</td>
<td>Generalized anxiety, seizure prevention, muscle relaxant, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>chlordiazepoxide (Librium®)</td>
<td>5-300</td>
<td>30-100</td>
<td>Sleep, anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>flurazepam (Dalmane®)</td>
<td>15-30</td>
<td>50-160</td>
<td>Sleep</td>
</tr>
<tr>
<td>Short-acting</td>
<td>alprazolam (Xanax®)</td>
<td>0.25-4.0</td>
<td>6-20</td>
<td>Panic disorder, high dependency rate</td>
</tr>
<tr>
<td></td>
<td>lorazepam (Ativan®)</td>
<td>0.5-6.0</td>
<td>10-20</td>
<td>Sleep, generalized anxiety, akathisia, alcohol withdrawal, sublingual available for very rapid action</td>
</tr>
<tr>
<td></td>
<td>oxazepam (Serax®)</td>
<td>10-120</td>
<td>8-12</td>
<td>Sleep, generalized anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>temazepam (Restoril®)</td>
<td>7.5-30</td>
<td>8-20</td>
<td>Sleep</td>
</tr>
<tr>
<td></td>
<td>triazolam (Halcion®)</td>
<td>0.125-0.5</td>
<td>1.5-5</td>
<td>Shortest t1/2, rapid sleep, but rebound insomnia</td>
</tr>
<tr>
<td>Azapirones</td>
<td>zopiclone (Imovane®)</td>
<td>5-7.5</td>
<td>3.8-6.5</td>
<td>Sleep</td>
</tr>
</tbody>
</table>

**Somatic Therapies**

**Electroconvulsive Therapy**

- Various methodological improvements have been made since the first treatment in 1938 to reduce adverse effects.
- Modern ECT: induction of a generalized seizure using an electrical pulse through scalp electrodes while the patient is under general anesthesia with a muscle relaxant.
- Considerations: unilateral vs. bilateral electrode placement, pulse rate, dose, number and spacing of treatments.
- Usual course is 6-12 treatments, 2-3 treatments per week.
- **Indications**
  - Depression refractory to adequate pharmacological trial (MDD or Bipolar I depression).
  - High suicide risk.
  - Medical risk in addition to depression (dehydration, electrolytes, pregnancy).
  - Previous good response to ECT.
  - Familial response to ECT.
  - Elderly.
  - Psychotic depression.
  - Catatonic features.
  - Marked vegetative features.
  - Acute schizophrenia unresponsive to medication.
  - Mania unresponsive to medications.
  - OCD refractory to conventional treatment.

- **Side effects**: Risk of anesthesia, memory loss (may be retrograde and/or anterograde, tends to resolve by 6-9 mo), permanent impairment (controversial), headaches, myalgias.
- Unilateral ECT causes less memory loss than bilateral but may not be as effective.
- **Contraindications**: Increased intracranial pressure, recent (<2 wk) MI (not absolute but requires special monitoring).

**Repetitive Transcranial Magnetic Stimulation (rTMS)**

- Noninvasive production of focal electrical currents in select brain areas using magnetic induction.
- **Indications**: Strong evidence for treatment-resistant depression, pain disorders; possibly efficacious for anxiety disorders, eating disorders, substance use disorders.
- **Adverse effects**: Common – transient local discomfort, hearing issues, cognitive changes; rare – seizure, syncope, mania induction.

**Magnetic Seizure Therapy (MST)**

- Seizure induction by magnetic current induction rather than direct stimulation.
- Early studies demonstrate efficacy for depression as well as anxiety, reduced memory side effects vs. ECT.

**ECT in Society**

Prior to the 1940s, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by barbaric depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients struggling with mental illness.

**Efficacy of ECT in Depression: A Meta-Analytic Review**

J of ECT 2004; 20:13-20

**Purpose**: To analyze the efficacy of electroconvulsive therapy (ECT) in depression.

**Methods**: Meta-analysis of randomized and non-randomized control trials, comparing ECT to simulated ECT and placebo in individuals with a diagnosis of unipolar or bipolar depression. Main outcome was the Hamilton Depression Rating scale.

**Results**: ECT was found to be superior to simulated ECT, placebo, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and antideperessants in general.

**Conclusion**: ECT is an valid treatment modality, including in severe and treatment-resistant depression cases.
Neurosurgical Treatments

Ablative/Lesion Procedures
- used for intractable MDD or OCD, efficacy ranges from 25-75% depending on procedure
- adverse effects: related to lesion location and size; high risk of suicide in those who are not helped by surgery

Deep Brain Stimulation
- placement of small electrode leads in specific brain areas to alter neuronal signaling, usually for intractable MDD
- response rates (>50% symptom reduction) of 40-70%, adverse effects related to surgical risks and poor treatment response

Vagus Nerve Stimulation
- direct, intermittent electrical stimulation of left cervical vagus nerve via implanted pulse generator
- used for chronic, recurrent MDD that has failed previous therapy and ECT; slow onset, approximately 30% response rate at 1 yr

Other Therapy Modalities

Phototherapy (Light Box Therapy)
- bright light source exposure, best in morning, for 30-60 min (usually 10,000 lux)
- proposed mechanisms: reverses pathological alterations in circadian rhythm through action on suprachiasmatic nucleus
- indications: SAD, non-seasonal depression (as augmentation), sleep disorders
- adverse effects: mania induction, reaction with photosensitizing drug or photosensitive eye or skin conditions

Aerobic Exercise
- moderate-intense aerobic exercise is associated with acute increased secretion of serotonin, phenethylamine, BDNF, endogenous opioids and cannabinoids (likely this combination is what contributes to the “runner’s high”)
- long term increases grey matter in multiple areas, as well as improvements in cognition, memory, and stress tolerance
- indications: Monotherapy for mild-moderate MDD, Adjunctive therapy for moderate-severe MDD; research suggests 30 min of supervised moderate-intensity exercise at least 3 times weekly for a minimum of 9 wk is effective
- may be helpful in PTSD, schizophrenia

Canadian Legal Issues

Table 23. Common Forms Under the Mental Health Act (in Ontario)

<table>
<thead>
<tr>
<th>Form</th>
<th>Who Signs</th>
<th>When</th>
<th>Expiration Date</th>
<th>Right of Patient to Review Board Hearing</th>
<th>Options Before Form Expires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form 1: Application by physician to hospitalize a patient for psychiatric assessment against his/her will to a schedule 1 facility (Form 42 given to patient)</td>
<td>Any MD</td>
<td>Within 7 d after examination of the patient</td>
<td>72 h after hospitalization</td>
<td>No</td>
<td>Form 3 + 30 or voluntary admission or Send home ≤ follow-up</td>
</tr>
<tr>
<td>Form 2: Order for a psychiatric assessment against his/her will which is ordered by Justice of the Peace (Form 42 given to patient)</td>
<td>Justice of the Peace</td>
<td>No statutory time restriction</td>
<td>7 d from when completed</td>
<td>Purpose of form is complete once patient brought to hospital</td>
<td>No</td>
</tr>
<tr>
<td>Form 3: Certificate of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)</td>
<td>Attending MD (different than MD who completed Form 1)</td>
<td>Before expiration of Form 1</td>
<td>14 d</td>
<td>No</td>
<td>Form 4 + 30 or Voluntary admission (Form 5)</td>
</tr>
<tr>
<td>Form 4: Certificate of renewal of involuntary admission to a schedule 1 facility (original Form 30 given to patient, notice to rights advisor)</td>
<td>Attending MD following patient on Form 3</td>
<td>Prior to expiration of Form 3</td>
<td>First: 1 mo Second: 2 mo Third: 3 mo (max)</td>
<td>Yes</td>
<td>Form 4 + 30 or Voluntary admission (Form 5)</td>
</tr>
</tbody>
</table>
### Table 23. Common Forms Under the Mental Health Act (in Ontario) continued

<table>
<thead>
<tr>
<th>Form</th>
<th>Who Signs</th>
<th>When</th>
<th>Expiration Date</th>
<th>Right of Patient to Review Board Hearing</th>
<th>Options Before Form Expires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form 5: Change to informal/voluntary status</td>
<td>Attending MD following patient on Form 3/4</td>
<td>Whenever deemed appropriate</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Form 30: Notice to patient that they are now under involuntary admission on either Form 3 or 4. Original to the patient, copy to chart</td>
<td>Attending MD</td>
<td>Whenever Form 3 or Form 4 filled</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Form 33: Notice to patient that patient is incapable of consenting to treatment of mental disorder, and/or management of property and/or disclosure of health information (original copy to patient)</td>
<td>Attending MD</td>
<td>Whenever deemed appropriate</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Schedule 1 Facilities: Able to provide intensive inpatient and outpatient care

### Consent

- see Ethical, Legal, and Organizational Medicine, ELOM7

### Community Treatment Order (CTO)

- purpose: a CTO orders a person suffering from a serious mental disorder to receive treatment and supervision in the community. Based on a comprehensive plan outlining medications, appointments, and other care believed necessary to allow the person to live in the community (vs. in a psychiatric facility, where things are more restrictive)
- intended for those who:
  - due to their serious mental disorder, experience a pattern of admission to a psychiatric facility where condition is usually stabilized
  - after being released, these patients often lack supervision and stop treatment, leading to destabilization
  - due to the destabilization of their condition, these patients usually require re-admission to hospital
  - if CTO violated (e.g. treatment not taken), patient brought in by police to hospital for treatment as per CTO
- criteria for a physician to issue a CTO:
  - patient with a prior history of hospitalization
  - a community treatment plan for the person has been made
  - examination by a physician within the previous 72 h before entering into the CTO plan
  - ability of the person subject to the CTO to comply with it
  - consultation with a rights advisor and consent of the person or the person's substitute decision maker
- CTOs are valid for 6 mo unless they are renewed or terminated at an earlier date such as
  - where the person fails to comply with the CTO
  - when the person or his/her substitute decision-maker withdraws consent to the community treatment plan
- CTO process is consent-based and all statutory protections governing informed consent apply
- the rights of a person subject to a CTO include
  - the right to a review by the Consent and Capacity Board with appeal to the courts each time a CTO is issued or renewed
  - a mandatory review by the Consent and Capacity Board every second time a CTO is renewed
  - the right to request a re-examination by the issuing physician to determine if the CTO is still necessary for the person to live in the community
  - the right to review findings of incapacity to consent to treatment
  - provisions for rights advice

### Duty to Inform/Warn

- see Ethical, Legal, and Organizational Medicine, ELOM6

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* CTO Legislature: Ontario passed CTO legislature on December 1, 2000 (known as “Brian’s Law”)  
  Similar CTOs have been implemented in Saskatchewan (1995), Manitoba (1997), and British Columbia (1999)
Acronyms .................................................. 2

Approach to the Respiratory Patient .......... 2
Basic Anatomy Review
Differential Diagnoses of Common Presentations
Pulmonary Function Tests
Chest X-Rays
Arterial Blood Gases

Airway Disease ............................... 7
Pneumonia
Asthma
Chronic Obstructive Pulmonary Disease
Bronchiectasis
Cystic Fibrosis

Interstitial Lung Disease ......................... 13
Unknown Etiologic Agents
Known Etiologic Agents

Pulmonary Vascular Disease ................. 17
Pulmonary Hypertension
Pulmonary Embolism
Pulmonary Vasculitis
Pulmonary Edema

Diseases of the Mediastinum and Pleura ... 21
Mediastinal Masses
Mediastinitis
Pleural Effusions
Complicated Effusion
Empyema
Atelectasis
Pneumothorax
Asbestos-Related Pleural Disease and
Mesothelioma

Respiratory Failure .............................. 26
Hypoxemic Respiratory Failure
Hypercapnic Respiratory Failure
Acute Respiratory Distress Syndrome

Neoplasms ........................................... 28
Lung Cancer
Approach to the Solitary Pulmonary Nodule

Sleep-Related Breathing Disorders ........... 32
Hypoventilation Syndromes
Sleep Apnea

Introduction to Intensive Care ............... 33
Intensive Care Unit Basics
Organ Failure
Shock
Sepsis

Common Medications .......................... 36

Landmark Respirology Trials ............... 39

References ........................................... 40
Approach to the Respiratory Patient

Basic Anatomy Review

Figure 1. Lung lobes and bronchi

Figure 2. Respiration patterns in normal and disease states

Respiration Pattern

Normal

Obstructive (prolonged expiration)
- Asthma, COPD

Bradyynes (slow respiratory rate)
- Drug-induced respiratory depression
- Diabetic coma (nonketotic)
- Increased ICP

Kussmaul's Breathing (fast and deep)
- Metabolic acidosis
- Exercise
- Anxiety

Biot's/Ataxic (irregular with long apneic periods)
- Drug-induced respiratory depression
- Increased ICP
- Brain damage (especially medullary)

Cheyne-Stokes Breathing (changing rates and depths with apneic periods)
- Drug-induced respiratory depression
- Brain damage (especially cerebral)
- CHF
- Uremia

Apneustic (prolonged inspiratory pause)
- Pontine lesion

Toronto Notes 2018

Raw Text

Acronyms

A-a alveolar-arterial
A-aO2 alveolar-arterial oxygen diffusion gradient
ABC arterial blood gas
ACE angiotensin converting enzyme inhibitor
ACV assist-control ventilation
AECOPD acute exacerbation of COPD
AFS acid-fast bacillus
AFP alpha-fetoprotein
AFOP acute fibrous and organizing pneumonia
AHF apnea hypopnea index
AIP acute interstitial pneumonia
ALC acute lung injury
ALS amyotrophic lateral sclerosis
ANA antinuclear antibody
ANOCA anti-neutrophil cytoplasmic antibody
AFTT activated partial thromboplastin time
ARDS acute respiratory distress syndrome
ASA aspirin
ASAID antiphospholipid antibody
ASAIDS antiphospholipid antibody syndrome
ASA/ANCA antiphospholipid antibody syndrome/
activiated partial thromboplastin time
ataxia
ATN acute tubular necrosis
AVM arteriovenous malformation
AVN atrioventricular nervous
BNP brain natriuretic peptide
BPD bronchopulmonary dysplasia
BSE body surface extension
BSA body surface area
BV blood volume
Bx biopsy
CA cardiac arrest
CABG coronary artery bypass graft
CAH chronic atrophic gastritis
CAH pyloromyotomy
CABP chronic obstructive pulmonary hypertension
CDO cardiac output
Ce cerebral cortex
CChC chronic obstructive pulmonary disease
COPD chronic obstructive pulmonary
disease
CPAP continuous positive airway pressure
CSA central sleep apnea
CT computed tomography
CTPH chronic total pulmonary
hypertension
CVP central venous pressure
### Differential Diagnoses of Common Presentations

#### Table 1. Differential Diagnosis of Dyspnea

<table>
<thead>
<tr>
<th>ACUTE DYSPNEA (MINUTES-DAYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>Upper airway obstruction</td>
</tr>
<tr>
<td>(anaphylaxis, aspiration, croup, EBV)</td>
</tr>
<tr>
<td>Airway disease (asthma, COPD exacerbation, bronchitis)</td>
</tr>
<tr>
<td>Parenchymal lung disease (ARDS, pneumonia)</td>
</tr>
<tr>
<td>Pulmonary vascular disease (PE, vasculitis)</td>
</tr>
<tr>
<td>Pleural disease (pneumothorax, tension pneumothorax)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHRONIC DYSPNEA (+4 WEEKS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Myocardial dysfunction (decreased CO)</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>Airway disease (asthma, COPD)</td>
</tr>
<tr>
<td>Parenchymal lung disease (interstitial disease)</td>
</tr>
<tr>
<td>Pulmonary vascular disease (pulmonary HTN, vasculitis)</td>
</tr>
<tr>
<td>Pleural disease (effusion)</td>
</tr>
</tbody>
</table>

| **Metabolic**           | **Gastrointestinal** |
| Medication              | Pancreatitis         |
| Severe Anemia           |                  |
| Hyperthyroidism         |                  |

| **Neuromuscular and chest wall disorders** |
| Deconditioning, obesity, pregnancy, neuromuscular disease |

| **Psychogenic** | **Psychiatric** |
| Anxiety         | Anxiety         |
| Panic attack    | Panic attack/disorder |

#### Table 2. Differential Diagnosis of Chest Pain

<table>
<thead>
<tr>
<th>NONPLEURITIC</th>
<th>PLEURITIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>PE</td>
<td>PE</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Neoplasm</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td><strong>Pericardial</strong></td>
</tr>
<tr>
<td>MI</td>
<td>Pleurisy</td>
</tr>
<tr>
<td>Myocarditis/periocarditis</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td><strong>Esophageal</strong></td>
<td><strong>TB</strong></td>
</tr>
<tr>
<td>GERD</td>
<td></td>
</tr>
<tr>
<td>Spasm</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Dressler’s syndrome</td>
</tr>
<tr>
<td>Achalasia</td>
<td></td>
</tr>
<tr>
<td>Neoplasm</td>
<td>GI</td>
</tr>
<tr>
<td>Esophageal rupture</td>
<td>Subphrenic abscess</td>
</tr>
</tbody>
</table>

| **Mediastinal** | **Psych** |
| Lymphoma       | Anxiety   |
| Thymoma        |           |
| **Subdiaphragmatic** | Panic attack/disorder |
| PUD            | |
| Gastritis      | |
| Biliary colic  | |
| Pancreatitis   | |

| **Vascular** | **Liver** |
| Aortic aneurysm | |
| Aortic dissection | |
| Aortic injury/rupture | |
| **MSK**       | |
| Costochondritis | |
| Skin           | |
| Breast         | |
| Ribs           | |
| **Rheumatic disease** | |
| PsA            | |

#### Table 3. Differential Diagnosis of Hemoptysis

<table>
<thead>
<tr>
<th><strong>Airway Disease</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or chronic bronchitis*</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Bronchogenic CA</td>
</tr>
<tr>
<td>Bronchial carcinoid tumour</td>
</tr>
<tr>
<td>CF</td>
</tr>
</tbody>
</table>

| **Parenchymal Disease** |
| Pneumonia              |
| TB                    |
| Lung abscess           |
| Fungal infection       |
| Primary lung cancer    |
| Pulmonary metastasis   |

| **Vascular Disease** |
| PE                   |
| Elevated pulmonary venous pressure: |
| LVF                  |
| Mitral stenosis       |
| **Vascular malformation** |
| Vasculitis            |
| Goodpasture’s syndrome |
| **Idiopathic pulmonary hemosiderosis** |

| **Miscellaneous** |
| Impaired coagulation |
| Pulmonary endometriosis |

*Most common cause of hemoptysis

Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008. With permission from Elsevier
Pulmonary Function Tests

- useful in differentiating the pattern of lung disease (obstructive vs. restrictive)
- assess lung volumes, flow rates, and diffusion capacity
- note: normal values for FEV$_1$ are approximately ±20% of the predicted values (for age, sex, and height); ethnicity may affect predicted values

<table>
<thead>
<tr>
<th>Table 5. Comparison of Lung Flow and Volume Parameters in Lung Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstructive</strong></td>
</tr>
<tr>
<td>Decreased flow rates (most marked during expiration)</td>
</tr>
<tr>
<td>Air trapping (increased RV/TLC)</td>
</tr>
<tr>
<td>Hyperinflation (increased FRC, TLC)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6. Common Respirology Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technique</td>
</tr>
<tr>
<td>Plethysmography (&quot;body box&quot;)</td>
</tr>
<tr>
<td>He Dilution</td>
</tr>
<tr>
<td>Bronchoscopy</td>
</tr>
</tbody>
</table>

DDx: Asthma, COPD, CF, bronchiolitis, bronchiectasis*  ILD, pleural disease, neuromuscular disease, chest wall disease

FEV$_1$/FVC: ↑ or N  ↓
TLC: ↑ or N  ↓
RV: ↑ or N  ↓
RV/TLC: ↑ or N  ↓
DLCO: ↑ or N  ↓

*L bronchiectasis can be obstructive or mixed

Figure 4A. Lung volumes and capacities

Figure 4B. Expiratory flow volume curves

Adapted with permission from Elsevier. Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008

Lung Volumes
- ERV - Expiratory Reserve Volume
- FEF - Forced Expiratory Flow Rate
- FEV$_1$ - Forced Expiratory Volume (in one second)
- FRC - Functional Residual Capacity
- IC - Inspiratory Capacity
- RV - Residual Volume
- TLC - Total Lung Capacity
- VC - Vital Capacity
- V$_t$ - Tidal Volume
**Figure 5. Interpreting PFTs**

### Chest X-Rays

- see Medical Imaging, MI4

**Table 7. CXR Patterns and Differential Diagnosis**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Signs</th>
<th>Common DDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation (&quot;Airspace disease&quot;)</td>
<td>Air bronchogram</td>
<td>Acute: water (pulmonary edema), pus (pneumonia), blood (hemorrhage)</td>
</tr>
<tr>
<td></td>
<td>Silhouette sign</td>
<td>Chronic: neoplasm (lymphoma), inflammatory (eosinophilic pneumonia), infection (TB, fungal)</td>
</tr>
<tr>
<td></td>
<td>Less visible blood vessels</td>
<td></td>
</tr>
<tr>
<td>Reticular (&quot;Interstitial disease&quot;)</td>
<td>Increased linear markings</td>
<td>ILD (IPF, collagen vascular disease, asbestos, drugs), hypersensitivity pneumonitis, asbestosis, collagen vascular disease, drug reactions</td>
</tr>
<tr>
<td></td>
<td>F ne or ground glass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Honeycombing (IPF)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>Cavitary vs. non-cavitary</td>
<td>Cavitary: neoplasm (primary vs. metastatic lung cancer), infectious (anaerobic or Gram negative, TB, fungal), inflammatory (RA, sarcoidosis, g anulomatosis with polyangitis [GPA]), IPF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-cavitary: above + sarcoi, Kaposi’s sarcoma (in HIV), silicosis and other pneumoconioses</td>
</tr>
</tbody>
</table>

**Arterial Blood Gases**

- provides information on acid-base and oxygenation status
- see Nephrology, NP15

**Approach to Acid-Base Status**

1. Is the pH acidemic (pH <7.35), alkalemic (pH >7.45), or normal (pH 7.35-7.45)?
2. What is the primary disturbance?
   - metabolic: change in HCO₃⁻ and pH in same direction
   - respiratory: change in HCO₃⁻ and pH in opposite directions
3. Is there appropriate compensation? (see Table 8)
   - metabolic compensation occurs over 2-3 d reflecting altered renal HCO₃⁻ production and excretion
   - respiratory compensation through ventilatory control of P.CO₂ occurs immediately
   - inadequate compensation may indicate a second acid base disorder
Table 8. Expected Compensation for Specific Acid-Base Disorders

<table>
<thead>
<tr>
<th>Disturbance</th>
<th>PaCO₂ (mmHg) (normal —40)</th>
<th>HCO₃⁻ (mmHg) (normal —24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Acidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↑ 10</td>
<td>↑ 1</td>
</tr>
<tr>
<td>Chronic</td>
<td>↑ 10</td>
<td>↑ 3</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↓ 10</td>
<td>↓ 2</td>
</tr>
<tr>
<td>Chronic</td>
<td>↓ 10</td>
<td>↓ 5</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>↓ 1</td>
<td>↓ 1</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>↑ 5-7</td>
<td>↑ 10</td>
</tr>
</tbody>
</table>

4. if there is metabolic acidosis, what is the anion gap and osmolar gap?
   - anion gap = [Na⁺]–([Cl⁻]+[HCO₃⁻]); normal ≤10-15 mmol/L
   - osmolar gap = measured osmolarity – calculated osmolarity = measured – (2[Na⁺] + glucose + urea); normal ≤10 mmol/L

5. if anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
   - if not, consider a mixed metabolic picture

Table 9. Differential Diagnosis of Respiratory Acidosis

<table>
<thead>
<tr>
<th>Increased P.CO₂: secondary to hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Centre Depression (Decreased RR)</td>
</tr>
<tr>
<td>Drugs (anesthesia, sedatives, narcotics)</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Central apnea</td>
</tr>
<tr>
<td>Supplemental O₂ in chronic CO₂ retainers (e.g. COPD)</td>
</tr>
<tr>
<td>Neumuscular Disorders (Decreased Vital Capacity)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Botulism</td>
</tr>
<tr>
<td>Polymyelitis</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>ALS</td>
</tr>
<tr>
<td>Myopathies</td>
</tr>
<tr>
<td>Chest wall disease (obesity, kyphoscoliosis)</td>
</tr>
<tr>
<td>Lung Disease</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>ILD (late stage)</td>
</tr>
<tr>
<td>ARDS</td>
</tr>
<tr>
<td>Mechanical Hypoventilation (Inadequate Mechanical Ventilation)</td>
</tr>
</tbody>
</table>

Table 10. Differential Diagnosis of Respiratory Alkalosis

<table>
<thead>
<tr>
<th>Decreased P.CO₂: secondary to hypoventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary disease (pneumonia, edema, PE, interstitial fibrosis)</td>
</tr>
<tr>
<td>Severe anemia</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>High altitude</td>
</tr>
<tr>
<td>Respiratory Centre Stimulation</td>
</tr>
<tr>
<td>Drugs (ASA, progesterone, theophylline, catecholamines psychotropics, nicotine, salicylates)</td>
</tr>
<tr>
<td>Chest wall disease (obesity, kyphoscoliosis)</td>
</tr>
<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Gram-negative sepsis</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Mechanical Hyperventilation (Excessive Mechanical Ventilation)</td>
</tr>
<tr>
<td>MUDPILSCEAT</td>
</tr>
<tr>
<td>Methanol</td>
</tr>
<tr>
<td>Uremia</td>
</tr>
<tr>
<td>Diabetic ketoacidosis/starvation ketoacidos s</td>
</tr>
<tr>
<td>Phenformin/Paraldehyde</td>
</tr>
<tr>
<td>Iron, Ibruprofen</td>
</tr>
<tr>
<td>Lactic acidiosity</td>
</tr>
<tr>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Salicylates</td>
</tr>
<tr>
<td>Cyanide, Carbon dioxide</td>
</tr>
<tr>
<td>Alcohol ketoacidosis</td>
</tr>
<tr>
<td>Toluene, Theophylline</td>
</tr>
</tbody>
</table>

- see Nephrology, NP16 for differential diagnosis of metabolic acidosis and alkalosis
Airway Disease

Pneumonia

- see Infectious Diseases, ID7

Asthma

- see Family Medicine, FM16 and Pediatrics, P82

Definition
chronic inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli

Epidemiology
- common, 7-10% of adults, 10-15% of children
- most children with asthma significantly improve in adolescence
- often family history of atopy (asthma, allergic rhinitis, eczema)
- occupational asthma (organic allergies, isocyanates, animals, etc.)
Pathophysiology
• airway obstruction → V/Q mismatch → hypoxemia → ↑ ventilation → ↓ P,CO₂ → ↑ pH and muscle fatigue → ↓ ventilation, ↑ P,CO₂/↓ pH

Signs and Symptoms
• dyspnea, wheezing, chest tightness, cough, sputum
• symptoms usually occur or worsen at night
• symptoms can be paroxysmal or persistent
• signs of respiratory distress
• pulsat paradoxxus

Table 11. Criteria for Determining if Asthma is Well Controlled

<table>
<thead>
<tr>
<th>Daytime symptoms &lt;4 d/wk</th>
<th>No asthma-related absence from work/school</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night-time symptoms &lt;1 night/wk</td>
<td>β2-agonist use &lt;4 times/wk</td>
</tr>
<tr>
<td>Physical activity unimpaired by symptoms</td>
<td>FEV₁ or PEF &gt;90% of personal best</td>
</tr>
<tr>
<td>Exacerbations mild, infrequent</td>
<td>PEF diurnal variation &lt;10-15%</td>
</tr>
</tbody>
</table>

Adapted from: Can Respir J 2012; 19:127-164

Table 12. Pulmonary Function Criteria for Diagnosis of Asthma

<table>
<thead>
<tr>
<th>Preferred Measurement</th>
<th>Alternative Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry Showing Reversible Airway Obstruction</td>
<td>Peak Expiratory Flow Variability</td>
</tr>
<tr>
<td>(1) ↓ FEV₁/FVC below lower limit of normal</td>
<td>(1) ↓ in PEF after a bronchodilator or course of controller therapy</td>
</tr>
<tr>
<td>Adults: &lt;0.75 to 0.8 in adults</td>
<td>Adults: PEF ↑ 60 L/min (min. 20%) OR</td>
</tr>
<tr>
<td>Children age 6+: &lt;0.8-0.9</td>
<td>Diurnal variation &gt;8% for twice daily readings (20% for multiple daily readings)</td>
</tr>
<tr>
<td>AND</td>
<td>Children age 6+: PEF ↑ 20%</td>
</tr>
<tr>
<td>(2) ↑ FEV₁ ≥12% and, 200 mL in adults after bronchodilator or controller therapy</td>
<td>Positive Challenge Test</td>
</tr>
<tr>
<td>(1) Methacholine challenge: PC₂₀ &lt;4 mg/mL (4-16 mg/mL is borderline; &gt;16 mg/mL is negative) OR</td>
<td>(2) Post-exercise: ↓ FEV₁ ≥10-15%</td>
</tr>
</tbody>
</table>

Adapted from: Can Respir J 2012; 19:127-164

Treatment
• environment: avoid triggers
• patient education: features of the disease, goals of treatment, self-monitoring
• pharmacological
  • symptomatic relief in acute episodes: short-acting β₂-agonist, anticholinergic bronchodilators, inhaled corticosteroids, addition of a long acting β₂-agonist
  • long-term maintenance: inhaled/oral corticosteroids, anti-allergic agents, long-acting β₂-agonists (do not use LABA alone), long-acting anticholinergics, methylxanthine, LTRA, anti-IgE antibodies (e.g. omalizumab), anti-IL5 drugs (e.g. mepolizumab)

Emergency Management of Asthma
• see Emergency Medicine, ER29
  1. inhaled β₂-agonist first line (MDI route and spacer device recommended)
  2. systemic steroids (PO or IV if severe)
  3. if severe add anticholinergic therapy ± magnesium sulfate
  4. rapid sequence intubation in life-threatening cases (plus 100% O₂, monitors, IV access)
  5. SC/IV adrenaline if caused by anaphylaxis, IV salbutamol if unresponsive
  6. corticosteroid therapy at discharge
**Chronic Obstructive Pulmonary Disease**

- See Family Medicine, FM16

**Definition**
-progressive and irreversible condition of the lung characterized by chronic obstruction to airflow with many patients having periodic exacerbations, gas trapping, lung hyperinflation, and weight loss
-2 subtypes: chronic bronchitis and emphysema (usually coexist to variable degrees)
-gradual decrease in FEV₁ over time with episodes of acute exacerbations

**Table 13. Clinical and Pathologic Features of COPD**

<table>
<thead>
<tr>
<th>Chronic Bronchitis</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined Clinically</td>
<td>Defined Pathologically</td>
</tr>
<tr>
<td>Productive cough on most days for at least 3 consecutive months in 2 successive years</td>
<td>Dilation and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis</td>
</tr>
<tr>
<td>Obstruction is due to narrowing of the airway lumen by mucosal thickening and excess mucus</td>
<td>Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse, and air trapping</td>
</tr>
</tbody>
</table>

-2 Types
  1. **Cent iacinar** (respiratory bronchiole)
     - Typical form seen in smokers, primarily affects upper lung zones
  2. **Panacinar** (all parts of acinus)
     - Accounts for about 1% of emphysema cases
     - α1-antitrypsin deficiency, primarily affects lower lobes

*Note that both chronic bronchitis and emphysema can exist without obstruction. Only if obstruction is also present is it termed COPD

**Risk Factors**
- smoking is #1 risk factor
- others
  - environmental: air pollution, occupational exposure, exposure to wood smoke or other biomass fuel for cooking
  - treatable factors: α1-antitrypsin deficiency, bronchial hyperactivity
  - demographic factors: age, family history of atopy, male sex, history of childhood respiratory infections, low socioeconomic status

- Inherited di order of defective production of α1-antitrypsin, a protein produced by hepatocytes. Acts in the alveolar tissue by inhibiting the action of proteases from destroying alveolar tissue. When deficient, proteases can destroy lung alveoli resulting in emphysema

- Toronto Notes 2018
Signs and Symptoms

**Table 14. Clinical Presentation and Investigations for Chronic Emphysema**

<table>
<thead>
<tr>
<th>Signs</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis (2° to hypoxemia and hypercapnia)</td>
<td>PFT: ↓ FEV₁, ↓ FEV₁/FVC</td>
</tr>
<tr>
<td>Prolonged expiration if obstructive</td>
<td>N TLC, ↓ or N D</td>
</tr>
<tr>
<td>Frequently obese</td>
<td>CXR: ↑ bronchovascular markings</td>
</tr>
<tr>
<td>Enlarged heart with cor pulmonale</td>
<td></td>
</tr>
</tbody>
</table>

**Table 15. Treatment of Stable COPD**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROLONG SURVIVAL</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>Nicotine replacement, bupropion, varenicline</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Influenza, pneumococcal vaccine</td>
</tr>
<tr>
<td>Home Oxygen</td>
<td>Prevents cor pulmonale and decreases mortality if used &gt;15h/d; indicated if (1) PaO₂ &lt; 55 mmHg or (2) PaO₂ &lt; 60 mmHg with cor pulmonale or polycythemia</td>
</tr>
<tr>
<td><strong>SYMPTOMATIC RELIEF (no mortality benefit)</strong></td>
<td></td>
</tr>
<tr>
<td>Bronchodilators (mainstay of current drug therapy, used in combination)</td>
<td>Short-acting ant cholinergics (e.g. ipratropium bromide) and short-acting β₂-agonists (e.g. salbutamol, terbutaline)</td>
</tr>
<tr>
<td>SABAs: rapid onset but significant side effects at high doses (e.g. hypokalemia)</td>
<td></td>
</tr>
<tr>
<td>Short-acting anticholinergics more effective than SABAs with fewer side effects but slower onset; take regularly rather than PRN</td>
<td></td>
</tr>
<tr>
<td>LABAs (e.g. salmeterol, formoterol, indacaterol) and long acting anticholinergics (e.g. tiotropium bromide, glycopyrronium bromide)</td>
<td></td>
</tr>
<tr>
<td>More sustained effects for moderate to severe COPD</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroid (ICS) + LABA combination (e.g. Advair®: fluticasone + salmeterol, Symbicort®: budesonide + formoterol)</td>
<td></td>
</tr>
<tr>
<td>ICS/LABA increases effectiveness vs LABA alone</td>
<td></td>
</tr>
<tr>
<td>Theophylline: weak bronchodilator; limited evidence to suggest combination with bronchodilator</td>
<td></td>
</tr>
<tr>
<td>Side effects: nervous tremor, nausea/vomiting/diarrhoea, tachycardia, arrhythmias, sleep changes</td>
<td></td>
</tr>
<tr>
<td>PDE4 inhibitor: roflumilast (Daxas®) anti-inflammatory medication useful in COPD with chronic bronchitis, severe airflow obstruction, frequent exacerbations</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>ICS monotherapy has been shown to increase the incidence of pneumonia in COPD; ICS should only be used with a LABA in combination in patients with a history of exacerbations</td>
</tr>
<tr>
<td>Oral steroids are important when treating exacerbations; chronic systemic glucocorticoids are generally not recommended due to unfavourable benefit to risk ratio</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>Lung volume reduction surgery (resection of emphysematous parts of lung, associated with higher mortality if FEV₁ &lt; 20%), lung transplant</td>
</tr>
<tr>
<td>Other</td>
<td>Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance</td>
</tr>
</tbody>
</table>

- Note that the distinction between “blue bloaters” and “pink puffers” is more of historical than practical interest as most COPD patients have elements of both.

**GOLD Classification of the Severity of COPD**

- **GOLD 1** Mild FEV₁ >80% of predicted
- **GOLD 2** Moderate 50% <FEV₁ <80% of predicted
- **GOLD 3** Severe 30% < FEV₁ <50% of predicted
- **GOLD 4** Very Severe FEV₁ <30% of predicted

**Influenza Vaccine for Patients with Chronic Obstructive Pulmonary Disease**

- Study: Cochrane systematic review. 11 RCTs included, 6 specifically in COPD patients.
- Population: 7,971 patients with acute COPD exacerbations.
- Intervention: Oral or parenteral corticosteroids vs. placebo.
- Outcome: Treatment failure, risk of relapse, time to next COPD exacerbation, length of hospital stay, lung function at end of treatment.
- Results: Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14.6 days, OR 0.49 (95% CI 0.35-0.68). The evidence was graded as high quality and it would have been necessary to treat nine people (weighting mean difference (WMD) 0.37, 95% CI 0.04-0.70) to prevent one failure. There was no increased risk of local and transient adverse events.

**Conclusion:** There appears to be a reduction in influenza-related infections, as well as exacerbations in patients with COPD receiving the vaccine.

**Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease**

- Study: Cochrane systematic review. 11 RCTs included, 6 specifically in COPD patients.
- Population: 1,787 patients with acute COPD exacerbations.
- Intervention: Oral or parenteral corticosteroids vs. placebo.
- Outcome: Treatment failure, risk of relapse, time to next COPD exacerbation, length of hospital stay, lung function at end of treatment.
- Results: Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14.6 days, OR 0.49 (95% CI 0.35-0.68). The evidence was graded as high quality and it would have been necessary to treat nine people (weighting mean difference (WMD) 0.37, 95% CI 0.04-0.70) to prevent one failure. There was no increased risk of local and transient adverse events.

**Conclusion:** There is high-quality evidence to support treatment of exacerbations in COPD with systemic corticosteroids by the oral or parenteral route in reducing the likelihood of treatment failure and relapse by 1.14, shortening length of stay in hospital exacerbations not requiring assisted ventilation in ICU and giving early improvement in lung function and symptoms. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid treatment as a result of relapse or mortality or any secondary outcomes.

**Conclusion:** There is high-quality evidence to support treatment of exacerbations in COPD with systemic corticosteroids by the oral or parenteral route in reducing the likelihood of treatment failure and relapse by 1.14, shortening length of stay in hospital exacerbations not requiring assisted ventilation in ICU and giving early improvement in lung function and symptoms. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid treatment as a result of relapse or mortality or any secondary outcomes.
Acute Exacerbations of COPD

**Definition**
- Sustained (>48 h) worsening of dyspnea, cough, or sputum production leading to an increased use of medications
- In addition, defined as either purulent or non-purulent (to predict need for antibiotic therapy)

**Etiology**
- Viral URTI, bacteria, air pollution, CHF, PE, MI must be considered

**Management**
- ABCs, consider assisted ventilation if decreasing LOC or poor ABGs
- O₂: target 88-92% SaO₂ for CO₂ retainers
- SABA + anticholinergic, e.g. salbutamol and ipratropium bromide via nebulizers × 3 back-to-back q15min
- Systemic corticosteroids: IV solumedrol or oral prednisolone or oral prednisone
- Antibiotics for exacerbations with increased sputum production and at least one of the following:
  - Increased dyspnea or sputum purulence
  - Simple exacerbation (no risk factors): amoxicillin, 2nd or 3rd generation cephalosporin, macrolide, or TMP/SMX
  - Complicated exacerbation (one of: FEV₁ ≤50% predicted, >4 exacerbations per year, ischemic heart disease, home O₂ use, chronic oral steroid use): fluoroquinolone or β-lactam + β-lactamase inhibitor (amoxicillin/clavulanate)
- Post exacerbation: rehabilitation with general conditioning to improve exercise tolerance
- ICU admission
- For life-threatening exacerbations
- Ventilatory support
- Non-invasive: NIPPV, BiPAP
- Conventional mechanical ventilation

**Prognosis in COPD**

**Prognostic factors**
- Level of dyspnea is the single best predictor
- Development of complications, e.g. hypoxemia or cor pulmonale
- 5 yr survival
- FEV₁ < 1 L = 50%
- FEV₁ < 0.75 L = 33%

**BODE index for risk of death in COPD**
- Greater score = higher probability the patient will die from COPD; score can also be used to predict hospitalization
- 10 point index consisting of four factors:
  - Body mass index (BMI): <21 (+1 point)
  - Obstruction (FEV₁): 50-64% (+1), 36-49% (+2), <35% (+3)
  - Dyspnea (MRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
  - Exercise capacity (6 min walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)

**Results**
- In four studies there was no difference in risk of treatment failure between short-duration and longer-duration treatment.
- Conclusions: Prevalence of PE in patients hospitalized for COPD exacerbation of unknown origin is 25%. Therefore, all patients presenting to hospital with COPD exacerbation without obvious cause require PE workup (Doppler or CTA – decision of which to use depends on pre-test probability of the patient).
Bronchiectasis

Definition
- irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently infected mucus
  - usually affects medium sized airways
- *P. aeruginosa* is the most common pathogen; *S. aureus*, *H. influenzae*, and nontuberculous mycobacteria also common

<table>
<thead>
<tr>
<th>Table 16. Etiology and Pathophysiology of Bronchiectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstruction</strong></td>
</tr>
<tr>
<td>Tumour</td>
</tr>
<tr>
<td>Foreign body</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Pertussis</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Nontuberculous mycobacterium (NTM)</td>
</tr>
</tbody>
</table>

Signs and Symptoms
- chronic cough, purulent sputum (but 10-20% have dry cough), hemoptysis (can be massive), recurrent pneumonia, local crackles (inspiratory and expiratory), wheezes
- clubbing
- may be difficult to differentiate from chronic bronchitis

Investigations
- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
  - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
  - specific: “ram tracking” – parallel narrow lines radiating from hilum, cystic spaces, honeycomb like structures
- high-resolution thoracic CT (diagnostic, gold standard)
  - 87-97% sensitivity, 93-100% specificity
  - “signet ring”: dilated bronchi with thickened walls where diameter bronchus > diameter of accompanying artery
- sputum cultures (routine + AFB)
- serum Ig levels
- sweat chloride if cystic fibrosis suspected (upper zone predominant)

Treatment
- vaccination: influenza and pneumococcal vaccination
- chest physiotherapy, breathing exercises, physical exercise
- antibiotics (oral, IV, inhaled): routinely used for mild exacerbations, driven by sputum sensitivity; macrolides may be used chronically for an anti-inflammatory effect
- inhaled antibiotics (tobramycin) used chronically to suppress *Pseudomonas* and reduce exacerbations
- mucolytics (e.g. hypertonic saline, N.B. DNAse only in CF)
- inhaled corticosteroids: decrease inflammation and improve FEV1; however, may increase risk of exacerbations
- oral corticosteroids for acute, major exacerbations
- pulmonary resection: in selected cases with focal bronchiectasis

Cystic Fibrosis

- see *Pediatrics, P82*

Pathophysiology
- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, skin, reproductive organs) and blockage of secretory ducts

Clinical Features
- results in severe lung disease, pancreatic insufficiency, diabetes, and azoospermia
- other manifestations: meconium ileus in infancy, distal ileal obstruction in adults, sinusitis, liver disease
- chronic lung infections
  - *S. aureus*: early
  - *P. aeruginosa*: most common
  - *B. cepacia*: worse prognosis but less common
  - Aspergillus fumigatus

Usually presents in childhood as recurrent lung infections that become persistent and chronic
Interstitial Lung Disease

Investigations
- Sweat chloride test
  - increased concentrations of NaCl and K+ (\([\text{Cl}^-] > 60 \text{ mmol/L}\) suggests diagnosis in children)
  - heterozygotes have normal sweat tests (and no symptoms)
- PFTs
  - early: airflow limitation in small airways
  - late: severe airflow obstruction, hyperinflation, gas trapping, decreased DLco (very late)
- ABGs
  - hypoxemia, hypercapnia later in disease with eventual respiratory failure and cor pulmonale
- CXR
  - hyperinflation, increased pulmonary markings (especially upper lobes)

Treatment
- chest physiotherapy and postural drainage
- pancreatic enzyme replacements, high calorie diet
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity), hypertonic saline DNase
- inhaled antibiotics (tobramycin, colistin, aztreonam)
- antibiotics (e.g. ciprofloxacin)
- CFTR potentiators (e.g. Ivacaftor)
- lung transplant

Prognosis
- depends on: infections (cepacia colonization), FEV1, acute pulmonary exacerbations, lung transplant vs. non-lung transplant
- female gender and low socioeconomic class have greater risk of early death

**Table 17. Interstitial Lung Diseases**

<table>
<thead>
<tr>
<th>UNKNOWN ETIOLOGY</th>
<th>KNOWN ETIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic interstitial pneumonias</td>
<td><strong>ILD Associated with Systemic Rheumatic Disorders</strong></td>
</tr>
<tr>
<td>UIP (usual interstitial pneumonia e.g. IPF)</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>NSIP (non-specific interstitial pneumonia)</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>LIP (lymphocytic interstitial pneumonia)</td>
<td>SLE</td>
</tr>
<tr>
<td>CDP (cryptogenic organizing pneumonia e.g. BOOP)</td>
<td>Polyposis/dermatomyositis</td>
</tr>
<tr>
<td>DIP (desquamative interstitial pneumonia)</td>
<td>Anti-synthetase syndromes</td>
</tr>
<tr>
<td>IPFPE (idiopathic pleuroparenchymal fibroelastosis)</td>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td><strong>Environment/Occupation Associated ILD</strong></td>
<td><strong>ILD Associated with Drugs or Treatments</strong></td>
</tr>
<tr>
<td>Langerhans-cell histiocytosis (eosinophilic granuloma)</td>
<td>Antibiotics (nitrofurantoin)</td>
</tr>
<tr>
<td>Lymphangioliomyomatosis</td>
<td>Anti-inflammatory agents (methotrexate)</td>
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<tr>
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<td>Cardiovascular drugs amiodarone</td>
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<td>Antineoplastic agents (chemotherapy agents)</td>
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<td></td>
<td>Illicit drugs (e.g. crack lung, talc granulomatosi)</td>
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<td>Radiation</td>
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<td></td>
<td><strong>ILD Associated with Pulmonary Vasculitits</strong></td>
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<tr>
<td>Farmer’s lung</td>
<td>Granulomatosis with Polyangiitis (GPA)</td>
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<tr>
<td>Air conditioner/humidifier lung</td>
<td>Goodpasture’s syndrome</td>
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<tr>
<td>Bird breeder’s lung</td>
<td>Idiopathic pulmonary hemosiderosis</td>
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<tr>
<td>Pneumocystis (inorganic dust)</td>
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<tr>
<td>Silicosis</td>
<td>Familial IPF</td>
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<tr>
<td>Asbestosis</td>
<td>Telomerase mutations</td>
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<tr>
<td>Coal worker’s pneumoconiosis</td>
<td>Neurofibromatosis</td>
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<tr>
<td>Chronic beryllium disease</td>
<td>Tuberculous sclerosis</td>
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<tr>
<td>Pneumonitis from gases/lumes/vapour</td>
<td>Gaucher’s disease</td>
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<td>Alveolar Filling Disorders</td>
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</table>
Signs and Symptoms
- dyspnea, especially on exertion
- nonproductive cough
- crackles (dry, fine, end-inspiratory)
- clubbing (especially in IPF and asbestosis)
- features of cor pulmonale
- note that signs and symptoms vary with underlying disease process
  - e.g. sarcoidosis is seldom associated with crackles and clubbing

Investigations
- CXR/high resolution CT (see Medical Imaging, MI7)
  - usually decreased lung volumes
  - reticular, nodular, or reticulonodular pattern (nodular <3 mm)
  - hilar mediastinal adenopathy (bilateral especially in sarcoidosis)
- PFTs
  - restrictive pattern: decreased lung volumes and compliance
  - normal or increased FEV1/FVC (>70-80%), e.g. flow rates are often normal or high when corrected for absolute lung volume
  - DLCO decreased due to V/Q mismatch (less surface area for gas exchange ± pulmonary vascular disease)
- ABGs
  - hypoxemia and respiratory alkalosis may be present with progression of disease
- other
  - bronchoscopy, bronchoalveolar lavage, lung biopsy
  - ESR, ANA (lupus), RF (RA), serum precipitating antibodies to inhaled organic antigens (hypersensitivity pneumonitis), c-ANCA (GPA), anti-GBM (Goodpasture's)

Unknown Etiologic Agents

IDIOPATHIC PULMONARY FIBROSIS

Definition
- pulmonary fibrosis of unknown cause with usual interstitial pneumonia (UIP) histology (found on biopsy or inferred from CT)
- a progressive, irreversible condition
- DDx: NSIP, COP, desquamative interstitial pneumonitis (DIP), lymphocytic interstitial pneumonitis (LIP), Sjögren's disease

Signs and Symptoms
- commonly presents over age 50, incidence rises with age; males > females
- dyspnea on exertion, nonproductive cough, constitutional symptoms, late inspiratory fine crackles at lung bases, clubbing

Investigations
- labs (nonspecific, autoimmune serology usually negative)
- CXR: reticular or reticulonodular pattern with lower lung predominance; often see honeycombing in advanced disease
- high resolution CT: lower zone peripheral reticular markings, traction bronchiectasis, honeycombing; ground glass, consolidation, or nodules should not be prominent in IPF
- biopsy: rarely for UIP as honeycombing usually makes radiologic diagnosis possible

Treatment
- O2
- pirfenidone and nintedanib can slow disease progression
- lung transplantation for advanced disease
- mean survival of 3-5 yr after diagnosis

SARCOIDOSIS

Definition
- idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
- characterized pathologically by non-caseating granulomas
- numerous HLA antigens have been shown to play a role and familial sarcoidosis is now recognized

Epidemiology
- typically affects young and middle-aged patients
- higher incidence among people of African descent and from northern latitudes e.g. Scandinavia, Canada
Signs and Symptoms
- asymptomatic cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
- chest exam often normal
- common extrapulmonary manifestations
  - cardiac (arrhythmias, sudden death)
  - eye involvement (anterior or posterior uveitis)
  - skin involvement (skin papules, erythema nodosum, lupus pernio)
  - peripheral lymphadenopathy
  - arthralgia
  - hepatomegaly ± splenomegaly
- less common extra-pulmonary manifestations involve bone, CNS, kidney
- two acute sarcoid syndromes
  - Lofgren’s syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
  - Heerfordt-Waldenstrom syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy

Investigations
- CBC (cytopenias from spleen or marrow involvement)
- serum electrolytes, creatinine, liver enzymes, calcium (hypercalcemia/hypercalciuria due to vitamin D activation by granulomas)
- hypergammaglobulinemia, occasionally RF positive
- elevated serum ACE (non-specific and non-sensitive)
- CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
- PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased DLCO, or mixed obstructive/restrictive pattern
- ECG: to rule out conduction abnormalities
- slit-lamp eye exam: to rule out uveitis

Diagnosis
- biopsy
  - transbronchial lung biopsy
  - transbronchial lymph node aspiration, endobronchial ultrasound guided surgical (EBUS) biopsy, or mediastinoscopic lymph node biopsy for granulomas
- in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

Staging
- radiographic, based on CXR
  - Stage 0: normal radiograph
  - Stage I: bilateral hilar lymphadenopathy ± paratracheal lymphadenopathy
  - Stage II: bilateral hilar lymphadenopathy with pulmonary infiltration
  - Stage III: pulmonary infiltration alone (reticulonodular pattern or nodular pattern)
  - Stage IV: pulmonary fibrosis (honeycombing)

Treatment
- 85% of stage I resolve spontaneously
- 50% of stage II resolve spontaneously
- steroids for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
- methotrexate or other immunosuppressives occasionally used

Prognosis
- approximately 10% mortality secondary to progressive fibrosis of lung parenchyma

Known Etiologic Agents

HYPERSENSITIVITY PNEUMONITIS
- also known as extrinsic allergic alveolitis
- non-IgE mediated inflammation of lung parenchyma (acute, subacute, and chronic forms) Type 4 hypersensitivity reaction (see Rheumatology, RH2)
- caused by sensitization to inhaled agents, usually organic dust
- pathology: airway-centred, poorly formed granulomas and lymphocytic inflammation
- exposure usually related to occupation or hobby
  - Farmer’s Lung (Thermophilic actinomycetes)
  - Bird Breeder’s/Bird fancier’s Lung (immune response to bird IgA)
  - Humidifier Lung (Aureobasidium pullulans)
  - Sauna Taker’s Lung (Aureobasidium spp.)

Signs and Symptoms
- acute presentation: (4-6 h after exposure)
  - dyspnea, cough, fever, chills, malaise (lasting 18-24 h)
  - CXR: diffuse infiltrates
  - type III (immune complex) reaction
• subacute presentation: more insidious onset than acute presentation
• chronic presentation
  • insidious onset
  • dyspnea, cough, malaise, anorexia, weight loss
  • PFTs: progressively restrictive
  • CXR: predominantly upper lobe reticulonodular pattern
• in both acute and chronic reactions, serum precipitins may be detectable (neither sensitive nor specific)

Treatment
• early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
• systemic corticosteroids can relieve symptoms and speed resolution

PNEUMOCONIOSES
• reaction to inhaled inorganic dusts 0.5-5 µm in size
• no effective treatment, therefore key is exposure prevention through the use of protective equipment
• smoking cessation, annual influenza and pneumococcal vaccination rehabilitation, lung transplant for endstage disease

Table 18 Pneumoconioses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Etiology</th>
<th>Signs/Symptoms</th>
<th>Investigations</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestosis</td>
<td>Exposure risks: insulation, shipyard, construction, brake linings, pipe fitters plumbers Slightly progressive diffuse interstitial fibrosis induced by inhaled asbestos fibres Usually requires &gt;10-20 yr of exposure Latency period: 20-30 yr</td>
<td>Insidious onset Dyspnea Cough: paroxysmal, non-productive Clubbing (much more likely in asbestosis than silicosis or CWP)</td>
<td>CXR Lower &gt; upper lobe Reticulonodular pattern, may develop IPF-like honeycombing Asbestos exposure can also cause pleural and diaphragmatic plaques (calcification), pleural effusion, round atelectasis Microscopic examination reveals ferruginous bodies: yellow-brown rod-shaped structures which represent asbestos fibres coated in macrophages</td>
<td>Asbestos exposure increases risk of bronchogenic CA and malignant mesothelioma Risk of lung cancer dramatically increased for smokers</td>
</tr>
<tr>
<td>Silicosis</td>
<td>At risk population: sandblasters, rock miners, stone cutters, quarry and highway workers Generally requires &gt;20 yr exposure; may develop with much shorter but heavier exposure</td>
<td>Dyspnea, cough, and wheezing</td>
<td>CXR Upper &gt; lower lobe Early: nodular disease (simple pneumoconiosis), lung function usually normal Late: nodules coalesce into masses (progressive massive fibrosis) Possible hilar lymph node enlargement (frequently calcified), especially “egg shell” calcification</td>
<td>Mycobacterial infection (e.g. TB)</td>
</tr>
<tr>
<td>Coal Worker’s Pneumoconiosis (CWP)</td>
<td>At risk population: coal workers, graphite workers Coal and silica, coal is less fibrogenic than silica</td>
<td>Simple CWP No signs or symptoms, usually normal lung function Complicated CWP (also known as progressive massive fibrosis) Dyspnea Course: few patients progress to complicated CWP</td>
<td>Simple CWP CXR: multiple nodular opacities, mostly upper lobe Pathologic hallmark is coal macule Complicated CWP CXR: opacities larger and coalesce</td>
<td>Caplan’s syndrome: rheumatoid arthritis and CWP present as larger nodules</td>
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</table>

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH DRUGS OR TREATMENTS

Drug-Induced
• antineoplastic agents: bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate, chlorambucil, BCNU (carmustine)
• antibiotics: nitrofurantoin, penicillin, sulfonamide
• cardiovascular drugs: amiodarone, tocainide
• anti-inflammatory agents: methotrexate, penicillamine
• gold salts
• illicit drugs (heroin, methadone)
• rituximab, anti-TNF-α agents (infliximab, etanercept, adalimumab)

Radiation-Induced
• early pneumonitis: approximately 6 wk post-exposure
• late fibrosis: 6-12 mo post-exposure
• infiltrates conform to the shape of the radiation field
Pulmonary Vascular Disease

Pulmonary Hypertension

Definition
mean pulmonary arterial pressure >25 mmHg at rest and >30 mmHg with exercise, or a systolic pulmonary artery pressure of >40 mmHg at rest

- in the past, pulmonary HTN was classified as primary or secondary pulmonary HTN, but this classification was modified to a more clinically useful, treatment based classification

Table 19. World Health Organization Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Classification</th>
<th>Some Causes</th>
<th>Treatment Options</th>
<th>Consider in All Patients with PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Pulmonary Arterial HTN</td>
<td>Idiopathic</td>
<td>CCBs in occasional patients with vasoreactivity (now used infrequently)</td>
<td>Oxygen therapy</td>
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<tr>
<td></td>
<td>Collagen vascular disease (scleroderma, SLE, RA)</td>
<td>advanced therapy often needed</td>
<td>Exercise</td>
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<td>Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome)</td>
<td>The latter includes: prostanoids, endothelin receptor antagonists, PDE5 inhibitors</td>
<td>Consider anticoagulation</td>
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<td>Persistent pulmonary hypertension of the newborn (PPHN)</td>
<td>Lung transplantation</td>
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<td>Portopulmonary HTN</td>
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<td>HIV infection</td>
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<td>Drugs and toxins (e.g. anorexigen)</td>
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<td>Pulmonary veno-occlusive disease</td>
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<td>Schistosomiasis</td>
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<td>Pulmonary capillary hemangiomatosis</td>
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<tr>
<td>II. Pulmonary HTN due to Left Heart Disease</td>
<td>Left-sided atrial or ventricular heart disease (e.g. LV dysfunction)</td>
<td>Treat underlying heart disease</td>
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<td>Left-sided valvular heart disease (e.g. aortic stenosis, mitral stenosis)</td>
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<td>Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
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<tr>
<td>III. Pulmonary HTN due to Lung Disease and/or Hypoxia</td>
<td>Parenchymal lung disease (COPD, interstitial fibrosis, cystic fibrosis)</td>
<td>Treat underlying cause of hypoxia and correct with supplemental oxygen (proven mortality benefit)</td>
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<td>Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep-disordered breathing)</td>
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<tr>
<td>IV. Chronic Thromboembolic Pulmonary HTN (CTEPH)</td>
<td>Thromboembolic obstruction of proximal pulmonary arteries</td>
<td>Anticoagulation, thromboendarterectomy, riociguat</td>
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<td>Obstruction of distal pulmonary arteries – PE (thrombus, foreign material, tumour, in situ thrombosis)</td>
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<tr>
<td>V. Pulmonary HTN with Unclear Multifactorial Mechanisms</td>
<td>Hematologic disorders (e.g. sickle cell)</td>
<td>Treat underlying cause</td>
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<td>Systemic disorders (e.g. sarcoidosis)</td>
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<td>Metabolic disorders</td>
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<td>Extrinsic compression of central pulmonary veins (tumour, adenopathy, fibrosing mediastinitis)</td>
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<td>Chronic hemolytic anemia</td>
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<td>Segmental pulmonary hypertension</td>
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IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (PRIMARY PULMONARY HYPERTENSION)

Definition
- pulmonary HTN in the absence of a demonstrable cause
- histology includes medial hypertrophy, intimal fibrosis and plexiform arteriopathy

- exclude:
  - left-sided cardiac valvular disease
  - myocardial disease
  - congenital heart disease
  - any clinically significant parenchymal lung disease
  - systemic connective-tissue disease
  - chronic thromboembolic disease

Epidemiology
- usually presents in young females (20–40 yr); mean age of diagnosis is 36 yr
- most cases are sporadic; familial predisposition in 10% of cases, some linked to mutations in BMPR2
- may be associated with the use of anorexic drugs (e.g. Aminorex®, Fenfluramine®), amphetamines, and cocaine
**Signs and Symptoms**

<table>
<thead>
<tr>
<th>Table 20. Signs and Symptoms of Pulmonary Hypertension</th>
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</thead>
<tbody>
<tr>
<td>Symptom</td>
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<tr>
<td>Dyspnea</td>
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<td>Fatigue</td>
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<tr>
<td>Retrosternal chest pain</td>
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<tr>
<td>Syncope</td>
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<tr>
<td>Symptoms of underlying disease</td>
</tr>
</tbody>
</table>

**Investigations**

- CXR: enlarged central pulmonary arteries, cardiac changes due to RV enlargement (filling of retrosternal air space)
- ECG
- RVH/right-sided strain (see Cardiology and Cardiac Surgery, C7)
- 2-D echo doppler assessment of right ventricular systolic pressure
- cardiac catheterization: direct measurement of pulmonary artery pressures (necessary to confirm diagnosis)
- PFTs to assess for underlying lung disease: DLco usually reduced; volumes and flows normal
- CT angiogram to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary HTN; other serologic markers can be used in the appropriate clinical setting

**Treatment**

- see Table 19

**Prognosis**

- 2-3 yr mean survival from time of diagnosis
- survival decreases to approximately 1 yr if severe pulmonary HTN or right-heart failure

**Pulmonary Embolism**

**Definition**

- lodging of a blood clot in the pulmonary arterial tree with subsequent increase in pulmonary vascular resistance, impaired V/Q matching, and possibly reduced pulmonary blood flow

**Etiology and Pathophysiology**

- one of the most common causes of preventable death in the hospital
- proximal leg thrombi (popliteal, femoral, or iliac veins) are the source of most clinically recognized pulmonary emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE
- fewer than 30% of patients have clinical evidence of DVT (e.g. leg swelling, pain, or tenderness)
- always suspect PE if patient develops fever, sudden dyspnea, chest pain, or collapse 1-2 wk after surgery

**Risk Factors**

- stasis
- immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
- obesity, CHF
- chronic venous insufficiency
- endothelial cell damage
- post-operative injury, trauma
- hypercoagulable states
- underlying malignancy (particularly adenocarcinoma)
- cancer treatment (chemotherapy, hormonal)
- exogenous estrogen administration (OCP, HRT)
- pregnancy, post-pregnancy
- prior history of DVT/PE, family history
- nephrotic syndrome
- coagulopathies: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease
- increasing age

Pulmonary arterial pressures are measured by pulmonary artery catheters (i.e. Swan-Ganz catheter) which are inserted into a large vein (often internal jugular). A balloon at the end of the catheter tip is inflated causing the catheter to advance through the right side of the heart and into the pulmonary artery. This allows for the measurement of RA, RV, PA, and pulmonary capillary wedge pressures as well as sampling of mixed venous blood. A thermistor near the end of the catheter also allows for assessment of cardiac output by thermodilution

Virchow’s Triad

- Venous stasis
- Endothelial cell damage
- Hypercoagulable states

Multidetector Computed Tomography for Acute Pulmonary Embolism (PROPED II Trial)

**Study**

Multicentre, prospective study investigating accuracy of computed tomography angiography (CTA) alone and combined with venous phase imaging (CTA-CTV) for the diagnosis of PE.

**Patients**

324 patients of several thousand eligible for study received reference diagnosis to confirm absence or presence of PE (V/Q scan, venous compression US of lower extremities, and pulmonary digital-subtraction angiography (DSA) if necessary). To confirm absence, patients in whom PE was excluded were telephoned 3-6 mo after enrollment. Any deaths were reviewed by an outcome committee. All patients enrolled also underwent clinical assessment of PE (including a Wells’ score) prior to imaging.

**Outcomes**

Diagnosis of pulmonary embolism.

**Results**

733 of 824 patients had adequate CTA for interpretation. PE was diagnosed in 182 of the 824 patients. Sensitivity was 83% (150 of 181 patients) with 95% CI 0.76-0.91 and specificity was 96% (567 of 592 patients, 95% CI 0.93-0.97). However, the predictive value of CTA-CTV varied when clinical pre-test probability was taken into account. PPV of CTA for high, intermediate, and low clinical probability were 96% (95% CI 0.78-0.99), 92% (95% CI 0.84-0.96), and 58% (95% CI 0.40-0.73), respectively. NPV of CTA for high, intermediate, and low clinical probability were 96% (95% CI 0.82-0.93), and 96% (95% CI 0.92-0.99) respectively.

**Conclusion**

CTA is effective for diagnosing or excluding PE in accordance with assessment of clinical pre-test probability. When clinical probability is inconsistent with imaging results, further investigations are required to rule out PE.
 Investigations (if highly suspicious, go straight to CT angiogram)
- see Emergency Medicine, ER33

Table 21. Common Investigations for Pulmonary Embolism

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Purpose/Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Angiogram (Gold Standard)</td>
<td>Filling defect indicative of embolus; negative angiogram excludes clinically relevant PE</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>More invasive, and harder to perform than CT, therefore done infrequently</td>
</tr>
<tr>
<td>Highly sensitive D dimer result can exclude DVT/PE if pretest probability is already low</td>
<td></td>
</tr>
<tr>
<td>Little value if pretest probability is high</td>
<td></td>
</tr>
<tr>
<td>If D-dimer positive, will need further evaluation with compression US (for DVT) and/or CT (for PE)</td>
<td></td>
</tr>
<tr>
<td>CT Angiogram</td>
<td>Both sensitive and specific for PE</td>
</tr>
<tr>
<td>Diagnosis and management uncertain for small filling defects</td>
<td></td>
</tr>
<tr>
<td>CT may identify an alternative diagnosis if PE is not present</td>
<td></td>
</tr>
<tr>
<td>CT scanning of the proximal leg and pelvic veins can be done at the same time and may be helpful</td>
<td></td>
</tr>
<tr>
<td>Venous Duplex U/S or Doppler</td>
<td>With leg symptoms</td>
</tr>
<tr>
<td>Positive test rules in proximal DVT</td>
<td></td>
</tr>
<tr>
<td>Negative test rules out proximal DVT</td>
<td></td>
</tr>
<tr>
<td>Without leg symptoms</td>
<td></td>
</tr>
<tr>
<td>Positive test rules in proximal DVT</td>
<td></td>
</tr>
<tr>
<td>Negative test does not rule out a DVT: patient may have non-occlusive or calf DVT</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>Findings not sensitive or specific</td>
</tr>
<tr>
<td>Sinus tachycardia most common; may see non-specific ST segment and T wave changes</td>
<td></td>
</tr>
<tr>
<td>RV strain, RAD, RBBB, S1-Q3-T3 with massive embolization</td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>Frequently normal; no specific features</td>
</tr>
<tr>
<td>Atelectasis (subsegmental), elevation of a hemidiaphragm</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion: usually small</td>
<td></td>
</tr>
<tr>
<td>Hampton’s hump: cone-shaped area of peripheral opacification representing infarction</td>
<td></td>
</tr>
<tr>
<td>Westermark’s sign: dilated proximal pulmonary artery with distal oligemia/decreased vascular markings (difficult to assess without prior films)</td>
<td></td>
</tr>
<tr>
<td>Dilatation of proximal PA: rare</td>
<td></td>
</tr>
<tr>
<td>V/Q Scan</td>
<td>Very sensitive but low specificity</td>
</tr>
<tr>
<td>Order scan if:</td>
<td></td>
</tr>
<tr>
<td>CXR normal, no COPD</td>
<td></td>
</tr>
<tr>
<td>Contraindication to CT (contrast allergy, renal dysfunction, pregnancy)</td>
<td></td>
</tr>
<tr>
<td>Avoid V/Q scan if:</td>
<td></td>
</tr>
<tr>
<td>CXR abnormal or COPD</td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td></td>
</tr>
<tr>
<td>Suspect massive PE</td>
<td></td>
</tr>
<tr>
<td>Results:</td>
<td></td>
</tr>
<tr>
<td>Normal: excludes the diagnosis of PE</td>
<td></td>
</tr>
<tr>
<td>High probability: most likely means PE present, unless pre test probability is low</td>
<td></td>
</tr>
<tr>
<td>60% of V/Q scans are nondiagnostic</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Useful to assess massive or chronic PE</td>
</tr>
<tr>
<td>Not routinely done</td>
<td></td>
</tr>
<tr>
<td>ABG</td>
<td>No diagnostic use in PE (insensitive and nonspecific)</td>
</tr>
<tr>
<td>May show respiratory alkalosis (due to hyperventilation)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment
- admit for observation (stable patients with DVT only may be sent home on LMWH) |
- oxygen: supplemental O₂ if hypoxic or short of breath |
- pain relief: analgesics if chest pain – narcotics or acetaminophen |
- acute anticoagulation: therapeutic-dose SC LMWH or rivaroxaban or IV heparin (only if concern for bleeding risk) – start ASAP |
- anticoagulation stops clot propagation, prevents new clots and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months get baseline CBC, INR, aPTT ± renal function ± liver function |
- for SC LMWH: dalteparin 200 U/kg once daily, enoxaparin 1 mg/kg bid or 1.5mg/kg once daily, or tinzaparin 175 U/kg once daily – no lab monitoring – avoid or reduce dose in renal dysfunction |
- for IV heparin: bolus of 75 U/kg (usually 5,000 U) followed by infusion starting at 20 U/kg/h – aim for aPTT 2-3x control |
- rivaroxaban is accepted alternative for acute PE

D-Dimer is elevated in patients with recent surgery, cancer, infection, inflammation, and severe renal dysfunction. It has good sensitivity and negative predictive value, but poor specificity and positive predictive value.

Classic ECG finding of PE is S1-Q3-T3 (inverted T3), but most commonly see only sinus tachycardia.

Clinical Prediction Rule for Pulmonary Embolism

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>More likely alternative diagnosis (using H&amp;P, CXR, ECG)</td>
<td>3.0</td>
</tr>
<tr>
<td>Immobilization or surgery in previous 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous PE/DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>HR &gt;100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Clinical Probability

- Low (0-2): 3%
- Intermediate (3-8): 28%
- High (>8): 78%

Modified Wells: >1 PE likely, <4 PE unlikely

JAMA 2006

PE Rule Out Criteria (PERC)
Prospective Multicentre Evaluation of the Pulmonary Embolism Rule Out Criteria

J Thromb Hemost 2009;83:416-420

Notes
- Use D-Dim is only if low clinical probability, otherwise use PE rule out criteria and get CT
- Positive V/Q scan rules out the diagnosis
- High probability V/Q scan rules only in the diagnosis if high clinical suspicion
- Inconclusive V/Q scan requires leg US to look for DVT or CT
• long-term anticoagulation
  ■ warfarin: start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 d and until INR in target range of 2-3 for at least 2 d
  ■ LMWH instead of warfarin for pregnancy, active cancer, or high bleeding risk patients
  ■ direct thrombin inhibitors: can treat from outset with rivaroxaban; dabigatran has been shown to have lower bleeding risk than warfarin; no monitoring required, however agents not reversible, so avoid if bleeding concerns

• IV thrombolytic therapy
  ■ if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
  ■ hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding

  • interventional thrombolytic therapy
    ■ massive PE may be treated with catheter-directed thrombolysis by an interventional radiologist
    ■ catheter-directed thrombolysis is not recommended over systemic thrombolysis
    ■ IVC filter: only if recent proximal DVT + absolute contraindication to anticoagulation
    ■ duration of long-term anticoagulation: individualized, however generally
      ■ if reversible cause for PE (surgery, injury, pregnancy, etc.): 3-6 mo
      ■ if PE unprovoked: 6 mo to indefinite
      ■ if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite

Thromboprophylaxis
• mandatory for most hospital patients: reduces DVT, PE, all-cause mortality, cost-effective
• start ASAP
• continue at least until discharge or recommend extending for 35 d post-operatively, if major orthopedic surgery

Table 22. VTE Risk Categories and Prophylaxis (see Hematology, H35)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Prophylaxis Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Thrombosis Risk</td>
<td></td>
</tr>
<tr>
<td>Medical patients: fully mobile</td>
<td>No specific prophylaxis</td>
</tr>
<tr>
<td>Surgery: &lt;30 min, fully mobile</td>
<td>Frequent ambulation</td>
</tr>
<tr>
<td>Moderate Thrombosis Risk</td>
<td></td>
</tr>
<tr>
<td>Most general, gynecologic, urologic surgery</td>
<td>LMWH</td>
</tr>
<tr>
<td>Sick medical patients</td>
<td>Low dose unfractionated heparin</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>High Thrombosis Risk</td>
<td></td>
</tr>
<tr>
<td>Arthroplasty, hip fracture surgery</td>
<td>LMWH</td>
</tr>
<tr>
<td>Major trauma, spinal cord injury</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td></td>
<td>Warfarin (INR 2-3)</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>Low dose unfractionated heparin</td>
</tr>
<tr>
<td>High Bleeding Risk</td>
<td></td>
</tr>
<tr>
<td>Neurosurgery, intracranial bleed</td>
<td>TED stockings, pneumatic compression devices</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>LMWH or low dose heparin when bleeding risk decreases</td>
</tr>
</tbody>
</table>

Thrombophilia Workup: recurrent or idiopathic DVT/PE, age <50, Fx, unusual location, massive
Malignancy Workup: 12% of patients with idiopathic VTE will have a malignancy

The Use of Unfractionated Heparin Should Be Limited to:
• Patients with severe renal dysfunction (CrCl <30 ml/min) n whom LMWH and novel oral anticoagulation should be avoided
• Patients at elevated risk of bleeding that may need rapid reversal of anticoagulation
• Patients who receive thrombolytic therapy

Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism
NEJM 2013;368:709-718
Study: Two double-blind, RCTs; one comparing against placebo, the other against active treatment.
Population: 4,199 patients (2,896 in active-control study, 1,343 in placebo-control study) with VTE who had completed at least 3 mo of therapy. Intervention: In the active-control study, patients randomized to either 150 mg dabigatran or warfarin (INR 2.5-3.0). Patients in the placebo-control study received either 100 mg dabigatran or placebo.
Outcome: Reocurrence of VTE, risk of major or clinically relevant bleed.
Results: In the active-control study, there was a hazard ratio (HR) of 1.44 (95% CI 0.78-2.64) for non-inferiority of recurrent VTE with dabigatran vs. warfarin. HR of major or clinically relevant bleed was 0.94 (95% CI 0.41-1.71). In the placebo-control study, the HR of VTE with dabigatran vs. placebo was 0.59 (96% CI 0.02-2.58). HR of major or clinically relevant bleed was 2.92 (95% CI 1.35-6.36).
Conclusions: Dabigatran appears to be non-inferior to warfarin in the prevention of VTE recurrence. Dabigatran is associated with a lower risk of major or clinically relevant bleed than warfarin, but greater than placebo.
Pulmonary Vasculitis

Table 23. Pulmonary Vasculitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Definition</th>
<th>Pulmonary Features</th>
<th>Extra-pulmonary Features</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPA and Wegener’s granulomatosis (see Nephrology, NP22)</td>
<td>Systemic vasculitis of medium and small arteries</td>
<td>Necrotizing granulomatous lesions of the upper and lower respiratory tract</td>
<td>Focal necrotizing lesions of arteries and veins; crescentic glomerulonephritis</td>
<td>CXR: nodules, cavities, and alveolar opacities c-ANCA Tissue confirmation</td>
<td>Corticosteroids and cyclophosphamide or rituximab</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with Polyangiitis (EGPA, Churg-Strauss)</td>
<td>Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia</td>
<td>Asthma Infiltrates</td>
<td>Life-threatening systemic vasculitis involving the lungs, pericardium and heart, kidneys, skin, and PNS (mononeuritis multiplexes)</td>
<td>Peripheral eosinophilia is the most common finding p-ANCA may be positive Biopsy involved tissue</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Anti-GBM Disease (Goodpasture’s) (see Nephrology, NP24)</td>
<td>A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung</td>
<td>Hemoptysis May follow an influenza infection</td>
<td>Anemia</td>
<td>CXR: may see alveolar infiltrates if hemorrhage is profuse ELISA test with anti-GBM antibodies Renal biopsy/indirect immunofluorescence shows linear staining</td>
<td>Acutely: corticosteroids, plasmapheresis, immunosuppressive therapy Severe cases: bilateral nephrectomy</td>
</tr>
</tbody>
</table>

Systemic Lupus Erythematosus, Rheumatoid Arthritis, Scleroderma

See Rheumatology, RH17

Pulmonary Edema

- see Cardiology and Cardiac Surgery, C36

Diseases of the Mediastinum and Pleura

Mediastinal Masses

Definition
- mediastinum: bound by the thoracic inlet, diaphragm sternum, vertebral bodies, and the pleura
- can be broken down into 3 compartments: anterior, middle, and posterior

Etiology and Pathophysiology
- diagnosis is aided by location and patient’s age
- anterior compartment: more likely to be malignant
  - “Four Ts” (see sidebar), lymphoma, lipoma, pericardial cyst
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumour, lymphoma, lymph node enlargement, aortic aneurysm
- posterior compartment
  - neurogenic tumours, meningocele, enteric cysts, lymphoma, diaphragmatic hernias, esophageal tumour, aortic aneurysm

Signs and Symptoms
- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner’s syndrome, facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes (e.g. myasthenia gravis [thymomas])

Investigations
- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumours
- U/S (best for assessment of structures in close proximity to the heart and pericardium)
- radionuclide scanning: 131I (for thyroid), gallium (for lymphoma)
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP, β hCG
- biopsy (mediastinoscopy, percutaneous needle aspiration)

Management
- excision if symptomatic enlarging benign masses or concerns of malignancy
- resect bronchogenic cysts and localized neurogenic tumours via minimally invasive video assisted procedures
- exploration via sternotomy or thoracotomy
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
- ± post operative radiotherapy/chemotherapy if malignant
Mediastinitis

- most common causes: post-operative complications of cardiovascular or thoracic surgical procedures

**Acute**
- etiology
  - complication of endoscopy (e.g. esophageal perforation providing entry point for infection)
  - esophageal or cardiac surgery
  - tumour necrosis
- signs and symptoms
  - fever, substernal pain
  - pneumomediastinum, mediastinal compression
  - Hamman’s sign (auscultatory “crunch” during cardiac systole)
- treatment
  - antibiotics (IV vancomycin + 3rd gen cephalosporin), drainage, ± surgical closure of perforation

**Chronic**
- usually granulomatous process or fibrosis related to previous infection (e.g. histoplasmosis, TB, sarcoidosis, syphilis)

Pleural Effusions

**Definition**
- excess amount of fluid in the pleural space (normally up to 25 mL)

**Etiology**
- disruption of normal equilibrium between pleural fluid formation/entry and/or pleural fluid absorption/exit
- pleural effusions are classified as transudative or exudative
  - distinguish clinically using Light’s Criteria, which has a sensitivity of 98% and specificity of 83% for identifying exudative pleural effusions

<table>
<thead>
<tr>
<th>Light’s Criteria</th>
<th>Modified Light’s Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein – Pleural/Serum</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>LDH – Pleural/Serum</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Pleural LDH</td>
<td>&gt;2/3 upper limit of N serum LDH</td>
</tr>
</tbody>
</table>

**Transudative Pleural Effusions**
- pathophysiology: alteration of systemic factors that affect the formation and absorption of pleural fluid (e.g. increased capillary hydrostatic pressure, decreased plasma oncotic pressure)
- etiology
  - CHF: usually right-sided or bilateral
  - cirrhosis leading to hepatic hydrothorax
  - nephrotic syndrome, protein losing enteropathy, cirrhosis
  - pulmonary embolism (may cause transudative but more often causes exudative effusion)
  - peritoneal dialysis, hypothyroidism, CF, urinothorax

**Exudative Pleural Effusions**
- pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction
- etiology (see Table 25)
Table 25. Exudative Pleural Effusion Etiologies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Parapneumonic effusion (associated with bacterial pneumonia, lung abscess)</td>
</tr>
<tr>
<td></td>
<td>Empyema (bacterial, fungal, TB)</td>
</tr>
<tr>
<td></td>
<td>TB pleuritis</td>
</tr>
<tr>
<td></td>
<td>Viral infection</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
</tr>
<tr>
<td></td>
<td>Parasitic</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Lung carcinoma (35%)</td>
</tr>
<tr>
<td></td>
<td>Lymphoma (10%)</td>
</tr>
<tr>
<td></td>
<td>Metastases: breast (25%), ovary, kidney</td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Myeloma</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Collagen vascular diseases: RA, SLE</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Benign asbestos related effusion</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>ARMS</td>
</tr>
<tr>
<td></td>
<td>Post-CABG or cardiac injury</td>
</tr>
<tr>
<td></td>
<td>Drug reaction</td>
</tr>
<tr>
<td>Intra-Abdominal</td>
<td>Subphrenic abscess</td>
</tr>
<tr>
<td></td>
<td>Pancreatic disease (elevated pleural fluid amylase)</td>
</tr>
<tr>
<td></td>
<td>Meigs’ syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)</td>
</tr>
<tr>
<td>Intra Thoracic</td>
<td>Esophageal perforation (elevated fluid amylase)</td>
</tr>
<tr>
<td>Trauma</td>
<td>Hemotherax: rupture of a blood vessel, commonly by trauma or tumours</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax (spontaneous, traumatic, tension)</td>
</tr>
<tr>
<td></td>
<td>Chylothorax</td>
</tr>
<tr>
<td></td>
<td>iatrogenic</td>
</tr>
<tr>
<td>Other</td>
<td>Drug-induced</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

**Signs and Symptoms**
- often asymptomatic
- dyspnea: varies with size of effusion and underlying lung function
- orthopnea
- pleuritic chest pain
- inspection: trachea deviates away from effusion, ipsilateral decreased expansion
- percussion: decreased tactile fremitus, dullness
- auscultation: decreased breath sounds, bronchial breathing and egophony at above fluid level, pleural friction rub

**Investigations**
- **CXR**
  - must have >200 mL of pleural fluid for visualization on PA film
  - lateral: >50 mL leads to blunting of posterior costophrenic angle
  - PA: blunting of lateral costophrenic angle
  - dense opacification of lung fields with concave meniscus
  - decubitus: fluid will layer out unless it is loculated
  - supine: fluid will appear as general haziness
- CT may be helpful in differentiating parenchymal from pleural abnormalities, may identify underlying lung pathology
- U/S: detects small effusions and can guide thoracentesis
- thoracentesis: indicated if pleural effusion is a new finding; be sure to send off blood work (LDH, glucose, protein) at the same time for comparison
  - risk of re-expansion pulmonary edema if >1.5 L of fluid is removed
  - inspect for colour, character, and odour of fluid
  - analyze fluid
- pleural biopsy: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology negative)

**Appearance of Pleural Fluid**
- Bloody: trauma, malignancy
- White: empyema, chylous or chyliform effusion
- Black: aspergillosis, amoebic liver abscess
- Yellow-green: rheumatoid pleurisy
- Viscous: malignant mesothelioma
- Ammonia odour: urinotherax
- Food particles: esophageal rupture

**Role of CT in Pleural Effusion**
- To assess for fluid loculation, pleural thickening and nodules, parenchymal abnormalities and adenopathy
- Helps to distinguish benign from malignant effusion and transudative from exudative effusion
- May not distinguish empyema from parapneumonic effusion

**Features of Malignant Effusion**
- Multiple pleural nodules

**Features of Exudative Effusion**
- Loculation
- Pleural thickening
- Pleural nodules
- Extrapleural fat of increased density
Table 26. Analysis of Pleural Effusion

<table>
<thead>
<tr>
<th>Measure</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, LDH</td>
<td>Transudate vs. exudate</td>
</tr>
<tr>
<td></td>
<td>LDH especially high (&gt;1000 IU/L) in empyema, rheumatoid, malignancy</td>
</tr>
<tr>
<td></td>
<td>Protein especially high in TB, myeloma</td>
</tr>
<tr>
<td>Gram Stain, Ziehl-Nielsen Stain (TB)</td>
<td>Looking for specific organisms</td>
</tr>
<tr>
<td>Culture</td>
<td></td>
</tr>
<tr>
<td>Cell Count Differential</td>
<td>Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, serositis)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Malignancy, infection</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Factor, ANA, Complement</td>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Amylase</td>
<td>Pancreatitis, esophageal perforation, malignancy</td>
</tr>
<tr>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Mostly traumatic, malignancy PE with infarction, TB</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Chylothorax from thoracic duct leakage, mostly due to trauma, lung CA, or lymphoma</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Distinguish between chylous and chyliform effusion (seen in inflammation, e.g. TB, RA)</td>
</tr>
</tbody>
</table>

Treatment
- thoracentesis
- treat underlying cause
- consider indwelling pleural catheter or pleurodesis in refractory effusions

Complicated Effusion
- persistent bacteria in the pleural space but fluid is non-purulent
- neutrophils, pleural fluid acidosis (pH < 7.00), and high LDH
- often no bacteria grown since rapidly cleared from pleural space
- fibrin layer leading to loculation of pleural fluid
- treatment: antibiotics depending on gram stain and chest tube drainage

Empyema

Definition
- pus in pleural space or an effusion with organisms seen on a Gram stain or culture (e.g. pleural fluid is grossly purulent)
- positive culture is not required for diagnosis

Etiology
- contiguous spread from lung infection (most commonly anaerobes) or infection through chest wall (e.g. trauma, surgery)

Signs and Symptoms
- fever, pleuritic chest pain

Investigations
- CT chest
- thoracentesis
- PMNs (lymphocytes in TB) ± visible organisms on Gram stain

Treatment
- antibiotic therapy for at least 4-6 wk (rarely effective alone)
- complete pleural drainage with chest tube
- if loculated, more difficult to drain – may require surgical drainage with video-assisted thorascopic surgery (VATS), or removal of fibrin coating (surgical or tPA/DNase) to allow lung re-expansion (decortication)

Atelectasis

- see General Surgery, GS10
**Pneumothorax**

**Definition**
- presence of air in the pleural space

**Pathophysiology**
- entry of air into pleural space raises intrapleural pressure causing partial lung deflation

**Etiology**
- traumatic: penetrating or non-penetrating chest injuries
- iatrogenic (central venous catheter, thoracentesis, mechanical ventilation with barotrauma)
- spontaneous (no history of trauma)
  - primary (no underlying lung disease)
    - spontaneous rupture of apical subpleural bleb (packets of air) of lung into pleural space
  - secondary (underlying lung disease)
    - rupture of subpleural bleb which migrates along bronchioalveolar sheath to the mediastinum then to the intrapleural space
    - necrosis of lung tissue adjacent to pleural surface
  - smoking, male, family history, Marfan’s syndrome

**Signs and Symptoms**
- can be asymptomatic
- acute-onset pleuritic chest pain, dyspnea
- tachypnea, tachycardia
- tracheal deviation (contralateral deviation in tension pneumothorax)
- ipsilateral diminished chest expansion
- decreased tactile/vocal fremitus
- hyperresonance
- ipsilateral diminished breath sounds

**Investigations**
- **CXR**
  - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  - large: decreased density and decreased volume of lung on side of pneumothorax
  - see Medical Imaging, MI8

**Treatment**
- primary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + O₂
  - if symptomatic or large (>3 cm): aspiration
  - unstable/tension pneumothorax: needle decompression then chest tube, and VATS if unsuccessful (25-50%)
- secondary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + O₂
  - if symptomatic, large, or unstable: chest tube, and VATS if unsuccessful

**Asbestos-Related Pleural Disease and Mesothelioma**

**Etiology and Pathophysiology**
- benign manifestations of asbestos exposure:
  - “benign asbestos pleural effusion”
    - exudative effusion, typically ~10 yr after exposure, resolves
    - pleural plaques, usually calcified
      - marker of exposure; usually an asymptomatic radiologic finding
  - mesothelioma
    - primary malignancy of the pleura
    - decades after asbestos exposure (even with limited exposure)
    - smoking not a risk factor, but asbestos and smoking synergistically increase risk of lung cancer

**Signs and Symptoms**
- persistent chest pain, dyspnea, cough, bloody pleural effusion, weight loss

**Investigations**
- biops (pleuroscopic or open)
- needle biopsy may seed needle tract with tumour

**Treatment**
- resection (extrapleural pneumonectomy) requires careful patient selection; rarely successful (average survival <1 yr)
Respiratory Failure

**Definition**
- failure of respiratory system to maintain normal blood gases
- hypoxemic (PaO₂ <60 mmHg)
- hypercapnic (PaCO₂ >50 mmHg)
- acute vs. chronic (compensatory mechanisms activated)

**Signs and Symptoms**
- signs of underlying disease
- hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale
- hypercapnia: headache, dyspnea, drowsiness, asterixis, warm periphery, plethora, increased ICP (secondary to vasodilatation)

**Investigations**
- serial ABGs
- CXR and/or CT, bronchoscopy to characterize underlying cause if unclear

---

**Hypoxemic Respiratory Failure**

**Definition**
- PaO₂ decreased, PaCO₂ normal or decreased

**Treatment**
- reverse the underlying pathology
- oxygen therapy: maintain oxygenation (if shunt present, supplemental O₂ is less effective; see Anesthesia and Perioperative Medicine, A10, for oxygen delivery systems)
- ventilation, BiPAP, and PEEP/CPAP (see Anesthesia and Perioperative Medicine, A10): positive pressure can recruit alveoli and redistribute lung fluid
- improve cardiac output: ± hemodynamic support (fluids, vasopressors, inotropes), reduction of O₂ requirements

**Table 27. Approach to Hypoxemia**

<table>
<thead>
<tr>
<th>Type of Hypoxemia</th>
<th>Settings</th>
<th>P.CO₂</th>
<th>A-aDO₂</th>
<th>Oxygen Therapy</th>
<th>Ventilation, BiPAP and PEEP</th>
<th>Improved Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ow F iO₂</td>
<td>Postop, high altitude</td>
<td>N or ↓</td>
<td>N</td>
<td>Improves</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>2 Hypoventilation</td>
<td>Drug overdose</td>
<td>↑</td>
<td>N</td>
<td>Improves</td>
<td>Improves with ventilation</td>
<td>No change</td>
</tr>
<tr>
<td>3a. Shunt (Intrapulmonary)</td>
<td>ARDS, pneumonia</td>
<td>N or ↓</td>
<td>↑</td>
<td>No change</td>
<td>Improves (except if one-sided)</td>
<td>Improves</td>
</tr>
<tr>
<td>3b. Shunt (Right to Left)</td>
<td>Pulmonary HTN</td>
<td>N or ↓</td>
<td>↑</td>
<td>No change</td>
<td>Worsens</td>
<td>Worsens</td>
</tr>
<tr>
<td>4. Low Mixed Venous</td>
<td>Shock</td>
<td>↓</td>
<td>↑</td>
<td>Improves or no change</td>
<td>Worsens</td>
<td>Improves</td>
</tr>
<tr>
<td>5. V/Q Mismatch</td>
<td>COPD</td>
<td>N or ↑</td>
<td>↑</td>
<td>Improves (small amounts)</td>
<td>Often improves</td>
<td>Improves</td>
</tr>
<tr>
<td>6. Diffusion Impairment</td>
<td>ILD, emphysema</td>
<td>N</td>
<td>↑</td>
<td>Imp oves</td>
<td>Improves with positive pressure</td>
<td>No change or worsens</td>
</tr>
</tbody>
</table>

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**Hypercapnic Respiratory Failure**

**Definition**
- PaCO₂ increased, PaO₂ decreased

**Pathophysiology**
- increased CO₂ production: fever, sepsis, seizure, acidosis, carbohydrate load
- alveolar hypoventilation: COPD, asthma, CF, chest wall disorder, dead space ventilation (rapid shallow breathing)
  - inefficient gas exchange results in inadequate CO₂ removal in spite of normal or increased minute volume
- hypoventilation
  - central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (opiates, benzodiazepines)
  - neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis, kyphoscoliosis
  - muscle fatigue

**Dead Space**
- Ventilation without perfusion
- The opposite of shunt

**Causes of Hypercapnia**
- High Inspired CO₂
- ow Total Ventilation
- High Deadspace Ventilation
- High CO₂ Production
Acute Respiratory Distress Syndrome

Definition
- Clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
- The Berlin Criteria (JAMA 2012; 307:2526-2533) for ARDS
  - Acute onset
    - Within 7 d of a defined event, such as sepsis, pneumonia, or patient noticing worsening of respiratory symptoms
    - Usually occurs within 72 h of presumed trigger
  - Bilateral opacities consistent with pulmonary edema on either CT or CXR
  - Not fully explained by cardiac failure/fluid overload, but patient may have concurrent heart failure
  - Objective assessment of cardiac function (e.g. echocardiogram) should be performed even if no clear risk factors

Etiology
- Direct lung injury
- Airway: aspiration (gastric contents, drowning), pneumonia, inhalation injury (oxygen toxicity, nitrogen dioxide, smoke)
- Circulation: embolism (fat, amniotic fluid), reperfusion injury
- Indirect lung injury
- Circulation: sepsis, shock, trauma, blood transfusion, pancreatitis
- Neurogenic: head trauma, intracranial hemorrhage, drug overdose (narcotics, sedatives, TCAs)

Pathophysiology
- Disruption of alveolar capillary membranes → leaky capillaries → interstitial and alveolar pulmonary edema → reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN

Clinical Course
A. Exudative Phase
- First 7 d of illness after exposure to ARDS precipitant
- Alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
- Patients develop dyspnea, tachypnea, increased work of breathing
  - These result in respiratory fatigue and eventually respiratory failure (see Hypoxic Respiratory Failure, R26)

B. Fibroproliferative Phase
- After day 7
- May still experience dyspnea, tachypnea, fatigue, and hypoxemia
- Most patients clinically improve and are able to wean off mechanical ventilation
- Some patients develop fibrotic lung changes that may require long term support on supplemental oxygen or even mechanical ventilation
- If fibrosis present, associated with increased mortality

Treatment
- Based on ARDS Network (see Landmark Respiratory Trials, R38)
- Treat underlying disorder (e.g. antibiotics if infection present)
- Mechanical ventilation using low tidal volumes (<6 mL/kg) to prevent barotrauma
  - Use optimal amount of PEEP (positive end-expiratory pressure) to keep airways open and allow the use of lower FiO2
  - May consider using prone ventilation, ± inhaled nitric oxide, short term paralytics (<48 h) or ECMO (extracorporeal membrane oxygenation) if conventional treatment is failing
- Fluids and inotropic therapy (e.g. dopamine, vasopressin) if cardiac output inadequate
- Pulmonary-arterial catheter now seldom used for monitoring hemodynamics
- Mortality: 30–40%, usually due to non-pulmonary complications
- Sequelae of ARDS include residual pulmonary impairment, severe debilitation, polyneuropathy and psychologic difficulties, which gradually improve over time
- Most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity

Risk Factors for Aspiration Pneumonia

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased level of consciousness</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Upper GI tract disorders</td>
<td>Dysphagia, esophageal disorders</td>
</tr>
<tr>
<td>Mechanical instrumentation</td>
<td>Intubation, nasogastric tube, feeding tubes</td>
</tr>
<tr>
<td>Neurologic conditions</td>
<td>Dementia, Parkinson disease</td>
</tr>
<tr>
<td>Others</td>
<td>Protracted vomiting</td>
</tr>
</tbody>
</table>

*In chronic hypercapnia, supplemental O2 may decrease the hypoxic drive to breathe, but do not deny oxygen if the patient is hypoxic.

In COPD patients with chronic hypercapnia ("CO2 retainers"), provide supplemental oxygen to achieve target SaO2 from 88-92%.

ALI vs. ARDS: Definition is the same, except ALI is a PaO2/FiO2 ≥ 300, while ARDS is a PaO2/FiO2 ≤ 200.

| Categorization of ARDS as Mild, Moderate or Severe – The Berlin Criteria |
|-----------------------------|-----------------------------|
| ARDS Severity   | P.O2/FiO2 (mmHg)* | Mortality (95% CI)# |
| Mild            | 200-300            | 27 (24-30)%        |
| Moderate        | 100-200            | 32 (29-34)%        |
| Severe          | < 100              | 45 (42-48)%        |

*On 5–10 cm H2O PEEP, P<0.001
JAMA 2012; 307:2526-2533

ALI: Acute Lung Injury
ARDS: Acute Respiratory Distress Syndrome
FiO2: Fraction of inspired oxygen
PaO2: Arterial partial pressure of oxygen
PEEP: Positive end-expiratory pressure
PaCO2: Arterial partial pressure of carbon dioxide
SaO2: Arterial oxygen saturation

References:
- Landmark Respiratory Trials
- Hypoxic Respiratory Failure
- JAMA 2012; 307:2526-2533
- Toronto Notes 2018

For more information, please consult the referenced articles and resources.
Neoplasms

Lung Cancer

Classification
- Lung tumours can be classified as primary or secondary, benign or malignant, endobronchial or parenchymal.
- Bronchogenic carcinoma (epithelial lung tumours) are the most common type of primary lung tumour (other types make up less than 1%).
  - Small cell lung cancer (SCLC): 10-15%
  - Non-small-cell lung cancer (NSCLC): 85-90%
    - Squamous cell carcinoma: arise from the proximal respiratory epithelium
    - Adenocarcinoma: incidence is increasing; most common subtype in nonsmokers
      - Mucinous adenocarcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring
  - Large cell undifferentiated cancer: diagnosis of exclusion
- Benign epithelial lung tumours can be classified as papillomas or adenomas.

Table 28. Characteristics of Bronchogenic Cancer

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Percentage of Bronchogenic Ca</th>
<th>Correlation with Smoking</th>
<th>Location</th>
<th>Histology</th>
<th>Metastasis</th>
<th>5 Yr Survival Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC</td>
<td>10-15%</td>
<td>Strong</td>
<td>Central</td>
<td>Oat cell, neuroendocrine</td>
<td>Disseminated at presentation</td>
<td>1% (poorest prognosis)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>M: 35% F: 40%</td>
<td>Weak</td>
<td>Peripheral</td>
<td>Glandular, mucin producing</td>
<td>Early, distant</td>
<td>12% (60% for mucinous adenocarcinoma, a subtype, with a resectable solitary lesion)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma (Scc)</td>
<td>30%</td>
<td>Strong</td>
<td>Central</td>
<td>Keratin, intercellular bridges</td>
<td>Local invasion and distant spread, may cavitate</td>
<td>25%</td>
</tr>
<tr>
<td>Large Cell Carcinoma</td>
<td>10-15%</td>
<td>Strong</td>
<td>Peripheral</td>
<td>Anaplastic, undifferentiated</td>
<td>Early, distant</td>
<td>13%</td>
</tr>
</tbody>
</table>

Risk Factors
- Cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers.
- Risk of lung cancer increases with number of cigarettes smoked per day (linear) and duration of smoking (exponential).
- Other risk factors include cigar smoking, pipe smoking, second-hand smoke, asbestos without smoking (relative risk is 3), asbestos with smoking (relative risk is 92), metals (e.g., chromium, arsenic, nickel), radon gas, ionizing radiation, genetics.

Signs and Symptoms
- May be due to primary lesion, metastasis, or paraneoplastic syndrome.
  - Primary lesion:
    - Cough (75%): beware of chronic cough that changes in character
    - Dyspnea (60%)
    - Chest pain (45%)
    - Hemothysis (35%)
    - Other pain (25%)
    - Clubbing (21%)
    - Constitutional symptoms: anorexia, weight loss, fever, fatigue
  - Metastasis:
    - Lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing, postobstructive pneumonia
    - Pericardium: pericardial effusion, pericardial tamponade
    - Esophageal compression: dysphagia
    - Phrenic nerve: paralyzed diaphragm
    - Recurrent laryngeal nerve: hoarseness

Summary of Recommendations on Screening for Lung Cancer

Canadian Task Force on Preventative Health Care (2016)
- Screening with CXR (+ sputum cytology) not recommended.
- Screening with low-dose CT recommended for high-risk patients (current or former smokers quit within last 15 yr, aged 55-74, ≥30 pack yr smoking Hx) for 3 consecutive years.
  - Number needed to screen = 322

American College of Chest Physicians (2013)
- Screening with CXR not recommended.
- Screening with low-dose CT recommended for high-risk patients (current or former smokers quit within last 15 yr, aged 55-74, ≥30 pack yr smoking Hx).

American Lung Association (2013)
- Screening with CXR not recommended.
- Screening with low-dose CT recommended for high-risk patients (current or former smokers aged 55-74, ≥30 pack yr smoking Hx, no Hx of lung cancer).

Malignant lung tumours are the most common cause of cancer mortality throughout the world in both men and women.
• superior vena cava syndrome
  • obstruction of SVC causing neck and facial swelling, as well as dyspnea and cough
  • other symptoms: hoarseness, tongue swelling, epistaxis, and hemoptysis
  • physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton’s sign (facial flushing, cyanosis, and distension of neck veins upon raising both arms above head)
  • milder symptoms if obstruction is above the azygos vein

• lung apex (Pancoast tumour): Horner’s syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
• rib and vertebrae: erosion
• distant metastasis to brain, bone, liver, adrenals

• paraneoplastic syndromes
  • a group of disorders associated with malignant disease, not related to the physical effects of the tumour itself
  • most often associated with SCLC

Table 29. Paraneoplastic Syndromes

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Presentation</th>
<th>Associated Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td>Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)</td>
<td>Non-small cell lung cancer (NSCLC)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Acanthosis nigricans</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td></td>
<td>Dermatomyositis</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypercalcemia (osteolysis or PTHP)</td>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Cushing’s syndrome (ACTH)</td>
<td>Small cell lung cancer (SCLC)</td>
</tr>
<tr>
<td></td>
<td>Somatostatinoma syndrome</td>
<td>Bronchial carcinoid</td>
</tr>
<tr>
<td></td>
<td>SIADH</td>
<td>SCLC</td>
</tr>
<tr>
<td>Neuromyopathic</td>
<td>Lambert Eaton syndrome</td>
<td>SCLC</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subacute cerebellar degeneration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar degeneration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>Vascular/Hematologic</td>
<td>Nonbacterial endocarditis</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td></td>
<td>Trousseau’s syndrome (migratory thrombophlebitis)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Renal</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Investigations

• initial diagnosis
  • imaging: CXR, CT chest + upper abdomen, PET scan
  • cytology: sputum
  • biopsy: bronchoscopy, EBUS, CT-guided percutaneous needle biopsy, mediastinoscopy

• staging workup
  • TNM staging system: T – primary tumour (size); N – regional lymph nodes; M – distant metastasis
  • blood work: electrolytes, LFTs, calcium, ALP
  • imaging: CXR, CT thorax and upper abdomen, bone scan, neuroimaging, PET scan
  • invasive: bronchoscopy (EBUS), mediastinoscopy, mediastinotomy, thoracotomy
  • screen adenocarcinoma for EGFR and ALK mutations

Horner has a MAP of the Coast
A Pancoast tumour compresses the cervical sympathetic plexus causing a Horner’s syndrome:
  • Miosis
  • Anhydrosis
  • Ptosis

Reduced Lung Cancer Mortality with Low-Dose CT Screening
NEJM 201;365:395-409
Study: Multicentre, RCT.
Methods: 53,454 participants at high risk for lung cancer (55-74 yr, >30 yr smoking, and smoking cessation for <5 y) were assigned to undergo three annual screenings with either low dose CT or single-view PA CXR.
Results: A relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI 6.8-26.7; p=0.004). Rate of death from any cause was reduced in the low-dose CT group as compared to the CXR group by 6.7% (95% CI 1.2-13.6; p=0.02).

<table>
<thead>
<tr>
<th></th>
<th>Low-dose CT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of positive screening test</td>
<td>24.2%</td>
<td>4.9%</td>
</tr>
<tr>
<td>False positives</td>
<td>96.4%</td>
<td>94.5%</td>
</tr>
<tr>
<td>Incidence of lung cancer</td>
<td>64/100 K person yr</td>
<td>572/100 K person yr</td>
</tr>
<tr>
<td>Deaths from lung cancer</td>
<td>247/100 K person yr</td>
<td>309/100 K person yr</td>
</tr>
</tbody>
</table>

Conclusions: Screening with low-dose CT reduces mortality from lung cancer.

Endobronchial Ultrasound (EBUS)
• Allows visualization of peri-bronchial structures and distal peripheral lung lesions
• Provides detailed assessment of the airway wall layers
• Allows for guided biopsies of lymph nodes and tumours
• Used for diagnosis and staging
Table 30. SCLC vs. NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Treatment</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCLC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited stage</td>
<td>Confined to single radiation port (one hemithorax and regional lymph nodes)</td>
<td>Radiotherapy ± chemotherapy ± prophylactic to brain</td>
<td>1-2 yr (12 wk without treatment)</td>
</tr>
<tr>
<td>Extensive stage</td>
<td>Extension beyond a single radiation port</td>
<td>Chemotherapy</td>
<td>6 mo 5 wk without treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Treatment</th>
<th>5 Yr Survival (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>IA</td>
<td>T1a-1bN0M0 or T2aN0M0</td>
<td>50-73</td>
</tr>
<tr>
<td></td>
<td>IB</td>
<td>T1a-2a,N1M0 or T2bN0M0</td>
<td>43-58</td>
</tr>
<tr>
<td></td>
<td>IIA</td>
<td>T1a-2bN2M0 or T3N1-2M0 or T4N1-1M0</td>
<td>36-46</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>T2bN1M0 or T3N0M0</td>
<td>25-36</td>
</tr>
<tr>
<td></td>
<td>IIIA</td>
<td>T1a-2bN2M0 or T3N1-2M0 or T4N1-1M0 Combined modality approach</td>
<td>19-24</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>T4N2M0 or T1 4N3M0</td>
<td>7-9</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>T1-4N0-3M1a 1b Systemic therapy or molecularly targeted therapy or symptom-based palliative management (radiation), isolated metastasis may be resected</td>
<td>2-13</td>
</tr>
</tbody>
</table>

* Depends on clinical vs. pathologic stage
Refer to AJCC Cancer Staging Manual, 7th ed. 2010 for complete TNM classification

**Treatment**
- options include surgery, radiotherapy, chemotherapy, and palliative care for end-stage disease
- surgery not usually performed for SCLC since it is generally non-curable
- contraindications for surgery
  - spread to contralateral lymph nodes or distant sites
  - patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
  - poor pulmonary status (e.g. unable to tolerate resection of lung)
  - post-op estimated FEV1 and DLCO must be at least 40% of predicted to tolerate surgery
- chemotherapy (used in combination with other treatments)
  - common agents: etoposide, platinum agents (e.g. cisplatinum), ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  - complications
    - acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
    - chronic: neurologic damage, leukemia, additional primary neoplasms

**Approach to the Solitary Pulmonary Nodule**

**Definition**
- a round or oval, sharply circumscribed radiographic lesion up to 3 cm, which may or may not be calcified, and is surrounded by normal lung
- can be benign or malignant

**Table 31. Differential Diagnosis for Benign vs. Malignant Solitary Nodule**

<table>
<thead>
<tr>
<th>Benign (70%)</th>
<th>Malignant (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious granuloma</td>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>(histoplasmosis, coccidiodymycosis, TB, atypical mycobacteria) - most common</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Other infections</td>
<td>Squamous cell carcroma</td>
</tr>
<tr>
<td>(bacterial abscess, PCP, aspergiloma)</td>
<td>Large cell carcinoma</td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>(hamartoma, lipoma, fibroma)</td>
<td></td>
</tr>
<tr>
<td>Vascular (AV malformation, pulmonary varix)</td>
<td></td>
</tr>
<tr>
<td>Developmental (O)chondrogenic cyst</td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td></td>
</tr>
<tr>
<td>(granulomatosis with polyangiitis, rheumatoid nodule, sarcoidosis amyloidosis)</td>
<td></td>
</tr>
<tr>
<td>Other (infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma)</td>
<td>Breast</td>
</tr>
<tr>
<td><strong>Metastatic lesions</strong></td>
<td>Breasts</td>
</tr>
<tr>
<td>Breast</td>
<td>Head and neck</td>
</tr>
<tr>
<td>Colon</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Kidney</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Germ cell tumours</td>
<td>Pulmonary carcino</td>
</tr>
</tbody>
</table>

**Hamartomas**
- 10% of benign lung lesions
- Composed of tissues normally present in lung (fat, epithelium, fibrous tissue, and cartilage), but they exhibit disorganized growth
- Peak incidence is age 60, more common in men
- Usually peripheral and clinically silent
- CT shows clustered "popcorn" pattern of calcification (pathognomonic for hamartoma)
**Investigations**
- CXR: always compare with previous CXR
- CT densitometry and contrast enhanced CT of thorax
- sputum cytology: usually poor yield
- biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy or thoracotomy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  - if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  - if a biopsy is non-diagnostic, whether to observe, re-biopsy, or resect will depend on the level of suspicion
- watchful waiting: repeat CXR and/or CT scan at 3, 6, 12 mo
- PET scan can help distinguish benign from malignant nodules

**Table 32. CT Characteristics of Benign vs. Malignant Solitary Nodule**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Nodule (&lt;3 cm)</td>
<td>Mass (&gt;3 cm)</td>
</tr>
<tr>
<td>Borders</td>
<td>Smooth or lobulated</td>
<td>Irregular or spiculated</td>
</tr>
<tr>
<td>Features</td>
<td>Calcified pattern: diffuse, central, laminated, “popcorn” pattern if hamartoma, usually no cavitation; if cavitating, wall is smooth and thin, no other lung pathology</td>
<td>Usually not calcified; if calcified, pattern is eccentric, stippled, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>Doubles in &lt;20 days or &gt;400 days</td>
<td>Doubles between 20 and 400 days</td>
</tr>
</tbody>
</table>

**Figure 11. Evaluation of a solitary pulmonary nodule**

Sleep-Related Breathing Disorders

Hypoventilation Syndromes

• primary alveolar hypoventilation: idiopathic
• obesity-hypoventilation syndrome (Pickwickian syndrome)
• respiratory neuromuscular disorders

Sleep Apnea

Definition

• episodic decreases in airflow during sleep
• quantitatively measured by the Apnea/Hypopnea Index (AHI) = # of apneic and hypopneic events per hour of sleep
• sleep apnea generally accepted to be present if AHI >15

Classification

• obstructive (OSA)
• caused by transient, episodic obstruction of the upper airway
• absent or reduced airflow despite persistent respiratory effort
  • central (CSA) (see Neurology, N47)
• caused by transient, episodic decreases in CNS drive to breathe
• no airflow because no respiratory effort
• Cheyne-Stokes Respiration: a form of CSA in which central apneas alternate with hyperpneas to produce a crescendo-decrescendo pattern of tidal volume; seen in severe LV dysfunction, brain injury, and other settings (see Figure 2)
• mixed (MSA)
• features of both OSA and CSA
• loss of hypoxic and hypercapnic drives to breathe secondary to "resuscitative breathing": overcompensatory hyperventilation upon awakening from OSA induced hypoxia

Risk Factors

• for OSA: obesity, upper airway abnormality, neuromuscular disease, hypothyroidism, alcohol/sedative use, nasal congestion, sleep deprivation, enlarged tonsils
• for CSA: LV failure, brainstem lesions, encephalitis, encephalopathy, myxedema, high altitude

Signs and Symptoms

• obtain history from spouse/partner
• secondary to repeated arousals and fragmentation of sleep: daytime somnolence, personality and cognitive changes, snoring
• secondary to hypoxemia and hypercapnia: morning headache, polycythemia, pulmonary/systemic HTN, cor pulmonale/CHF, nocturnal angina, arrhythmias
• the typical presentation for OSA is a middle-aged obese male who snores

Investigations

• sleep study (polysomnography)
• evaluates sleep stages, airflow, ribcage movement, ECG, SaO2, limb movements
• indications
  • excessive daytime sleepiness
  • unexplained pulmonary HTN or polycythemia
  • daytime hypercapnia
  • titration of optimal nasal CPAP
• assessment of objective response to other interventions

Treatment

• modifiable factors: weight loss, decreased alcohol/sedatives, nasal decongestion, treatment of underlying medical conditions
• OSA or MSA: nasal CPAP, postural therapy (e.g. no supine sleeping), dental appliance, uvulopalatopharyngoplasty, tonsillectomy
• CSA or hypoventilation syndromes: nasal BiPAP/CPAP, respiratory stimulants (e.g. acetazolamide, theophylline, progesterone) adaptive servoventilation (e.g. progesterone) in select cases
• tracheostomy rarely required and should be used as last resort for OSA

Complications

• depression, weight gain, decreased quality of life, workplace and vehicular accidents, cardiac complications (e.g. HTN), reduced work/social function

Normal Respiratory Changes during Sleep

• Tidal volume decreases
• Arterial CO2 increases (due to decreased minute ventilation)
• Pharyngeal dilator muscles relax causing increased upper airway resistance

Continuous Positive Airways Pressure for Obstructive Sleep Apnea

Cochrane DB Syst Rev 2006;CD001106

Study: Pooled analysis of 36 RCTs (n=1,718) comparing nocturnal CPAP with an inactive control or oral appliances in adults with OSA.

Conclusions: The use of CPAP showed significant improvements in objective and subjective measures including cognitive function, sleepiness, measures of quality of life, and a lower average systolic and diastolic blood pressure. People who responded equally well to CPAP and oral appliances expressed a strong preference for oral appliances; however, participants on oral appliances were more likely to withdraw from therapy.

CPAP has been shown to reduce cardiovascular risk and cardiovascular related deaths in patients with obstructive sleep apnea.
Introduction to Intensive Care

Intensive Care Unit Basics

- goal is to provide stabilization for critically ill patients: hemodynamic, respiratory or cardiac instability, or need for close monitoring

Lines and Catheters

- arterial lines
  - monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs
  - common sites are the radial and femoral arteries
- central venous catheter (central line)
  - administer IV fluids, monitor CVP, insert pulmonary artery catheters
  - administer TPN and agents too irritating for peripheral line (e.g. vasopressors, chemotherapy)
  - common sites: internal jugular vein, subclavian vein, femoral vein
- pulmonary arterial catheter
  - balloon guides the catheter from a major vein to the right heart
  - measures pulmonary capillary wedge pressure (PCWP) via a catheter wedged in distal pulmonary artery
  - PCWP reflects the LA and LV diastolic pressure (barring pulmonary venous or mitral valve disease)
- indications (now used infrequently due to associated complications)
  - diagnosis of shock states, primary pulmonary HTN, valvular disease, intracardiac shunts, cardiac tamponade, PE
  - assessment of hemodynamic response to therapies
  - differentiation of high- versus low-pressure pulmonary edema
  - management of complicated MI, multigang system failure and/or severe burns, or hemodynamic instability after cardiac surgery
  - absolute contraindications
    - tricuspid or pulmonary valve mechanical prosthesis
    - right heart mass (thrombus or tumour)
    - tricuspid or pulmonary valve endocarditis

Table 33. Useful Equations and Cardiopulmonary Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA</td>
<td>( \text{BSA} = \frac{\text{Ht (cm)} + \text{Wt (kg)} - 60}{100} )</td>
</tr>
<tr>
<td>PCWP</td>
<td>( \text{PCWP = LVEDP} )</td>
</tr>
<tr>
<td>SV</td>
<td>( \text{SV} = \text{CI} / \text{BSA} )</td>
</tr>
<tr>
<td>CI</td>
<td>( \text{CI} = \frac{\text{CO}}{\text{BSA}} )</td>
</tr>
<tr>
<td>SVRI</td>
<td>( \text{SVRI} = \frac{(\text{MAP} - \text{RAP}) \times 80}{\text{CI}} )</td>
</tr>
<tr>
<td>P:F ratio</td>
<td>( \text{P:F ratio} = \frac{\text{PaO}_2}{\text{FiO}_2} )</td>
</tr>
<tr>
<td>MAP</td>
<td>( \text{MAP} = \frac{1}{3} \text{sBP} + \frac{2}{3} \text{dBP} = \text{dBP} + \frac{1}{3} \text{PP} )</td>
</tr>
<tr>
<td>PP</td>
<td>( \text{PP} = \text{sBP} - \text{dBP} )</td>
</tr>
<tr>
<td>CI</td>
<td>( \text{CI} = \frac{\text{CO}}{\text{BSA}} )</td>
</tr>
<tr>
<td>SVI</td>
<td>( \text{SVI} = \frac{\text{CI}}{\text{HR}} )</td>
</tr>
<tr>
<td>RV Ejection Fraction</td>
<td>( \text{RV Ejection Fraction} = \frac{\text{SV}}{\text{RVEDV}} )</td>
</tr>
<tr>
<td>MAP</td>
<td>( \text{MAP} = \frac{1}{3} \text{sBP} + \frac{2}{3} \text{dBP} = \text{dBP} + \frac{1}{3} \text{PP} )</td>
</tr>
</tbody>
</table>

Table 34. Types of Organ Failure

<table>
<thead>
<tr>
<th>Type of Failure</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Failure (see Respiratory Failure, R26)</td>
<td>Hypoxemia, Hypercapnia</td>
<td>Treat underlying cause (e.g. lung disease, shunt, V/Q mismatch, drug-related, cardiac) Manage mechanical ventilation settings</td>
</tr>
<tr>
<td>Cardiac Failure (see Cardiology and Cardiac Surgery, C24)</td>
<td>Hypotension, Decreased urine output, Altered mental status, Arhythmia, Hypoxia</td>
<td>Treat underlying cause (e.g. bradycardia, tachycardia, blood loss, adrenal insufficiency) Volume resuscitation, Vasopressors, Inotropes, Intra-aortic balloon pump</td>
</tr>
<tr>
<td>Coagulopathy (see Hematology, H53)</td>
<td>Increased INR or PT, Low platelet count, Bleeding, bruising</td>
<td>Treat underlying cause (e.g. thrombocytopenia, drug-related, immune-related, DIC) Transfusion of blood products, clotting factors</td>
</tr>
<tr>
<td>Liver Failure (see Gastroenterology, G35)</td>
<td>Elevated transaminases, Bilirubin, Coagulopathy, Jaundice, Altered mental status (encephalopathy), Hypoglycemia</td>
<td>Treat underlying cause (e.g. viral hepatitis, drug related, metabolic) Lactulose, Liver transplant</td>
</tr>
<tr>
<td>Renal Failure (see Nephrology, NP37)</td>
<td>Elevated creatinine, Reduced urine output, Signs of volume overload (e.g. CHF, effusions)</td>
<td>Treat underlying cause (e.g. shock, drug-related, obstruction) Correct volume and electrolyte status, eliminate toxins Diuretics, Dialysis</td>
</tr>
</tbody>
</table>

Organ Failure
Shock

- see *Emergency Medicine*, ER3
- inadequate tissue perfusion potentially resulting in end organ injury
  - categories of shock
    - hypovolemic: hemorrhage, dehydration, vomiting, diarrhea, interstitial fluid redistribution
    - cardiogenic: myopathic (myocardial ischemia ± infarction), mechanical, arrhythmic pharmacologic
    - obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
    - distributive: sepsis, anaphylaxis, neurogenic, endocrine, toxins

### Table 35. Changes Seen in Different Classes of Shock

<table>
<thead>
<tr>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Obstructive</th>
<th>Distributive</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR ↑</td>
<td>↑, N, or ↓</td>
<td>↑</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>BP ↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>JVP ↓</td>
<td>↑</td>
<td>↑ or ↓</td>
<td>↑</td>
</tr>
<tr>
<td>Extremities</td>
<td>Look for visible hemorrhage or signs of dehydration</td>
<td>Bilateral crackles on chest exam</td>
<td>Depending on cause, may see pulsus paradoxus, Kussmaul’s sign, or tracheal deviation</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- treat underlying cause (hypovolemia is the most common cause)
- treatment goal is to return critical organ perfusion to normal (e.g. normalize BP)
- common treatment modalities include
  - fluid resuscitation (NOT in cardiogenic shock)
  - inotropes (e.g. dobutamine), vasopressors (e.g. norepinephrine), vasopressin
  - revascularization or thrombolytics for ischemic events
  - needle decompression or tube thoracostomy for suspected tension pneumothorax

Sepsis

- the leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- the predominant theory is that sepsis is attributable to uncontrollable immune system activation

### Definitions

- the Third International Consensus Definition for Sepsis and Septic Shock (Singer et al. JAMA 2016: 315(8), 801-810) significantly revised sepsis definitions
- sepsis: life threatening organ dysfunction caused by dysregulated host response to infection (see Table 36)
- septic shock: a subset of sepsis, where sufficient circulatory and/or cellular/metabolic abnormalities substantially increase mortality Clinically defined as sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate ≥2 mmol/L (18 mg/dL) despite adequate fluid resuscitation

### Signs and Symptoms

- new guidelines recommend the use of quick SOFA (qSOFA) criteria and SOFA score to replace SIRS criteria
- in patients with suspected infection, bedside application of qSOFA criteria identifies individuals with high likelihood of poor outcomes, including prolonged ICU stay and/or death
- a positive qSOFA (≥2 criteria) should prompt application of the SOFA score, and further evaluation of possible infection and organ dysfunction
- in the context of suspected infection, a SOFA score ≥2 reflects an overall mortality risk of 10%
- the absence of ≥2 criteria on either qSOFA or SOFA score should not delay or defer investigation or treatment of infection or any other aspect of care deemed necessary by the practitioners
Table 36. Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) Score

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2, mmHg (kPa)</td>
<td></td>
</tr>
<tr>
<td>≥400 (53.3)</td>
<td></td>
</tr>
<tr>
<td>&lt; 400 (53.3)</td>
<td></td>
</tr>
<tr>
<td>&lt; 300 (40)</td>
<td></td>
</tr>
<tr>
<td>&lt; 200 (26.7) with respiratory support</td>
<td></td>
</tr>
<tr>
<td>&lt; 100 (13.3) with respiratory support</td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
</tr>
<tr>
<td>Platelets, x103/µL</td>
<td></td>
</tr>
<tr>
<td>≥150</td>
<td></td>
</tr>
<tr>
<td>&lt; 150</td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Bilirubin, µmol/L (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>&lt; 20 (1.2)</td>
<td></td>
</tr>
<tr>
<td>20-32 (1.2-1.9)</td>
<td></td>
</tr>
<tr>
<td>33-101 (2.0-5.9)</td>
<td></td>
</tr>
<tr>
<td>102-204 (6.0-11.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 204 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>MAP ≥70 mmHg</td>
<td></td>
</tr>
<tr>
<td>MAP &lt; 70 mmHg</td>
<td></td>
</tr>
<tr>
<td>Dopamine &lt; 3a or dobutamine (any dose)</td>
<td></td>
</tr>
<tr>
<td>Dopamine 5.1-15a or epinephrine &lt; 0.1a or norepinephrine &lt; 0.1a</td>
<td></td>
</tr>
<tr>
<td>Dopamine &gt; 15a or epinephrine &gt; 0.1a or norepinephrine &gt; 0.1a</td>
<td></td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
</tr>
<tr>
<td>Glasgow coma scale score</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
</tr>
<tr>
<td>13-14</td>
<td></td>
</tr>
<tr>
<td>10-12</td>
<td></td>
</tr>
<tr>
<td>6-9</td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Creatinine, µmol/L (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>&lt; 110 (1.2)</td>
<td></td>
</tr>
<tr>
<td>110-170 (1.2-1.9)</td>
<td></td>
</tr>
<tr>
<td>171-299 (2.0-3.4)</td>
<td></td>
</tr>
<tr>
<td>300-440 (3.5-4.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 440 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
</tr>
<tr>
<td>&lt; 500</td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td></td>
</tr>
</tbody>
</table>

*Note: aDopamine doses are given as µg/kg/min for at least 1hr*

Table adapted from Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801-810

### Figure 12. Approach to sepsis

Figure adapted from Singer et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801-810.

#### Treatment

- Identify the cause and source of infection: blood, sputum, urine Gram stain, and C&S
- Initiate empiric antibiotic therapy
- Monitor, restore, and maintain hemodynamic function

#### Surviving Sepsis (adapted from International Guidelines for Management of Severe Sepsis and Septic Shock 2012)

- Adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with demand
- Initial resuscitation (goals during first 6 h of resuscitation for sepsis induced hypotension persisting after initial fluid challenge or blood lactate ≥ 4 mmol/L)
- Maintain CVP ≥ 12 mmHg with IV crystalloids/colloids
  - Maintain MAP ≥ 65 mmHg with use of vasopressor agents, first line: norepinephrine
  - Urine output ≥ 0.5 mL/kg/hr
  - Central venous (SVC) or mixed oxygen saturation 70% or 65% respectively
- in patients with elevated lactate levels target resuscitation to normalize lactate
- corticosteroid replacement therapy not indicated if adequate hemodynamic stability achieved with fluid resuscitation and vasopressor therapy
- infection control
  - prompt diagnosis of infection
    - cultures as clinically indicated prior to antibiotic therapy if no significant delay
    - imaging studies performed promptly to confirm possible infectious source
  - antibiotic therapy
- administer effective IV antimicrobials within first hour of recognition of sepsis
- choice of anti-infective therapy should consider activity against all likely pathogens and penetration of adequate concentration into tissue presumed to be source of infection
- antimicrobial regimen should be reassessed daily for potential deescalation
- surgical source control when appropriate
- supportive oxygenation and ventilation using lung-protective regimen
- early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier
- DVT/PE prophylaxis
- advanced care planning, including the communication of likely outcome and realistic goals of treatment with patients and families

### Table 37. Common Medications for Respiratory Diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β2-AGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-Acting</td>
<td>salbutamol/albuterol (Ventolin®, Airomir®) (light blue/navy MDI or diskus), terbutaline (Bricanyl®) (blue turbuhaler)</td>
<td>1-2 puffs q4-6h prn Bronchodilator in acute reversible airway obstruction</td>
<td>CV (angina, flushing, palpitations, tachycardia, can precipitate atrial fibrillation), CNS (dizziness, H/A, insomnia, anxiety), GI (diarrhea, N/V), rash, hypokalemia, paroxysmal bronchospasm</td>
</tr>
<tr>
<td>Long-Acting</td>
<td>salmeterol (Serevent®) (green diskus), formoterol (Oxace®, Foradil®) (blue/green turbuhaler or aerolizer) indacaterol (Onbrez®) (blue/white breezhaler)</td>
<td>1-2 puffs bid 1 puff daily Maintenance treatment (prevention of bronchospasm) in COPD, asthma</td>
<td></td>
</tr>
<tr>
<td>Combination Long-Acting</td>
<td>fluticasone and salmeterol (Advair®) (purple MDI or diskus) budesonide and formoterol (Symbicort®) (red turbuhaler) Mometasone and formoterol (Zenhale®) (blue MDI)</td>
<td>1 puff bid 2 puffs bid COPD and asthma Common: CNS, H/A, dizziness Resp: URTI, GI (N/V, diarrhea, pain/discomfort, oral candidiasis)</td>
<td></td>
</tr>
<tr>
<td>Combination Short-Acting</td>
<td>ipratropium/salbutamol (Combivent®, Respimat®) (orange respimat)</td>
<td>1 puff qid Bronchodilator used in COPD Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs</td>
<td></td>
</tr>
<tr>
<td>Combination Long-Acting</td>
<td>umeclidinium/vilanterol (Anoro®) (red elipta) aclidinium/formoterol (Duaklir®) (yellow genuair) tiotropium/olodaterol (InspiQ®) (green respimat) indacaterol/glycopyrronium (Ultibro®) (yellow breezhaler)</td>
<td>1 puff daily 1 puff bid 1 puff daily 1 puff daily Bronchodilator used in COPD Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs</td>
<td></td>
</tr>
<tr>
<td><strong>ANTICHOLINERGICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-Acting Anti-Cholinergic</td>
<td>ipratropium bromide (Atrovent®) (clear/green MDI)</td>
<td>2-3 puffs qid Bronchodilator used in asthma and COPD Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs</td>
<td></td>
</tr>
<tr>
<td>Long-Acting Anti-Cholinergic</td>
<td>tiotropium bromide (Spira®) (green handihaler or respimat) glycopyrronium bromide (Seebri®) (orange breezhaler), umclidinium (Incute®) (green elipta), aclidinium (Genuair®, Tudorza®) (green inhaler)</td>
<td>1 puff qam 1 puff daily Bronchodilator used in asthma and COPD Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drug</td>
<td></td>
</tr>
</tbody>
</table>
# Common Medications

## Table 37. Common Medications for Respiratory Diseases (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CORTICOSTEROIDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluticasone (Flovent®) (orange/peach MDI or diskus) budesonide (Pulmicort®) (brown turbuhaler) ciclesonide (Alvesco®) (red MDI) beclomethasone (QVAR®, Vanceril®) (brown MDI), mometasone (Asmanex®) (pink/grey/ brown wisthaler) fluticasone furoate (Arnuity®) (orange ellipta)</td>
<td>2-4 puffs bid 2 puffs bid 1 puff daily or bid 1-4 puffs bid 1 puff daily or bid 1 puff daily</td>
<td>Maintenance treatment of asthma</td>
<td>H/A, fever, N/V, MSK pain, URTI, throat irritation, growth velocity reduction in children/adolescents, HPA axis suppression, increased pneumonia risk in COPD</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prednisone (Apo-prednisone®, Deltasone®) methylprednisolone (Depo-Medrol®, Solu-Medrol®)</td>
<td>Typically 40-60 mg per day PO 125 mg q8h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q8h for 5 d</td>
<td>Acute exacerbation of COPD; severe, persistent asthma, PCP Status asthmaticus</td>
<td>Endocrine (hirsutism, DM/glucose intolerance, Cushing’s syndrome, HPA axis suppression), GI (increased appetite, indigestion), ocular (cataracts, glaucoma), edema, AVN, osteoporosis, H/A, psychiatric (anxiety, insomnia), easy bruising</td>
</tr>
<tr>
<td><strong>ADJUNCT AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>theophylline (Uniphyll®)</td>
<td>400-600 mg OD</td>
<td>Treatment of symptoms of reversible airway obstruction due to COPD</td>
<td>Gl upset, diarrhea, N/V, anxiety, H/A, insomnia, muscle cramp, tremor, tachycardia, PVCs, arrhythmias Toxicity: persistent, repetitive vomiting, seizures</td>
</tr>
<tr>
<td><strong>LEUKOTRIENE ANTAGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>montelukast (Singular®) zafirlukast (Accolate®)</td>
<td>10 mg PO qhs, now only available as once daily slow release 20 mg bid</td>
<td>Prophylaxis and chronic treatment of asthma</td>
<td>H/A, dizziness, fatigue, fever, rash, dyspepsia cough, flu-like symptoms</td>
</tr>
<tr>
<td><strong>ANTI-IgE MONOCLONAL ANTIBODIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>omalizumab (Xolair®)</td>
<td>150-350 mg SC q2-4wk</td>
<td>Moderate-severe persistent asthma</td>
<td>H/A, sinusitis, pharyngitis, URTI, viral infection, thrombocytopenia, anaphylaxis</td>
</tr>
<tr>
<td><strong>PDE 4 INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>roflumilast (Daxas®)</td>
<td>500 µg PO OD</td>
<td>Severe emphysema, with frequent exacerbations</td>
<td>Weight loss, suicidal ideation</td>
</tr>
<tr>
<td><strong>ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Macrolide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin azithromycin clarithromycin</td>
<td>250-500 mg PO tid x 7-10 d 500 mg PO x 1 dose, then 250 mg OD x 4 1,000 mg od or 500 mg PO bid x 7 10 d</td>
<td>Alternate to doxycycline or fluoroquinolone</td>
<td>GI (abdominal pain, diarrhea, N/V), H/A, prolonged QT, ventricular arrhythmias, hepatic impairment GI (diarrhea, N/V, abdominal pain), renal failure, deafness H/A, rash GI (diarrhea, N/V, abnormal taste, heartburn, abdominal pain), increased urea</td>
</tr>
<tr>
<td><strong>Doxycycline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg PO bid x 7-10 d</td>
<td>Alternate to macrodil or fluoroquinolone</td>
<td>Photosensitivity, rash, urticaria, anaphylaxis, diarrhea, enterocolitis, tooth discoloration in children</td>
</tr>
<tr>
<td><strong>Fluoroquinolone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levofloxacin (Levaquin®) moxifloxacin (Avelox®)</td>
<td>500 mg PO OD x 7-10 d 400 mg PO OD x 7 d</td>
<td>Alternate to macrodil or doxycycline</td>
<td>CNS (dizziness, fever, H/A), GI (N/V, diarrhea, constipation), prolonged QT</td>
</tr>
</tbody>
</table>
### Table 37. Common Medications for Respiratory Diseases (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd gen Cephalosporin</td>
<td>ceftriaxone (Rocephin®)</td>
<td>1-2 g IV OD x 7-10 d</td>
<td>Combine with fluoroquinolone or macrolide</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>levofloxacin</td>
<td>750 mg PO OD x 5 d 400 mg PO OD x 7 d (5 d for AECOPD)</td>
<td>Combine with 3rd gen cephalosporin</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>moxifloxacin</td>
<td>750 mg PO OD x 5 d 400 mg PO OD x 7 d (5 d for AECOPD)</td>
<td>See above</td>
</tr>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td></td>
<td>1 g IV bid x 7-10 d</td>
<td>Suspect MRSA</td>
</tr>
<tr>
<td>Macrolide</td>
<td>azithromycin</td>
<td>500 mg IV OD x 2 d, then 500 mg PO OD x 5 d 1,000 mg od or 500 mg PO bid x 7-10 d</td>
<td>Suspect Legionella</td>
</tr>
<tr>
<td>ICU MEDICATIONS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressors/Inotropes</td>
<td>norepinephrine (Levophed®)</td>
<td>0.5-30 µg/min IV 0.5 µg/kg/min IV 2-20 µg/kg/min IV</td>
<td>Acute hypotension</td>
</tr>
<tr>
<td></td>
<td>phenylephrine</td>
<td></td>
<td>Severe hypotension</td>
</tr>
<tr>
<td></td>
<td>dobutamine</td>
<td></td>
<td>Inotropic support</td>
</tr>
<tr>
<td>Sedatives/Analgesia</td>
<td>fentanyl (opioid class)</td>
<td>50-100 µg then 50 unlimited µg/h IV 1 3 mg/kg then 0.3-5 mg/kg/h IV</td>
<td>Sedation and/or analgesia</td>
</tr>
<tr>
<td></td>
<td>propofol (anesthetic)</td>
<td></td>
<td>Sedation and/or analgesia</td>
</tr>
</tbody>
</table>

See Infectious Diseases, ID26 – for the management of pulmonary tuberculosis
## Landmark Respiratory Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS Network</td>
<td>NEJM 2000;342:1301-8</td>
<td>Mortality decreased in ARDS patients ventilated with a low tidal volume strategy</td>
</tr>
<tr>
<td>Berlin Criteria</td>
<td>JAMA 2012;307:2526-33</td>
<td>The new definition of ARDS, better predicts mortality</td>
</tr>
<tr>
<td>CPAP and Apnea</td>
<td>NEJM 2005;353:2025-33</td>
<td>CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>NEJM 2012;366:1287-97</td>
<td>Fixed dose of rivoxabarin was non-inferior to standard therapy (Vit K antagonist) initial and long-term treatment of PE</td>
</tr>
<tr>
<td>Emphysema Treatment Trial</td>
<td>NEJM 2003;348:2059-73</td>
<td>Lung volume reduction surgery benefits patients with upper lobe disease and low exercise capacity</td>
</tr>
<tr>
<td>iELCAP</td>
<td>NEJM 2006;355:1763-71</td>
<td>High survival rate in patients with early stage lung cancer detected by low dose CT screening</td>
</tr>
<tr>
<td>Lung Health</td>
<td>JAMA 1994;272:1497-505</td>
<td>Aggressive smoking intervention significantly decreases the age-related decline in FEV₁ in middle-aged smokers with mild airways obstruction</td>
</tr>
<tr>
<td>OSCILLATE</td>
<td>NEJM 2013;368:795-805</td>
<td>Early high-frequency oscillatory ventilation in patients with moderate to severe ARDS might increase in-hospital mortality</td>
</tr>
<tr>
<td>ILD</td>
<td>NEJM 1978;298:801-9</td>
<td>Interstitial lung disease subsets have different prognoses and response to treatment (e.g. desquamative but not usual interstitial pneumonia respond well to corticosteroids)</td>
</tr>
<tr>
<td>POET-COPD</td>
<td>NEJM 2011;364:1093-103</td>
<td>Tiotropium decreases the number of moderate-to-severe exacerbations in comparison to salmeterol</td>
</tr>
<tr>
<td>REDUCE</td>
<td>JAMA 2013;309:2222-2231</td>
<td>5 d course of glucocorticoids is non-inferior to a 14 d course for treatment of acute COPD exacerbations</td>
</tr>
<tr>
<td>ROFLUMILAST</td>
<td>Lancet 2009;374:695-703</td>
<td>Phosphodiesterase-4 inhibitor improves FEV₁ when used as add-on therapy in COPD patients on tiotropium or salmeterol</td>
</tr>
<tr>
<td>TORCH</td>
<td>NEJM 2007;356:775-89</td>
<td>Combination of inhaled steroids and long-acting β₂-agonists improves COPD symptoms, reduces exacerbations, and shows a trend to lower mortality</td>
</tr>
<tr>
<td>UPLIFT</td>
<td>NEJM 2008;359:1543-54</td>
<td>Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect FEV₁ decline</td>
</tr>
</tbody>
</table>
Acronyms ............................................. 2

Anatomy of Joint Pathology .................... 2

Basics of Immunology .............................. 2
Immune Mechanisms of Disease
Immunogenetics and Disease

Differential Diagnoses of Common
Presentations .............................. 3

Synovial Fluid Analysis ................. 4

Septic Arthritis ............................ 5

Degenerative Arthritis: Osteoarthritis .... 5

Seropositive Rheumatic Disease ........... 6

Connective Tissue Disorders .............. 8
Rheumatoid Arthritis
Systemic Lupus Erythematosus
Antiphospholipid Antibody Syndrome
Scleroderma (i.e. Systemic Sclerosis)
Idiopathic Inflammatory Myopathy
Sjögren’s Syndrome
Mixed Connective Tissue Disease
Overlap Syndrome

Vasculitides ........................................... 17
Small Vessel Non-ANCA Associated Vasculitis
Small Vessel ANCA-Associated Vasculitis
Medium Vessel Vasculitis
Large Vessel Vasculitis

Seronegative Rheumatic Disease ........... 21
Ankylosing Spondylitis
Enteropathic Arthritis
Psoriatic Arthritis
Reactive Arthritis

Crystal-Induced Arthropathies....... 25
Gout
Pseudogout (Calcium Pyrophosphate
Dihydrate Disease)

Non-Articular Rheumatism ................. 27
Polymyalgia Rheumatica
Fibromyalgia

Common Medications ..................... 29

Landmark Rheumatology Trials .......... 31

References ............................................. 32
Acronyms

Ab: antibody  DEXA: dual energy X-ray absorptiometry  IE: infective endocarditis  RA: rheumatoid arthritis
ACPA: anti-citrullinated protein antibodies  DIP: distal interphalangeal joint  ILD: interstitial lung disease  RBC: red blood cell
Ag: antigen  DM: diabetes mellitus  IPT: idiopathic thrombocytopenic purpura  RIA: reactive arthritis
ANA: antinuclear antibody  DMARD: disease-modifying anti-rheumatic drug  MCP: metacarpal phalangeal joint  RF: rheumatoid factor
ANCA: antineutrophil cytoplasmic antibody  DMM: dermatomyositis  MCTD: mixed connective tissue disease  ROM: range of motion
Anti-BSPI: anti-Smith antibodies  dsDNA: double stranded DNA  MPO: myeloperoxidase  SLE: systemic lupus erythematosus
APLA: antiribonuclear protein  EACAS: enteric-coated acetylsalicylic acid  MTP: metatarsal phalangeal joint  SNRP: serotonin-noradrenaline
Anti-CCP: cyclic citrullinated peptide  ESR: erythrocyte sedimentation rate  OA: osteoarthritis  SSB: Sjögren’s syndrome
Anti-CBP: calcium channel blocker  GC: giant cell arteritis  PIP: proximal interphalangeal joint  SSA: Sjögren’s syndrome antigen A
CBC: complete blood count  GCA: granulomatosis with polyangiitis  PM: polymyositis  SSB: Sjögren’s syndrome antigen B
BUN: blood urea nitrogen  H/L: head, neck,  OA: osteoarthritis  PAN: purpura
AVN: avascular necrosis  HAMA: human anti-mouse antibody  PMN: polymorphonuclear leukocytes  PTC: purpura thrombocytopenic
AVP: avascular pupil  HLA: human leukocyte antigen  PMP: polymyalgia rheumatica  RA: rheumatoid arthritis
Rheumatology

Table 1. Mechanisms of Immune-Mediated Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathophysiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Hypersensitivity</td>
<td>Formation of IgE → release of immunologic mediators from basophils/mast cells → diffuse inflammation</td>
<td>Asthma, Allergic rhinitis, Anaphylaxis</td>
</tr>
<tr>
<td>Type I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytotoxic, Type II</td>
<td>Formation of Ab → deposit and bind to Ag on cell surface → phagocytosis or lysis of target cell</td>
<td>Autoimmune hemolytic anemia, Anti glomerular membrane disease (Goodpasture’s syndrome), Graves’ disease, pemphigus vulgaris, rheumatic fever, ITP</td>
</tr>
<tr>
<td>Immune Complex, Type III</td>
<td>Formation and deposition of Ag-Ab complexes → activate complement → leukocyte recruitment and activation → tissue injury</td>
<td>SLE, PAN, post-streptococcal glomerulonephritis, serum sickness, viral hepatitis</td>
</tr>
<tr>
<td>Cell-Mediated/Delayed Hypersensitivity, Type IV</td>
<td>Release of cytokines by sensitized T-cells and T-cell mediated cytotoxicity</td>
<td>Contact dermatitis, insect venom, mycobacterial proteins</td>
</tr>
</tbody>
</table>

Anatomy of Joint Pathology

- **Joint swelling**: effusion/synovial thickening
- **Decreased ROM**: range of motion
- **Stress pain (pain at the end of ROM)**
- **Increased warmth**

**Arthralgia**: perception of joint pain without obvious clinical findings

**Active Joint**: swollen joint, joint line tenderness, or stress pain

**Inflammatory Joint**:Joint space narrowing

**Degenerative Joint**: Cartilage destruction, joint space narrowing, osteoarthritis

**Normal Joint**: Normal synovium, joint space, articular cartilage

**Terminology in Rheumatology**

**Arthritis**:
- Joint swelling: effusion/synovial thickening
- Decreased ROM
- Stress pain (pain at the end of ROM)
- Increased warmth

**Articular**: perception of joint pain without obvious clinical findings

**Active Joint**: swollen joint, joint line tenderness, or stress pain

**Innate Immune Cells**

- **Neutrophil (PMN)**: circulate in blood and respond to inflammatory stimuli, kill invading organisms by phagocytosis, degranulation and neutrophil extracellular traps
- **Natural Killer Cell**: innate immunity against intracellular infections (especially viruses), killing function and produce cytokines
- **Macrophage**: active after PMNs, suppress PMN efflux and phagocytosis PMN debris, secrete pro-inflammatory cytokines in response to microbial debris
- **Dendritic Cell**: actively phagocytic when immature, activated by signals from toll-like receptor (TLR) release pro-inflammatory cytokines, present antigens to T cells in lymph nodes
- **Eosinophil**: respond to inflammatory cytokines and degranulate releasing reactive oxygen species, and cytokines, associated with allergy, asthma and parasitic infection
- **Basophils**: present in connective tissue and mucosa, allergen cross-linking of IgE bound to mast cell triggers degranulation and release of inflammatory mediators

**Key Cytokine Targets of Biologic Drugs**

- **TFN**: Source: T cells, macrophages
- **Major Functions**: cachexia, induces other cytokines, T cell stimulation, induces metalloproteases and prosta glandinls, increases expression of adhesion molecules, increases vascular permeability leading to increased entry of IgG, complement and cells into tissues

- **IL-6**: Source: Many cells
- **Major Functions**: proliferation of B and T cells, acute phase reactant, induces natural protease inhibitor

**Immunogenetics and Disease**

- cell surface molecules called HLAs play a role in mediating immune reactions
- MHC a-g genes on the short arm of chromosome 6 that encode HLA molecules
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases
Table 2. Classes of MHCs

<table>
<thead>
<tr>
<th>MHC Class</th>
<th>Types</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>HLA-A, B, C</td>
<td>All cells</td>
<td>Recognized by CD8+ (cytotoxic) T-lymphocytes</td>
</tr>
<tr>
<td>II</td>
<td>HLA-DP, DQ, DR</td>
<td>Ag presenting cells (mononuclear phagocytes, B cells, etc.)</td>
<td>Recognized by CD4+ (helper) T-lymphocytes</td>
</tr>
<tr>
<td>III</td>
<td>Some components of the complement cascade</td>
<td>In plasma</td>
<td>Chemotaxis, opsonization, lysis of bacteria and cells</td>
</tr>
</tbody>
</table>

Table 3. HLA-Associated Rheumatic Disease

<table>
<thead>
<tr>
<th>HLA Type</th>
<th>Associated Conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27</td>
<td>Ankylosing Spondylitis (AS) Reactive Arthritis (ReA) Enteropathic arthritis (EA)</td>
<td>Relative risk 20x for developing AS and ReA</td>
</tr>
<tr>
<td>DR4, DR1</td>
<td>Rheumatoid Arthritis (RA)</td>
<td>In RA, relative risk = 2-10x; found in 93% of patients</td>
</tr>
<tr>
<td>DR3</td>
<td>Sjögren’s syndrome (SS) Systemic Lupus Erythematosus (SLE)</td>
<td>DR3 is associated with the production of anti-Ro/SSA and anti-La/SSB antibodies</td>
</tr>
</tbody>
</table>

Differential Diagnoses of Common Presentations

Figure 2. Clinical approach to joint pain

Table 4. Differential Diagnosis of Monoarthritis

<table>
<thead>
<tr>
<th>ACUTE MONOAORTHRITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Inflammatory</strong></td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Crystal induced</td>
</tr>
<tr>
<td>Monosodium urate (MSU-gout)</td>
</tr>
<tr>
<td>Calcium pyrophosphate</td>
</tr>
<tr>
<td>dehydrate (CPPD) or pseudogout</td>
</tr>
<tr>
<td>Hydroxyapatite (HA)</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
</tr>
<tr>
<td>Gout</td>
</tr>
<tr>
<td>Pseudogout</td>
</tr>
<tr>
<td>Hydroxyapatite</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
</tr>
<tr>
<td>S. aureus, GC</td>
</tr>
<tr>
<td><strong>Hemorrhagic</strong></td>
</tr>
<tr>
<td>Trauma, fracture,</td>
</tr>
<tr>
<td>blood dyscrasias and</td>
</tr>
<tr>
<td>anticoagulants</td>
</tr>
<tr>
<td>Congenital cloting</td>
</tr>
<tr>
<td>disorders e.g. hemophilia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHRONIC MONOAORTHRITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Inflammatory</strong></td>
</tr>
<tr>
<td>OA and osteonecrosis</td>
</tr>
<tr>
<td>Seropositive and seronegative</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
</tr>
<tr>
<td>TB and fungi</td>
</tr>
<tr>
<td><strong>Hemorrhagic</strong></td>
</tr>
<tr>
<td>Tumour</td>
</tr>
</tbody>
</table>

Table 5. Differential Diagnosis of Oligoarthritis/Polyarthritis

<table>
<thead>
<tr>
<th>ACUTE (&lt;6 wk)</th>
<th>CHRONIC (&gt;6 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-viral infection (parvovirus B19, HIV)</td>
<td>Seropositive inflammatory arthritis</td>
</tr>
<tr>
<td>Post bacterial Infection (GC and non-GC, rheumatic fever)</td>
<td>Seronegative inflammatory arthritis</td>
</tr>
<tr>
<td>Crystal induced Other (sarcoidosis lyme disease)</td>
<td>Degenerative OA</td>
</tr>
<tr>
<td>RA</td>
<td>AS</td>
</tr>
<tr>
<td>SLE</td>
<td>EA</td>
</tr>
<tr>
<td>DMM/PM</td>
<td>PsA</td>
</tr>
<tr>
<td>ReA</td>
<td>Crystal (polyarticular gout)</td>
</tr>
</tbody>
</table>
Synovial Fluid Analysis

- Synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage.

**Indications**
- Diagnostic tests advised if crystal arthritis or hemoarthritis is suspected or if there is unexplained joint, bursa or tendon sheath swelling.
- Therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection.

**Contraindications**
- Absolute: open lesion or suspected infection of overlying skin or soft tissue.
- Relative: bleeding diathesis, thrombocytopenia, prosthetic joint.

### Table 6. Symptoms of Inflammatory Arthritis vs. Degenerative Arthritis

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Degenerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at rest, relieved by motion</td>
<td>Pain with motion, relieved by rest</td>
</tr>
<tr>
<td>Morning stiffness &gt; 1 h</td>
<td>Morning stiffness &lt; 1/2 h</td>
</tr>
<tr>
<td>Warmth, swelling, erythema</td>
<td>Joint instability, buckling, locking</td>
</tr>
<tr>
<td>Malalignment/deformity</td>
<td>Bone enlargement, malalignment/deformity</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td>Evening pain</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7. Seropositive vs. Seronegative Rheumatic Diseases

<table>
<thead>
<tr>
<th></th>
<th>Seropositive</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>F &gt; M</td>
<td>M &gt; F</td>
</tr>
<tr>
<td><strong>Peripheral Arthritis</strong></td>
<td>Symmetrical</td>
<td>Usually asymmetrical</td>
</tr>
<tr>
<td></td>
<td>Small (PIP, MCP) and medium joints (wrist, knee, ankle, elbow) common</td>
<td>Usually larger joints, lower extremities (exception: PsA)</td>
</tr>
<tr>
<td></td>
<td>DIP less often involved</td>
<td>DIP in PsA</td>
</tr>
<tr>
<td><strong>Pelvic/Axial Disease</strong></td>
<td>No (except for C-spine)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Enthesitis</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Extra Articular</strong></td>
<td>Nodules</td>
<td>Iritis (anterior uveitis)</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
<td>Oral ulcers</td>
</tr>
<tr>
<td></td>
<td>Sica</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>Raynaud’s phenomenon</td>
<td>Dermatologic features</td>
</tr>
<tr>
<td></td>
<td>Rashes, internal organ involvement (lung, cardiac)</td>
<td>Genitourinary inflammation</td>
</tr>
</tbody>
</table>

### Table 8. Seropositive vs. Seronegative Rheumatic Diseases

<table>
<thead>
<tr>
<th><strong>Parameter</strong></th>
<th><strong>Seropositive</strong></th>
<th><strong>Seronegative</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colour</strong></td>
<td>Pale yellow</td>
<td>Pale yellow</td>
</tr>
<tr>
<td><strong>Clarity</strong></td>
<td>Clear</td>
<td>Opaque</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>High (due to hyaluronic acid)</td>
<td>High</td>
</tr>
<tr>
<td><strong>WBC/mm³</strong></td>
<td>&lt; 200</td>
<td>&lt; 2,000</td>
</tr>
<tr>
<td><strong>% PMN</strong></td>
<td>&lt; 25%</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td><strong>Culture/Gram Stain</strong></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Trauma OA, Neuropathy, Hypertrophic arthritis</td>
<td>Seropositive Seronegative Crystal arthropathies, S. aureus Gram negative GC → difficult to culture</td>
</tr>
</tbody>
</table>

**Synovial Fluid Analysis**

- Synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage.

**Indications**
- Diagnostic tests advised if crystal arthritis or hemoarthritis is suspected or if there is unexplained joint, bursa or tendon sheath swelling.
- Therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection.

**Contraindications**
- Absolute: open lesion or suspected infection of overlying skin or soft tissue.
- Relative: bleeding diathesis, thrombocytopenia, prosthetic joint.

**Synovial Fluid Analysis**

- Most important to assess the 3Cs: culture and gram stain, cell count (WBC) and differential, and crystal analysis.
- Other parameters to consider are listed in Table 8.

### Table 8. Synovial Fluid Analysis

<table>
<thead>
<tr>
<th><strong>Parameter</strong></th>
<th><strong>Normal</strong></th>
<th><strong>Non-Inflammatory</strong></th>
<th><strong>Inflammatory</strong></th>
<th><strong>Infectious</strong></th>
<th><strong>Hemorrhagic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colour</strong></td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Yellow to white</td>
<td>Red/brown</td>
</tr>
<tr>
<td><strong>Clarity</strong></td>
<td>Clear</td>
<td>Clear</td>
<td>Opaque</td>
<td>Opaque</td>
<td>Sanguinous</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>High (due to hyaluronic acid)</td>
<td>High</td>
<td>Low</td>
<td>Low or paradoxically high if purulent</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>WBC/mm³</strong></td>
<td>&lt; 200</td>
<td>&lt; 2,000</td>
<td>≥ 2,000</td>
<td>Higher cell counts (particularly &gt; 50,000) suggestive</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>% PMN</strong></td>
<td>&lt; 25%</td>
<td>&lt; 25%</td>
<td>≥ 25%</td>
<td>&gt; 75%</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Culture/Gram Stain</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Usually positive</td>
<td>–</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Trauma OA, Neuropathy, Hypertrophic arthritis</td>
<td>Seropositive Seronegative Crystal arthropathies, S. aureus Gram negative GC → difficult to culture</td>
<td>Trauma</td>
<td>Hemophilia</td>
<td></td>
</tr>
</tbody>
</table>

**Choosing Wisely Canada Recommendations**

1. Do not order ANA as a screening test in patients without specific signs or symptoms of SLE or another CTD.
2. Do not order an HLA-B27 unless spondyloarthritis is suspected based on specific signs or symptoms.
3. Do not repeat DEXA scans more often than every 2 years.
4. Do not prescribe bisphosphonates for patients at low risk of fracture.
5. Do not perform whole body bone scans (e.g. scintigraphy) for diagnostic screening for peripheral and axial arthritis in the adult population.
Septic Arthritis

- Septic arthritis is a medical emergency because it can lead to rapid joint destruction and has a 10-15% risk of mortality.
- Knee and hip are most commonly affected joints.
- Most commonly caused by hematogenous spread of bacterial infection (gram positive cocci > gram negative bacilli).
- Risk factors: very young, portal of entry, recent infection.
- Poor prognostic factors: older age, immunocompromised, delay in treatment, previously damaged joint, joint prosthesis.
- Consider empiric antibiotic therapy until septic arthritis is excluded from history, physical examination and synovial fluid analysis.

- See Infectious Diseases, Gonococcal Arthritis ID14 and Orthopedics, Spetic Joint OR10.

Degenerative Arthritis: Osteoarthritis

- See Family Medicine, FM40

Definition
- Progressive deterioration of articular cartilage and surrounding joint structures caused by genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation.

Classification (Based on Etiology)
- Primary (idiopathic)
  - Most common, unknown etiology.
- Secondary
  - Post-traumatic or mechanical
  - Post-inflammatory (e.g. RA) or post-infectious
  - Heritable skeletal disorders (e.g. scoliosis)
  - Endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
  - Metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
  - Neuropathic (e.g. Charcot joints)
    - Atypical joint trauma due to peripheral neuropathy (e.g. diabetes mellitus, syphilis)
  - Avascular necrosis (AVN)
  - Other (e.g. congenital malformation).

Pathophysiology
- The process appears to be initiated by abnormalities in biomechanical forces and/or, less often, in cartilage.
- Elevated production of pro-inflammatory cytokines is important in OA progression.
- Tissue catabolism > repair.
- Contributing factors (mechanisms unknown): genetics, alignment (bow-legged, knock-kneed), joint deformity (hip dysplasia), joint injury (meniscal or ligament tears), obesity, environmental, mechanical loading, age and gender.
- Now considered to be a systemic musculoskeletal disorder rather than a focal disorder of synovial joints.

Epidemiology
- Most common arthropathy (accounts for ~75% of all arthritis).
- Increased prevalence with increasing age (35% of 30 yr olds, 85% of 80 yr olds).

Risk Factors
- Genetic predisposition, advanced age, obesity (for knee and hand OA), female, trauma.

Signs and Symptoms
- Localized to affected joints (not a systemic disease).
- Pain is often insidious, gradually progressive, with intermittent flares and remissions; neuropathic pain may also be present.
- Fatigue, poor sleep, impact on mood (depression, anxiety).

Table 9. Signs and Symptoms of OA

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint line tenderness; stress pain ± joint effusion</td>
<td>Joint pain with motion; relieved with rest</td>
</tr>
<tr>
<td>Bony enlargement at affected joints</td>
<td>Short duration of stiffness (&lt;1/2 h) after immobility</td>
</tr>
<tr>
<td>Malalignment/deformity (angulation)</td>
<td>Joint instability/buckling</td>
</tr>
<tr>
<td>Limited ROM</td>
<td>Joint locking due to “joint mouse” (bone or cartilage fragment)</td>
</tr>
<tr>
<td>Crepitus on passive ROM</td>
<td>Loss of function or other internal derangements (e.g. meniscal tear)</td>
</tr>
<tr>
<td>Inflammation (mild if present)</td>
<td>Peniarticular muscle atrophy</td>
</tr>
</tbody>
</table>

ESR can also be elevated in anemia, end-stage renal disease, females, increased age, and obesity.

Figure 3. Common sites of joint involvement in OA

1. Thumb squaring
2. Heberden's nodes
3. Bouchard's nodes

Figure 4. Hand findings in OA
Joint Involvement
- generalized osteoarthritis: 3+ joint groups
- asymmetric (knees usually affected bilaterally)
- hand
  - DIP (Heberden’s nodes = osteophytes → enlargement of joints)
  - PIP (Bouchard’s nodes)
  - CMC (usually thumb squaring)
  - 1st MCP (other MCPs are usually spared)
- hip
  - usually presents as groin pain ± dull or sharp pain in the trochanteric area, internal rotation and abduction are lost first
  - pain can radiate to the anterior thigh, but generally does not go below the knee
- knee
  - initial narrowing of one compartment, medial > lateral; seen on standing x-rays, often patellar-femoral joint involved
- foot
  - common in first MTP and midfoot
- lumbar spine
  - very common, especially L4-L5, L5-S1
  - degeneration of intervertebral discs and facet joints
  - reactive bone growth can contribute to neurological impingement (e.g. sciatica, neurogenic claudication) or spondylolisthesis (forward or backward movement of one vertebra over another)
- cervical spine
  - commonly presents with neck pain that radiates to scapula, especially in mid-lower cervical area (C5 and C6)

Investigations
- blood work
  - normal CBC and ESR, CRP
  - negative RF and ANA
- radiology: 4 hallmark findings, see sidebar
- synovial fluid: non-inflammatory (see Table 8)

Treatment
- presently no treatment alters the natural history of OA
- prevention: prevent sports injury, healthy weight management
- non-pharmacological therapy
  - weight loss (minimum 5-10 lb loss) if overweight
  - physiotherapy: heat/cold, low impact exercise programs
  - occupational therapy: aids, splints, cane, walker, bracing
- pharmacological therapy (see Table 33)
  - 1st line- oral: acetaminophen/NSAIDs
  - treat neuropathic pain if present (anti-depressants, anti-epileptics, etc.)
  - joint injections: corticosteroid (effective for short-term treatment), hyaluronic acid (evidence of long-term benefits)
  - topical: capsaicin, NSAIDs
  - glucosamine ± chondroitin (efficacy not well supported)
- surgical treatment
  - joint debridement, osteotomy, total and/or partial joint replacement, fusion (see Orthopedics, OR6)
<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Disease</th>
<th>Healthy Controls</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>RA 80%</td>
<td>&lt;5%</td>
<td>Autoantibodies directed against Fc domain of IgG</td>
</tr>
<tr>
<td></td>
<td>SS 50%</td>
<td>10-20%</td>
<td>Sensitive in RA (can be negative early in disease course), levels correlate with disease activity</td>
</tr>
<tr>
<td></td>
<td>SLE 20%</td>
<td>&gt; 65</td>
<td>Present in most seropositive diseases</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>RA 80%</td>
<td></td>
<td>Specific for RA (94-98%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May be useful in early disease and to predict aggressive disease</td>
</tr>
<tr>
<td>ANA</td>
<td>SLE 98%</td>
<td>High titer &lt;5%</td>
<td>Ab against nuclear components (DNA, RNA, histones, centromere)</td>
</tr>
<tr>
<td></td>
<td>MCTD 100%</td>
<td>Low titer Up to 30%</td>
<td>Sensitive but not specific for SLE</td>
</tr>
<tr>
<td></td>
<td>SS 40-70%</td>
<td>Often seen in other CTDs</td>
<td>Given high false positive rate - only measure when high pre-test probability of CTD</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>SLE 50-70%</td>
<td>0%</td>
<td>Specific for SLE (95%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Levels correlate with disease activity (i.e. SLE flare)</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>SLE &lt;30%</td>
<td>0%</td>
<td>Specific but not sensitive for SLE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Does not correlate with SLE disease activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If positive, will remain positive through disease course</td>
</tr>
<tr>
<td>Anti Ro (SSA)</td>
<td>SS 40-95%</td>
<td>0.5%</td>
<td>Subacute cutaneous SLE (74%)</td>
</tr>
<tr>
<td></td>
<td>SSc 21%</td>
<td></td>
<td>May be only Ab present in ANA negative SLE</td>
</tr>
<tr>
<td></td>
<td>SLE 32%</td>
<td></td>
<td>Increases risk of having child with neonatal lupus syndrome</td>
</tr>
<tr>
<td>Anti-La (SSB)</td>
<td>SS 40%</td>
<td>0%</td>
<td>Usually occurs with anti-Ro</td>
</tr>
<tr>
<td></td>
<td>SLE 10%</td>
<td></td>
<td>Specific for SS and SLE when anti-Ro is also positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increases risk of having child with neonatal lupus syndrome</td>
</tr>
<tr>
<td>Antiphospholipid Ab (LAC, aCL, aB2GP)</td>
<td>APLS 100%</td>
<td>&lt;5%</td>
<td>By definition present in APLS</td>
</tr>
<tr>
<td></td>
<td>SLE 31-40%</td>
<td></td>
<td>Only small subset of SLE patients develop clinical syndrome of APLA</td>
</tr>
<tr>
<td>Anti-Histone</td>
<td>Drug-induced SLE 95%</td>
<td>0%</td>
<td>Highly specific for drug-induced SLE</td>
</tr>
<tr>
<td></td>
<td>SLE 30-90%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>MCTD</td>
<td></td>
<td>High titres present in MCTD; present in many other CTD</td>
</tr>
<tr>
<td></td>
<td>SLE</td>
<td></td>
<td>(especially SLE)</td>
</tr>
<tr>
<td>Anti-Centromere</td>
<td>CREST &gt;80%</td>
<td>0%</td>
<td>Specific for CREST, cutaneous variant of systemic sclerosis</td>
</tr>
<tr>
<td>Anti-Topoisomerase I (formerly Scl-70)</td>
<td>Diffuse SSc 26-76%</td>
<td>0%</td>
<td>Specific for SSc Increased risk pulmonary fibrosis in SSc</td>
</tr>
<tr>
<td>Anti-Jo1</td>
<td>PM DMM</td>
<td>0%</td>
<td>Less frequent for DMM</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>Active GPA &gt; 80%</td>
<td>0%</td>
<td>Specific and sensitive</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>GPA 0%</td>
<td>Other vasculitits</td>
<td>Nonspecific and poor sensitivity (found in ulcerative colitis, PAN, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis)</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>DMM 15-20%</td>
<td>0%</td>
<td>Specific but not sensitive (not available in all centres)</td>
</tr>
<tr>
<td>Anti-Topoisomerase I (formerly Scl 70)</td>
<td>Diffuse SSc 26-76%</td>
<td>0%</td>
<td>Specific for SSc Increased risk pulmonary fibrosis in SSc</td>
</tr>
<tr>
<td>Anti Jo1</td>
<td>PM DMM</td>
<td>0%</td>
<td>Less frequent for DMM</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>Active GPA &gt; 80%</td>
<td>0%</td>
<td>Specific and sensitive</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>GPA 10%</td>
<td>Other vasculitits</td>
<td>Nonspecific and poor sensitivity (found in ulcerative colitis, PAN, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis)</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>DMM 15-20%</td>
<td>0%</td>
<td>Specific but not sensitive (not available in all centres)</td>
</tr>
<tr>
<td>Ab Against RBCs, WBCs, or Platelets</td>
<td>SLE</td>
<td>Perform direct antiglobulin tests (DAT) Test Hb, reticulocyte, leukocyte and platelet count, antiplatelet Abs</td>
<td></td>
</tr>
<tr>
<td>Anti-mitochondria</td>
<td>Primary biliary cholangitis</td>
<td>0%</td>
<td>Sensitive and specific</td>
</tr>
</tbody>
</table>

Note: some individuals in the normal population test positive for RF and/or ANA, but do not have the conditions listed above.
# Connective Tissue Disorders

## Table 11. Features of Seropositive Arthropathies

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>SLE</th>
<th>Scleroderma</th>
<th>Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Symmetrical polyarthritis (small joint involvement) Morning stiffness (&gt;1 h)</td>
<td>Multisystemic disease: rash, photosensitivity, Raynaud’s, alopecia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis</td>
<td>Skin tightness, stiffness of fingers, Raynaud’s, heartburn, dysphagia, pulmonary HTN, renal crisis with new onset HTN or hypertensive urgency/emergency dyspnea on exertion</td>
<td>HELIOTROPE RASH (PERIORBITAL), GOTTRON’S PAPULES (VIOLACEOUS PAPULES OVER KNUCKLES AND IP JOINTS) ± POIKILODERMA SHAWL SIGN: MACULAR RHYTHMA OVER CHEST AND SHOULDER PROXIMAL MUSCLE WEAKNESS ± PAIN DYSPEEUA ON EXERTION</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td>Effused joints Tenosynovitis Subcutaneous nodules Joint deformities Bone-on-bone crepitus in advanced disease</td>
<td>Confirm historical findings (rash, serositis, renal, CVS, etc.) ± effused (typically small) joints (can be minimal, look for soft tissue swelling)</td>
<td>Skin tightness on dorsum of hand, facial skin tightening, telangiectasia, calcinosis, non-effused joint, inspiratory crackles</td>
<td>RASH, PROXIMAL MUSCLE WEAKNESS, INSPIRATORY CRACKLES</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td>↑ ESR in 50-60% ↑ Platelets ↓ Hb</td>
<td>↑ ESR ↓ Platelets (autoimmune) ↓ Hb (autoimmune) ↓ WBC (leukopenia, lymphopenia)</td>
<td>↑ ESR ↓ Hb Normal WBC</td>
<td>Possible increased ESR ↓ Hb Normal WBC</td>
</tr>
<tr>
<td><strong>Non-Specific</strong></td>
<td>RF +ve in ~80% Anti-CCP +ve in ~80%</td>
<td>ANA +ve in 98% Anti-dsDNA +ve in 50-70% Anti-SM +ve in 30% ↓ C3, C4, total hemolytic complement False positive VDRL (in SLE subtypes) ↓ PTT (in SLE subtypes, e.g. APLA)</td>
<td>ANA +ve in &gt;90% Anti-topoisomerase 1 (diffuse) Anti-centromere (usually in CREST see RH13)</td>
<td>CX elevated in 80% ANA +ve in 33% Anti-Jo-1, anti-Mi-2 Muscle biopsy EMG MRI</td>
</tr>
<tr>
<td><strong>Specific</strong></td>
<td>Periarticular osteopenia Joint space narrowing Erosions Absence of bone repair Symmetric/concentric</td>
<td>Non-erosive ± Osteopenia ± Soft tissue swelling</td>
<td>± Pulmonary fibrosis ± Esophageal dysmotility ± Calcification ± ILD</td>
<td>± Esophageal dysmotility ± ILD ± Calcifications</td>
</tr>
</tbody>
</table>

## Rheumatoid Arthritis

### Definition
- chronic, symmetric, erosive synovitis of peripheral joints (e.g. wrists, MCPs, MTPs)
- characterized by a number of extra-articular features

### Table 12. 2010 ACR/EULAR Classification Criteria for RA

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Joint involvement (swollen or tender)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 large joint (shoulders, elbows, hips, knees, and ankles)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4-10 small joints</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2. Serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative Anti-CCP</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low-positive RF or low-positive Anti-CCP (&lt;3x ULN)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>High-positive RF or high-positive Anti CCP (&gt;3x ULN)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Total score of ≥6: definite RA</strong></td>
<td></td>
<td>Must have ≥1 joint with definite clinical swelling, not better explained by other disease</td>
</tr>
<tr>
<td>3. Acute phase reactants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abnormal CRP and abnormal ESR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4. Duration of symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 wk</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥6 wk</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

RA is an independent risk factor for atherosclerosis and CV disease. RA is associated with increased overall mortality/morbidity from all causes: CV disease, neoplasm (especially lymphoma), infection

Common Presentation
- Morning stiffness >1 h, improves with use
- Symmetric joint involvement
- Initially involves small joints of hands and feet
- Constitutional symptoms
Pathophysiology
- autoimmune disorder, unknown etiology
- complex interaction of genes and environment leading to breakdown of immune tolerance; many pathways result in autoreactivity leading to a final common pathway to synovial inflammation
  - genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type), cytokine promoters, T cell signaling
  - induction of enzymes that convert arginine to citrulline caused by environmental stress (cigarette smoking)
  - RA: propensity for immune reactivity to neoepitopes created by protein citrullination and production of anti-citrullinated protein antibodies
- once inflammatory process is established, synovium organizes itself into an invasive tissue that degrades cartilage and bone
- progressive bone destruction with absence of bone repair in response to inflammation
  - elevated TNF level increases osteoclasts and decreases osteoblasts at the site of inflammation
  - upregulation of RANK ligand increases osteoclast-mediated destruction

Epidemiology
- most common inflammatory arthritis: prevalent in 1% of population
- F:M = 3:1
- age of onset 20-40 yr

Signs and Symptoms
- variable course of exacerbations and remissions
- morning stiffness >1 h, improves with use, worsens with rest
- polyarthritis: symmetric joint involvement (tender, swollen), small joints affected, most commonly in hands and feet (MCP, PIP, MTP)
- extra-articular (systemic) symptoms: profound fatigue, depression, myalgia, weight loss
- limitation of function and decrease in global functional status
- complications of chronic synovitis
  - signs of mechanical joint damage: loss of motion, instability, deformity, crepitus, joint deformities
    - swan neck deformity boutonnière deformity
    - ulnar deviation of MCP, radial deviation of wrist joint
    - hammer toe, mallet toe, claw toe
    - flexion contractures
    - atlanto-axial and subaxial subluxation
    - C-spine instability
    - neurological impingement (long tract signs)
      difficult/dangerous intubation: risk of worsening subluxation and damage to spinal cord
- limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
- tenosynovitis may cause rupture of tendons
- carpal tunnel syndrome
- ruptured Baker’s cyst (outpouching of synovium behind the knee); presentation similar to acute DVT
- poor prognostic factors include: young age of onset, high RF titer, elevated ESR, activity of >20 joints, and presence of extra-articular features

Table 13. Extra-Articular Features of RA Classified by Underlying Pathophysiology

<table>
<thead>
<tr>
<th>System</th>
<th>Vasculitic</th>
<th>Lymphocytic Infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Peniturnal infarction, cutaneous ulcers, palpable purpura</td>
<td>Rheumatoid nodules (may have vasculitic component)</td>
</tr>
<tr>
<td>Ocular</td>
<td>Episcleritis, scleritis</td>
<td>Keratoconjunctivitis sicca</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Xerostomia, Hashimoto’s thyroiditis (see Endocrinology, E27)</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>Peri-/myocarditis, valvular disease, conduction defects</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary fibrosis, pleural effusion, pleuritis, pulmonary nodules</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Peripheral neuropathy: sensory stocking glove, mononeuritis multiplex</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Splenomegaly, neutropenia (Felty’s syndrome)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Amyloidosis – caused by accumulation of abnormal proteins</td>
<td></td>
</tr>
</tbody>
</table>

Classification of Global Functional Status in RA
- Class I: able to perform usual ADLs (self-care, vocational, avocational)
- Class II: able to perform self-care and vocational activities, restriction of avocational activities
- Class III: able to perform self-care, restriction of vocational and avocational activities
- Class IV: limited ability to perform self-care, vocational, and avocational activities
Investigations
- blood work
  - RF: 80% sensitivity but non-specific; may not be present at onset of symptoms; levels DO NOT correlate with disease activity
  - can be associated with more erosions, more extra-articular manifestations, and worse function
  - anti-CCP: 80% sensitivity but more specific (94-98%); may precede onset of symptoms
- increased disease activity is associated with decreased Hb (anemia of chronic disease), increased platelets, ESR, CRP, and RF
- imaging
  - x-rays may be normal at onset
  - first change is periarticular osteopenia, followed by erosions
  - U/S (with power doppler) MRI may be used to image hands to detect early synovitis and erosions
    - MRI T1 inflamed synovium is hypointense and hyperintense on T1; bone marrow edema can be seen as well as areas of increased uptake gadolinium contrast

Treatment
- goals of therapy: remission or lowest possible disease activity
  - key is early diagnosis and early intervention with DMARDs
  - “window of opportunity” = early treatment within first 3 mo of disease may allow better control/remission
  - assess poor prognostic factors at baseline (RF positive, functional limitations and extra-articular features)
- behavioural
  - exercise program (isometrics and active, gentle ROM exercise during flares, aquatic/aerobic/strengthening exercise between flares), assistive devices as needed
  - job modification may be necessary
- pharmacologic: alter disease progression
  - only DMARDs and biologics (not analgesics or NSAIDs) can alter the course of RA
  - DMARDs
    - methotrexate (MTX) is the gold standard and is first-line unless contraindicated
      - chest X-ray should be assessed prior to MTX therapy
      - if inadequate response (3-6 mo) → combine or switch
      - consider including add-on medications to MTX if patients have poor prognostic features or high disease activity
      - add-ons include: hydroxychloroquine, sulfasalazine, leflunomide
  - biologics
    - should be combined with DMARD therapy (initiating with combination therapy is associated with faster response rates) or used if inadequate response to DMARDs
    - first-line (anti-TNF) options: infliximab, etanercept, adalimumab, golimumab and certolizumab
    - non-anti-TNF agents include anakinra, abatacept, rituximab and tocilizumab
  - reassess every 3-6 mo and monitor disease severity
- pharmacologic: reduce inflammation and pain
  - NSAIDs
    - individualize according to efficacy and tolerability
    - contraindicated/cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy)
  - add acetaminophen ± opioid prn for synergistic pain control
- corticosteroids
  - local: injections to control symptoms in a specific joint
  - systemic (prenisone)
    - low dose (5-10 mg/d) useful for short-term to improve symptoms if NSAIDs are ineffective to bridge gap until DMARDs take effect
    - severe RA: add low dose prednisone to DMARDs
  - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy if using corticosteroids >3 mo at 7.5 mg/d
  - cautions/contraindications: active infection, TB, osteoporosis, HTN, gastric ulcer, DM
  - surgical
    - indicated for structural joint damage
- surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair

Follow-Up Management and Clinical Outcomes
- follow-up every 3-6 mo, then 6-12 mo after inflammation has been suppressed
- examine joints for active inflammation – if active, consider adjusting medications, PT/OT
- if assessment reveals joint damage – consider analgesia, referral to PT/OT, surgical options
- outcome depends on disease activity, joint damage, physical functional status, psychological health, and comorbidities
- functional capacity is a useful tool for determining therapeutic effectiveness; many tools for evaluation have been validated
- patients with RA have an increased prevalence of other serious illnesses: infection (e.g. pulmonary, skin, joint), renal impairment, lymphoproliferative disorders, cardiovascular disease (correlates with disease activity and duration)
- increased risk of premature mortality, decreased life expectancy (most mortality not directly caused by RA)
Systemic Lupus Erythematosus

- see Nephrology, NP24

Definition
- chronic inflammatory multi-system disease of unknown etiology
- characterized by production of autoantibodies and diverse clinical manifestations

Table 14. Diagnostic Criteria of SLE*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>Classic “butterfly rash”, sparing of nasolabial folds, no scarring</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>May cause scarring due to invasion of basement membrane</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash in reaction to sunlight</td>
</tr>
<tr>
<td>Oral/nasal ulcers</td>
<td>Usually painless</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Symmetric, involving ≥2 small or large peripheral joints, non-erosive</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis or pericarditis</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Proteinuria (&gt;0.5 g/d or 3+)</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Anti-dsDNA or anti-Sm or antiphospholipid Ab (anticardiolipin Ab SLE anticoagulant) or false positive VDRL with 6 mo confirmatory negative</td>
</tr>
<tr>
<td>ANA</td>
<td>Most sensitive test (98%), not specific</td>
</tr>
</tbody>
</table>

*Note: “4, 7, 11” rule → 4 (o more) out of 11 criteria (4 lab, 7 clinical) must be present, serially or simultaneously, for diagnosis
American College of Rheumatology, 1997 update

Etiology and Pathophysiology
- production of cytotoxic autoantibodies and immune complex formation
- multi-factorial etiology

- genetics
  - common association with HLA-B8/DR3; ~10% have positive family history
  - strong association with defects in apoptotic clearance → fragments of nuclear particles captured by antigen-presenting cells → develop anti-nuclear antibodies
  - cytokines involved in inflammatory process and tissue injury: B-lymphocyte stimulator (BlyS), IL-6, IL-17, IL-18, TNF-α

- environment
  - UV radiation, cigarette smoking, infection, vitamin D deficiency
  - estrogen
    - increased incidence after puberty, decreased incidence after menopause
    - men with SLE have higher concentration of estrogenic metabolites

- infection
  - viral (non-specific stimulant of immune response)

- drug-induced
  - anti-hypertensives (hydralazine), anti-convulsants (phenytoin), anti-arrhythmics (procanamide), isoniazid, biologics, oral contraceptive pills
  - anti-histone Abs are commonly seen in drug-induced SLE
  - symptoms resolve with discontinuation of offending drug

Epidemiology
- prevalence: 0.05% overall
- F:M = 10:1
- age of onset in reproductive yr (13–40)
- more common and severe in African-Americans and Asians
- bimodal mortality pattern
  - early (within 2 yr)
    - active SLE, active nephritis, infection secondary to steroid use
  - late (>10 yr)
    - inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation

Signs and Symptoms
- characterized by periods of exacerbation and remission
Table 15. Signs and Symptoms of SLE

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Fatigue, malaise, weight loss, fever, lymphadenopathy</td>
</tr>
<tr>
<td>Renal</td>
<td>HTN, peripheral edema, glomerulonephritis, renal failure</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura, panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Polyarthalgias, polyarthritis, myalgias, AVN; reducible deformities of hand = Jaccoud’s arthritis</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Keratoconjunctivitis sicca, episceratitis, scleritis, cytoid bodies (cotton wool exudates on fundoscopy = infarction of nerve cell layer of retina)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Pericarditis, CAD, non-bacterial endocarditis (Libman-Sachs), myocarditis</td>
</tr>
<tr>
<td>Note: SLE is an independent risk factor for atherosclerosis and CAD</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Raynaud’s phenomenon, livedo reticularis (mottled discoloration of skin due to narrowing of blood vessels, characteristic lacy or net-like appearance), thrombosis, vasculitis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pleuritis, I LD, pulmonary HTN, PE, alveolar hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Pancreatitis, SLE enteropathy, hepatitis, hepatomegaly, splenomegaly</td>
</tr>
<tr>
<td>Neurologic/Psychiatric</td>
<td>H/A, depression, psychosis, seizures, cerebritis, transverse myelitis, peripheral neuropathy, stroke</td>
</tr>
<tr>
<td>Life/Organ-Threatening</td>
<td>Cardiac: coronary vasculitis, malignant HTN, tamponade</td>
</tr>
<tr>
<td></td>
<td>Hematologic: hemolytic anemia, neutropenia, thrombocytopepy, TTP, thrombosis</td>
</tr>
<tr>
<td></td>
<td>Neurologic: seizures, CVA, stroke</td>
</tr>
<tr>
<td></td>
<td>Respiratory: pulmonary hypertension, pulmonary hemorrhage, emboli</td>
</tr>
</tbody>
</table>

Investigations
- ANA (98% sensitivity, but poor specificity → used as a screening test; ANA titres are not useful to follow disease course)
- anti-dsDNA and anti-Sm are specific (95-99%)
- anti-dsDNA titre and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant (anti-dsDNA, C3, and C4 also fluctuate with disease activity)
- antiphospholipid Ab (anti-cardiolipin Ab, SLE anticoagulant, An i-β2 glycoprotein-I Ab), may cause increased risk of clotting and increased aPTT

Treatment
- goals of therapy
  - treat early and avoid long-term steroid use, if unavoidable see Endocrinology, E40 for osteoporosis management
  - if high doses of steroids necessary for long term control, add steroid-sparing agents and taper when possible
  - treatment is tailored to organ system involved and severity of disease
  - all medications used to treat SLE require periodic monitoring for potential toxicity
- dermatologic
  - sunscreen, avoid UV light and estrogens
  - topical steroids, hydroxychloroquine
- musculoskeletal
  - NSAIDs ± gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
  - hydroxychloroquine improves long-term control and prevents flares
  - bisphosphonates, calcium, vitamin D to combat osteoporosis
- organ-threatening disease
  - high-dose oral prednisone or IV methylprednisolone in severe disease
  - steroid-sparing agents: azathioprine, MTX, mycophenolate mofetil
  - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or lupus nephritis) see Nephrology, Systemic Lupus Erythematosus NP24 for clinical features of lupus nephritis

Antiphospholipid Antibody Syndrome

Definition
- multi-system vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions, and thrombocytopenia
- often presents with migraine type H/As
- circulating antiphospholipid autoantibodies interfere with coagulation
- **primary APLS**: occurs in the absence of other disease
- **secondary APLS**: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- **catastrophic APLS**: development within 1 wk of small vessel thrombotic occlusion in ≥3 organ systems with positive antiphospholipid Ab (high mortality)
Table 16. Classification Criteria of APLS*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
</tr>
<tr>
<td>Vascular thrombosis</td>
<td>Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia Venous: DVT, PE, renal and retinal vein thrombosis Must be confirmed by imaging or histopathology</td>
</tr>
<tr>
<td>Pregnancy morbidity</td>
<td>Fetal death (&gt;10 wk GA), recurrent spontaneous abortions (&lt;10 wk GA) or premature birth (&lt;34 wk GA)</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
</tr>
<tr>
<td>SLE anticoagulant</td>
<td>Prolonged aPTT not corrected by the addition of normal plasma</td>
</tr>
<tr>
<td>Anti-cardiolipin Ab IgG</td>
<td>IgG and/or IgM</td>
</tr>
<tr>
<td>Anti-beta 2 glycoprotein-I Ab IgG and/or IgM</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>Most sensitive test (88%), not specific</td>
</tr>
</tbody>
</table>

* 1 clinical and 1 laboratory criteria must be present  

Signs and Symptoms
- see clinical criteria in Table 16
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud’s phenomenon, purpura, leg ulcers, and gangrene

Treatment
- thrombosis
  - lifelong anti-coagulation with warfarin  
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent and/or arterial event
- recurrent fetal loss
  - heparin/low molecular weight heparin ± ASA during pregnancy
- catastrophic APLA
  - high-dose steroids, anti-coagulation, cyclophosphamide, plasmapheresis

Scleroderma (i.e. Systemic Sclerosis)

Definition
- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction causing fibrosis

![Scleroderma Types](image)

Table 17  The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Criteria for Scleroderma*

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Skin thickening of fingers of both hands extending proximal to the MCP (sufficient criterion)</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>2. Skin thickening of the fingers</td>
<td>Puffy fingers</td>
<td>2</td>
</tr>
<tr>
<td>3. Fingertip lesions</td>
<td>Digital tip ulcers</td>
<td>2</td>
</tr>
<tr>
<td>4. Telangiectasia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>5. Abnormal nailfold capillaries</td>
<td>Sclerodactyly</td>
<td>4</td>
</tr>
<tr>
<td>6. Pulmonary arterial HTN ± ILD (max score 2)</td>
<td>Pulmonary arterial HTN ILD</td>
<td>2</td>
</tr>
<tr>
<td>7. Raynaud’s phenomenon</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>8. Scleroderma related Ab</td>
<td>Anti-centromere</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Anti-topoisomerase I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-RNA polymerase III</td>
<td></td>
</tr>
</tbody>
</table>

* Score of ≥9 is sufficient to classify a patient as having definite scleroderma (sensitivity 0.95, specificity 0.93)  
Arthritis & Rheum 2013;65(11):2737-2747
Etiology and Pathophysiology
- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
- intimal proliferation and media mucinous degeneration → progressive obliteration of vessel lumen → fibrotic tissue
- resembles malignant HTN
- lung disease is the most common cause of morbidity and mortality

Epidemiology
- F:M = 3-4:1, peaking in 5th and 6th decades
- associated with HLA-DR1
- associated with environmental exposure (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)
- limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)

Signs and Symptoms

### Table 18. Clinical Manifestations of Scleroderma

<table>
<thead>
<tr>
<th>System</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Painless non-pitting edema → skin tightening</td>
</tr>
<tr>
<td></td>
<td>Ucerations, calcinosis, periungual erythema, hypo-hyperpigmentation, puritus, telangiectasias</td>
</tr>
<tr>
<td></td>
<td>Characteristic face: mask-like faces with tight lips, beer nose, radial peroral furrows</td>
</tr>
<tr>
<td>Vascular</td>
<td>Raynaud’s phenomenon → digital pits, gangrene</td>
</tr>
<tr>
<td>Gastrointestinal  (~90%)</td>
<td>Distal esophageal hypertrophy → dysphagia</td>
</tr>
<tr>
<td></td>
<td>Loss of lower esophageal sphincter function →GERD, ulcerations, strictures</td>
</tr>
<tr>
<td></td>
<td>Small bowel hypertrophy → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss</td>
</tr>
<tr>
<td></td>
<td>Large bowel hypertrophy → wide mouth diverticuli are pathognomonic radiographic finding on barium study</td>
</tr>
<tr>
<td>Renal</td>
<td>Mild proteinuria, Cr elevation, HTN</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>“Scleroderma renal crisis” (10-15%) may lead to malignant arterial HTN, o igur a, and microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Polyarthralgias</td>
</tr>
<tr>
<td></td>
<td>“Resorption of distal tufts” (radiological finding)</td>
</tr>
<tr>
<td></td>
<td>Proximal weakness 2° to disease, atrophy, low grade myopathy</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

Investigations
- blood work
  - CBC, Cr, ANA
  - anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis
  - anti-centromere: favours diagnosis of CREST (limited systemic sclerosis)
- PFT
  - assess for interstitial lung disease
- imaging
  - CXR for fibrosis, echo for pulmonary HTN

Treatment
- dermatologic
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), MTX (limited evidence)
- vascular
  - patient education on cold avoidance
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE2 inhibitors, PDE5 inhibitors)
- gastrointestinal
  - GERD: PPIs are first line, then H2-receptor agonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
- renal disease
  - ACEI for hypertensive crisis
  - see Nephrology, NP32 for scleroderma renal crisis
- pulmonary
  - early interstitial disease: cyclophosphamide
  - pulmonary HTN: vasodilators (e.g. bosentan, epoprostenol, and PDE5 inhibitors)
- cardiac
  - pericarditis: systemic steroids
  - musculoskeletal
    - arthritis: NSAIDs
    - myositis: systemic steroids

Features of Pathologic Raynaud’s Syndrome
- New onset
- Asymmetric
- Precipitated by stimuli other than cold or emotion
- Associated with distal pulp pitting or tissue reabsorption
- Digit ischemia
- Capillary dilatation by capillaroscopy

Cyclophosphamine versus Placebo in Scleroderma Lung Disease

- **Study:** Double-blind, randomized, placebo-controlled trial
- **Outcome:** Lung function and health-related symptoms
- **Results:** The mean absolute difference in adjusted 12-month FVC percent predicted between cyclophosphamide and placebo groups was 2.55 percent, favouring cyclophosphamide. There were also treatment-related differences in physiological and symptom outcomes, and the difference in FVC was maintained at 24 months
- **Conclusion:** Cyclophosphamide has a significant but modest beneficial effect on lung function, dyspnea, thickening of skin and health-related quality of life in patients with symptomatic, scleroderma-related interstitial lung disease.
**Idiopathic Inflammatory Myopathy**

**Definition**
- autoimmune diseases characterized by proximal muscle weakness ± pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process
- associated with malignancy
  - increased risk of malignancy: age >50, DMM>PM, normal CK, refractory disease
  - associated with other connective tissue disease, Raynaud's phenomenon, autoimmune disorders

**Classification**
- PM/DMM
- adult and juvenile form

**Inclusion Body Myositis**
- age >50, M>F, slowly progressive, vacuoles in cells on biopsy
- suspect when patient unresponsive to treatment
- distal as well as proximal muscle weakness
- muscle biopsy positive for inclusion bodies

**POLYMYOSITIS/DERMATOMYOSITIS**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symmetric proximal muscle weakness</td>
<td>Typical involvement of shoulder girdle and hip girdle</td>
</tr>
<tr>
<td>2. Elevated muscle enzymes</td>
<td>↑ CK, aldolase, LDH, AST, ALT</td>
</tr>
<tr>
<td>3. EMG changes</td>
<td>Short polyphasic motor units, high frequency repetitive discharge, insertional irritability</td>
</tr>
<tr>
<td>4. Muscle biopsy</td>
<td>Segmental fibre necrosis, basophilic regeneration, perivascular inflammation (DMM), endomysial inflammation (PM) and atrophy</td>
</tr>
<tr>
<td>5. Typical rash of dermatomyositis</td>
<td>Required for diagnosis of DMM (see below)</td>
</tr>
</tbody>
</table>

*Definite if 4 present, probable if 3 present*  
*NEJM 1975;292:403-407*

**Etiology and Pathophysiology**
- PM is CD8 cell-mediated muscle necrosis, found in adults
- DMM is B-cell and CD4 immune complex-mediated, and causes peri-fascicular vascular abnormalities

**Signs and Symptoms**
- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over weeks to months
  - difficulty lifting head off pillow, arising from chair, climbing stairs
  - dermatological
    - DMM has characteristic dermatological features (F>M, children and adults)
      - Gottron's papules
        - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
      - Gottron's sign
        - erythematous, smooth or scaly patches over the dorsal IPs, MCPs, elbows, knees, or medial malleoli
      - heliotrope rash: violaceous rash over the eyelids, usually with edema
      - shawl sign: poikilodermatous erythematous rash over neck, upper chest, and shoulders
      - mechanic's hands: dark, dry, thick scale on palmar and lateral surface of digits
      - periangual erythema
    - cardiac
      - arrhythmias, CHF, conduction defect, ventricular hypertrophy, pericarditis
    - gastrointestinal
      - oropharyngeal and lower esophageal dysphagia, reflux
    - pulmonary
      - weakness of respiratory muscles, ILD, aspiration pneumonia

**Investigations**
- blood work: CK, ANA, anti-Jo-1 (DMM), anti-Mi-2, anti-SRP
- imaging: MRI may be used to localize biopsy site
- EMG, muscle biopsy

**Malignancies Associated with DMM**
- Breast
- Lung
- Colon
- Ovarian

**Signs of DMM**
- Gottron’s papules and Gottron’s sign are pathognomonic of DMM (occur in 70% of patients)
Treatment
• non-pharmacological treatment
  • physical therapy and occupational therapy
• pharmacological treatment
  • high-dose corticosteroid (1-2 mg/kg/d) and slow taper
  • add immunosuppressive agents (azathioprine, MTX, cyclosporine)
  • IVIG if severe or refractory
  • hydroxychloroquine for DMM rash
• malignancy surveillance
  • detailed history and physical (breast, pelvic, and rectal exam)
  • CXR, abdominal and pelvic U/S, fecal occult blood, Pap test, mammogram ± CT scan (thoracic, abdominal, pelvic)

Sjögren’s Syndrome

Definition
• autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca/xerophthalmia) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
• may evolve into systemic disorder with diminished exocrine gland activity in respiratory tract and skin
• primary and secondary form (associated with RA, SLE, DMM, and HIV)
• prevalence, F>>M, 40-60 yo
• increased risk of non-Hodgkin’s lymphoma

Table 20. American College of Rheumatology Classification for Sjögren’s*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 1. Positive serum anti-SSA/Ro and/or anti-SSB/La or positive RF and ANA titer > 1:320 | Focus scores are histopathologic grading systems
| 2. Labial salivary gland biopsy with focal lymphocytic sialadenitis with focus score ≥ 1 focus /4mm² | Strongly associated with phenotypic ocular and serological component’s of Sjögren’s
| 3. Keratoconjunctivitis sicca with ocular staining score > 3 | Ocular staining score based on fluorescein dye examination of conjunctiva and come to determine clinical changes

*Sjögren’s Syndrome classification criteria is met in patients with signs/symptoms of Sjögren’s, who have at least 2 of the above features

Signs and Symptoms
• “sicca complex”: dry eyes (keratoconjunctivitis sicca/xerophthalmia), dry mouth (xerostomia)
• staphylococcal blepharitis
• dental caries, oral candidiasis, angular cheilitis (inflammation and fissuring at the labial commissures of the mouth)
• systemic complications
  • sinusitis
  • autoimmune thyroid dysfunction
  • arthralgias, arthritis
  • subclinical diffuse ILD, xerotrachea leading to chronic dry cough
  • renal disease, glomerulonephritis
  • palpable purpura, vasculitis
  • peripheral neuropathy
  • lymphoma risk greatly increased

Treatment
• ocular
  • artificial tears or surgical punctal occlusion for dry eyes
• oral
  • good dental hygiene, hydration
  • parasympathomimetic agents that stimulate salivary flow (e.g. pilocarpine)
  • topical nystatin or clotrimazole x 4-6 wk for oral candidiasis
• systemic (e.g. hydroxychloroquine, corticosteroids)

Mixed Connective Tissue Disease
• syndrome with features of 3 different connective tissue diseases (e.g. SLE, scleroderma, PM)
• common symptoms: Raynaud’s phenomenon, swollen fingers
• blood work: anti-RNP (see Table 10)
• treatment is generally guided by the severity of symptoms and organ system involvement
• prognosis
  • 50-60% will evolve into SLE
  • 40% will evolve into scleroderma
  • only 10% will remain as MCTD for the rest of their lives
• cardiac involvement (arrhythmia) common, renal or lung involvement rare
Overlap Syndrome

- syndrome with sufficient diagnostic features of 2+ different connective tissue diseases

Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction of any organ system
- diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection; constitutional symptoms such as fever, weight loss, anorexia, fatigue
  - labs non-specific: anemia, increased WBC and ESR, abnormal U/A
  - investigations: biopsy if tissue accessible; angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressive agents

Table 21. Classification of Vasculitis and Characteristic Features

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMALL VESSEL</td>
<td></td>
</tr>
<tr>
<td>Non-ANCA-associated</td>
<td>Immune complex-mediated (most common mechanism)</td>
</tr>
<tr>
<td>Predominantly cutaneous vasculitis</td>
<td>Also known as hypersensitivity/leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>IgA vasculitis (formely Henoch-Schönlein purpura [HSP]) (see Pediatrics, P86)</td>
<td>Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting; most common in childhood</td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis (CV)</td>
<td>Systemic vasculitis caused by circulating cryoproteins forming immune complexes; 60-80% of cases are due to Hepatitis C, 5-10% are due to a CTD (SLE, RA, SS), 5-10% are due to a lymphoproliferative disorder and the remaining 5-10% are idiopathic or &quot;essential&quot;. CV may be associated with underlying infection (e.g. hepatitis C) or connective tissue disease</td>
</tr>
<tr>
<td>ANCA-associated (i.e. PR3-ANCA) Granulomatosis with polyangiitis (GPA, formerly Wegener’s)</td>
<td>Granulomatous inflammation of vessels of respiratory tract and kidneys; initially have URTI symptoms; most common in middle age</td>
</tr>
<tr>
<td>ANCA-associated (i.e. PR3-ANCA)</td>
<td></td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis (CV)</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (50% ANCA positive)</td>
<td>Granulomatous inflammation of vessels with hypereosinophilia and eosinophilic tissue infiltration frequent lung involvement (asthma, allergic rhinitis), associated with MPO-ANCA in 40 50% of cases. Other manifestations include peripheral neuropathy (70%), GI involvement, myocardiitis and rare coronary arteries; average age 40s</td>
</tr>
<tr>
<td>Microangiopathic polyangiitis (70% ANCA positive, usually MPO)</td>
<td>Pauci-immune necrotizing vasculitis, affecting kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin; most common in middle age</td>
</tr>
<tr>
<td>MEDIUM VESSEL</td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Segmental, non-granulomatous necrotizing inflammation Unknown etiology in most cases, any age (average 40-50s), M&gt;F</td>
</tr>
<tr>
<td>Kawasaki disease (see Pediatrics, P87)</td>
<td>Arteritis and mucocutaneous lymph node syndrome</td>
</tr>
<tr>
<td>LARGE VESSEL</td>
<td></td>
</tr>
<tr>
<td>GCA/Temporal arteritis</td>
<td>Inflammation predominantly of the aorta and its branches &gt;50 yr of age, F&gt;M</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>“Pulseless disease”, unequal peripheral pulses, chronic inflammation, most often the aorta and its branches Usually young adults of Asian descent, F&gt;M, risk of aortic aneurysm</td>
</tr>
</tbody>
</table>

OTHER VASCULITIDES

- Buerger’s disease ("Thromboangiitis Obliterans") | Inflammation and clotting of small and medium-sized arteries and veins of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking. Most common in young Asian males |
| Behçet’s disease | Multi-system disorder presenting with ocular involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement; more common in Mediterranean and Asian, average age 30 yr old, M>F |
| Vasculitis mimicry (i.e. pseudovasculitis) | Cholesterol emboli, atrial myxoma, bacterial endocarditis (SBE), APLS |
Small Vessel Non-ANCA Associated Vasculitis

CUTANEOUS VASCULITIS

- subdivided into
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases (CTD, infections, malignancies – hematologic > solid tumours)

Etiology and Pathophysiology

- cutaneous vasculitis following:
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes

- small vessels involved (post-capillary venules most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Signs and Symptoms

palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules
- renal or joint involvement may occur, especially in children

Investigations

- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment

- stop possible offending drug
- NSAID, low dose corticosteroids
- immunosuppressive agents in resistant cases
- usually self-limiting

Small Vessel ANCA-Associated Vasculitis

GRANULOMATOSIS WITH POLYANGIITIS
(GPA formerly known as Wegener’s Granulomatosis)

Definition

- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis) lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA by indirect immunofluorescence (IIF) and pR3-ANCA by ELISA; however, changes in ANCA levels do not predict remission or relapse
- incidence 2-3 per 100,000; more common in Northern latitudes

Table 22. Classification Criteria for GPA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nasal or oral involvement</td>
<td>Inflammation, ulcers, epistaxis</td>
</tr>
<tr>
<td>2. Abnormal findings on CXR</td>
<td>Nodules, cavitations, etc.</td>
</tr>
<tr>
<td>3. Urinary sediment</td>
<td>Microscopic hematuria ± RBC casts</td>
</tr>
<tr>
<td>4. Biopsy of involved tissue</td>
<td>Lungs show granulomas; kidneys show necrotizing segmental glomerulonephritis</td>
</tr>
</tbody>
</table>

*Diagnosed if 2 or more of the above 4 criteria present
American College of Rheumatology, 1990

Classic Features of GPA

- Necrotizing granulomatous vasculitis of lower and upper respiratory tract
- Focal segmental glomerulonephritis
Etiology
- pathogenesis depends on genetic susceptibility and environmental triggers (e.g. infection)
  - dysregulated immune response due to loss of B and T-cell tolerance
  - acute vascular injury mediated by neutrophils and monocytes

Signs and Symptoms
- systemic
  - malaise, fever, weakness, weight loss
- HEENT
  - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, saddle nose deformity
  - proptosis due to inflammation/vasculitis involving extra-ocular muscles, granulomatous retrobulbar space occupying lesions or direct extension of masses from the upper respiratory tract
  - hearing loss due to involvement of CN VIII
- pulmonary
  - cough, hemoptysis, granulomatous upper respiratory tract masses
- renal
  - hematuria, proteinuria, elevated creatinine
- other
  - joint, skin, eye complaints, vasculitic neuropathy

Investigations
- blood work: anemia (normal MCV), increased WBC, increased Cr, increased ESR, elevated platelet count, ANCA (PR3 > MPO)
- urinalysis: proteinuria, hematuria, RBC casts
- CXR: pneumonitis, lung nodules, infiltrations, cavitary lesions
- biopsy: renal (segmental necrotizing glomerulonephritis), lung (granulomas, tracheobronchial erosion)
- c-ANCA and ESR often correlate with disease activity and used to monitor response to treatment in some patients

Treatment
- for severe, life or organ threatening disease
  - pulse methylprednisolone x 3 days followed by prednisone 1 mg/kg/d PO + cyclophosphamide 2 mg/kg/d PO for 36 mo OR rituximab 375 mg/m² followed by high dose MTX (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/d PO OD)
  - consider plasmapheresis in patients with rapidly deteriorating renal failure or pulmonary hemorrhage

Medium Vessel Vasculitis

POLYARTERITIS NODOSA

Definition
- systemic, necrotizing vasculitis of medium sized vessels
- ANCA negative
- 5-10% associated with hepatitis B positivity
- incidence 0.7 per 100,000; affects individuals between 40-60 yr; M:F = 2:1

Table 23. Classification Criteria for PAN*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight loss</td>
<td>&gt;4 kg, not due to dieting or other factors</td>
</tr>
<tr>
<td>2. Myalgias, weakness, or leg tenderness</td>
<td>Diffuse myalgias or weakness</td>
</tr>
<tr>
<td>3. Livedo reticularis</td>
<td>Mottled, reticular pattern over skin</td>
</tr>
<tr>
<td>4. Neuropathy</td>
<td>Mononeuropathy, mononeuropathy multiplex, or polyneuropathy</td>
</tr>
<tr>
<td>5. Testicular pain or tenderness</td>
<td>Not due to infection, trauma, or other causes</td>
</tr>
<tr>
<td>6. dBP &gt;90 mmHg</td>
<td>Development of HTN with dBP &gt;90 mmHg</td>
</tr>
<tr>
<td>7. Elevated Cr or BUN</td>
<td>Cr &gt;130 mg/dL (1.5 mg/dL, BUN &gt;14.3 mg/dL (40 mg/dL)</td>
</tr>
<tr>
<td>8. Hepatitis B positive</td>
<td>Presence of hepatitis B surface antigen or Ab</td>
</tr>
<tr>
<td>9. Arteriographic abnormality</td>
<td>Commonly aneurysms</td>
</tr>
<tr>
<td>10. Biopsy of artery</td>
<td>Presence of granulocytes and/or mononuclear leukocytes in the artery wall</td>
</tr>
</tbody>
</table>

*Diagnosed if 3 or more of the above 10 criteria present

Etiology and Pathophysiology
- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion
Investigations
- blood work: CBC, ESR, Cr, BUN, p-ANCA, hepatitis B serology
- imaging: angiography
- arterial biopsy

Treatment
- prednisone 1 mg/kg/d PO and cyclophosphamide 2 mg/kg/d PO
  ± anti-viral therapy to enhance clearance of hepatitis B virus

**Large Vessel Vasculitis**

**GCA/TEMPORAL ARTERITIS**

Table 24. Classification Criteria for GCA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age at onset ≥50</td>
<td></td>
</tr>
<tr>
<td>2. New H/A</td>
<td>Often temporal</td>
</tr>
<tr>
<td>3. Temporal artery abnormality</td>
<td>Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis</td>
</tr>
<tr>
<td>4. Elevated ESR</td>
<td>ESR ≥50 mm/h</td>
</tr>
<tr>
<td>5. Abnormal artery biopsy</td>
<td>Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
</tr>
</tbody>
</table>

*Diagnosed if 3 or more of the above 5 criteria present. American College of Rheumatology, 1990

**Epidemiology**
- most frequent vasculitis in North America
- patients >50 yr
- F:M = 2:1
- North-South gradient (predominance in Northern Europe/US)
- affects extracranial arteries

**Signs and Symptoms**
- new onset temporal H/A ± scalp tenderness due to inflammation of involved portion of the temporal or occipital arteries
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
- tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
- PMR (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta resulting in pulseless disease), aortic aneurysm ± rupture are late complications
- constitutional symptoms and shoulder/pelvic girdle pain and stiffness

**Investigations**
- diagnosis made by clinical suspicion, increased ESR, increased CRP, temporal artery biopsy, and possibly U/S or MRI

**Treatment**
- if suspect GCA, immediately start high dose prednisone 1 mg/kg in divided doses for approximately 4 wk, and then tapering prednisone as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
- consider low dose ASA to help decrease visual loss

**Prognosis**
- increased risk of thoracic aortic aneurysm and aortic dissection
- yearly CXR ± abdominal U/S as screening
Seronegative Rheumatic Disease

### Table 25 A Comparison of the Spondyloarthropathies*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ankylosing Spondylitis (AS)</th>
<th>Psoriatic Arthritis (PsA)</th>
<th>Reactive Arthritis (ReA)</th>
<th>Enteropathic Arthritis (EA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>3:1</td>
<td>1:1</td>
<td>8:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>20s</td>
<td>35 45</td>
<td>20s</td>
<td>Any</td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td>96%</td>
<td>80%</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>Distribution</td>
<td>Axial, LE</td>
<td>LE</td>
<td>LE</td>
<td>LE</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>40%</td>
<td>40%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Uncommon</td>
<td>Common</td>
<td>Occasional</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Less Common</td>
</tr>
<tr>
<td>Skin Lesions</td>
<td>Rare</td>
<td>100%</td>
<td>Occasional Keratoderma</td>
<td>Occasional Pyoderma, erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>bottleneck</td>
<td>nodosum</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Common</td>
<td>Occasional</td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>90-95%</td>
<td>40%</td>
<td>80%</td>
<td>30%</td>
</tr>
</tbody>
</table>

*LE = lower extremities  **Spondylarthropathy: inflammatory joint disease f the vertebral column

### Ankylosing Spondylitis

**Definition**
- chronic inflammatory arthritis involving the sacroiliac joints and vertebrae
- enthesitis is a major feature
- prototypical spondyloarthritis

**Table 26. ASAS Classification Criteria for Axial Spondyloarthritis***

<table>
<thead>
<tr>
<th>AS Features</th>
<th>Sacroiliitis on Imaging plus ≥1 AS Feature or HLA-B27 Positive plus ≥2 AS Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27 positive</td>
<td>Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with AS</td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>Definite radiographic sacroiliitis ≥ grade 2 bilaterally or grade 3-4 unilaterally</td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Enthesitis (heel)</td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
</tr>
<tr>
<td>Dactylitis</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease/colitis</td>
<td></td>
</tr>
<tr>
<td>Good response to NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Family history of AS</td>
<td></td>
</tr>
<tr>
<td>Elevated CRP</td>
<td></td>
</tr>
</tbody>
</table>

*For patients with ≥3 mo back pain and age at onset <45 yr

**Etiology and Pathophysiology**
- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

**Epidemiology**
- M:F = 3:1; females have milder disease which may be under-recognized and more peripheral arthritis and upper spine spondylitis
- 90-95% of patients have HLA-B27 (9% HLA-B27 positive in general population)
Table 27. Types of Back Pain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mechanical</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past History</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Family History</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Age</td>
<td>15-90 yr</td>
<td>&lt;45 yr</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>±</td>
<td>+ (worse during 2nd half of night)</td>
</tr>
<tr>
<td>Morning Stiffness</td>
<td>&lt;30 min</td>
<td>&gt;1 h</td>
</tr>
<tr>
<td>Involvement of Other Systems</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Exercise</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Rest</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Radiation of Pain</td>
<td>Anatomic (L5-S1)</td>
<td>Diffuse (thoracic, buttoc)</td>
</tr>
<tr>
<td>Sensory Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Motor Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

Signs and Symptoms

- **axial**
  - mid and lower back stiffness, morning stiffness >1 h, night pain, persistent buttock pain, painful sacroiliac joint (+ FABER test)
  - spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion, normal >5 cm at T4), cervical (global decrease, often extension first)
  - postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance (>5 cm)

- **peripheral**
  - asymmetrical large joint arthritis, most often involving lower limb
  - enthesitis: tenderness over tibial tuberosity, or Achilles tendon and plantar fascia insertions into the calcaneus

- **extra-articular manifestations**
  - ophthalmic: acute anterior uveitis is common (25-30% patients)
  - renal: amyloidosis (late and rare), IgA nephropathy
  - gastrointestinal: IBD
  - cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
  - respiratory: apical fibrosis (rare)
  - neurologic: cauda equina syndrome (rare)
  - skin: psoriasis

Investigations

- x-ray of SI joint: “pseudowidening” of joint due to erosion with joint sclerosis → bony fusion (late), symmetric sacroiliitis
- x-ray of spine: “squaring of edges” from erosion and sclerosis on corners of vertebral bodies (shiny corner sign) leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes) → “bamboo spine” radiographically
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes. Best seen on T2 STIR (short tau inversion recovery) images (suppress fat and see bone edema)

Treatment

- **non-pharmacological therapy**
  - prevent fusion from poor posture and disability through: exercise (e.g. swimming), postural and deep breathing exercises, outpatient PT, smoking cessation

- **pharmacological therapy**
  - NSAIDs (first line of treatment)
  - glucocorticoids (topical eye drops, local injections)
  - DMARDs only for peripheral arthritis (sulfasalazine, MTX)
  - anti-TNF agents for axial and peripheral involvement
  - manage extra-articular manifestations

- **surgical therapy**
  - hip replacement and vertebral osteotomy for marked deformity

Prognosis

- spontaneous remissions and relapses are common and can occur at any age
- function may be excellent despite spinal deformity
- favourable prognosis if female and age of onset >40 yr
- early onset with hip disease may lead to severe disability; may require arthroplasty
**Enteropathic Arthritis**

- see *Gastroenterology, Inflammatory Bowel Disease, G19*
- MSK manifestations in the setting of either ulcerative colitis or Crohn's disease include peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthropathy
- non-arthritic MSK manifestations can occur 2º to steroid treatment of bowel inflammation (arthralgia, myalgia, osteoporosis, AVN)
- NSAIDs should be used cautiously as they may exacerbate bowel disease

**Table 28. Comparing Features of Spondylitis vs. Peripheral Arthritis in EA**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spondylitis</th>
<th>Peripheral Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27 Association</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gender</td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td>Onset Before IBD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Parallels IBD Course</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Type of IBD</td>
<td>UC=CD</td>
<td>CD</td>
</tr>
</tbody>
</table>

**Psoriatic Arthritis**

**Definition**
- arthritic inflammation associated with psoriasis

**Etiology and Pathophysiology**
- unclear but many genetic, immunologic, and some environmental factors involved (e.g. bacterial, viral, and trauma)

**Epidemiology**
- psoriasis affects 1% of population
- arthropathy in 15% of patients with psoriasis
- 15-20% of patients will develop joint disease before skin lesions appear

**Signs and Symptoms**

- **dermatologic**
  - well-demarcated erythematosus plaques with silvery scale
  - nail involvement: pitting, transverse or longitudinal ridging, discoloration, subungual hyperkeratosis, onycholysis, and oil drops
- **musculoskeletal**
  - 5 general patterns
    - asymmetric oligoarthritis (most common – 70%)
    - arthritis of DIP joints with nail changes
    - destructive in small joints
    - symmetric polyarthritis (similar to RA)
    - sacroiliitis and spondylitis (usually older, male patients)
  - other findings: dactylitis, enthesopathy
- **ophthalmic**
  - conjunctivitis, iritis (anterior uveitis)
- **cardiac and respiratory** (late findings)
  - aortic insufficiency
  - apical lung fibrosis
  - neurologic
  - cauda equina syndrome
- **radiologic**
  - floating syndesmophytes
  - pencil-in-cup appearance at IP joints
  - osteolysis, periostitis

**Treatment**
- treat skin lesions (e.g. steroid cream, salicylic acid/or retinoic acid, tar, UV light)
- NSAIDs or IA steroids
- DMARDs (methotrexate, sulfasalazine or leflunomide); biologic therapies to minimize erosive disease (use early if peripheral joint involvement). The latter include anti-TNF agents, anti-IL-17 (secukinumab) and anti-IL-12/23 (ustekinumab)
Table 29. CASPAR Criteria for PsA*

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidenc of psoriasis</td>
<td>Current, past, or family history</td>
</tr>
<tr>
<td>2. Psoriatic nail dystrophy</td>
<td>Onycholysis, pitting, hyperkeratosis</td>
</tr>
<tr>
<td>3. Negative results for RF</td>
<td></td>
</tr>
<tr>
<td>4. Dactylitis</td>
<td>Current or past history</td>
</tr>
<tr>
<td>5. Radiological evidence</td>
<td>Juxta-articular bone formation on hand or foot x-rays</td>
</tr>
</tbody>
</table>

* To meet the CASPAR (Classification criteria for Psoriatic Arthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the above 5 categories.


---

**Reactive Arthritis**

**Definition**
- one of the seronegative spondyloarthropathies in which patients have a peripheral arthritis (≥1 mo duration) accompanied by one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tracts
- this term should not be confused with rheumatic fever or viral arthritides.

**Etiology**
- onset following an infectious episode either involving the GI or GU tract
  - GI: *Shigella, Salmonella, Campylobacter, Yersinia, C. Difficile species*
  - GU: *Chlamydia* (isolated in 16-44% of ReA cases), *Mycoplasma species*
- acute clinical course
  - 1-4 wk post-infection
  - lasts weeks to years
  - often recurring
  - spinal involvement persists

**Epidemiology**
- in HLA-B27 patients, axial > peripheral involvement
- M>F

**Signs and Symptoms**
- **musculoskeletal**
  - peripheral arthritis, asymmetric pattern, spondylitis, Achilles tendinitis, plantar fasciitis, dactylitis
- **ophthalmic**
  - iritis (anterior uveitis), conjunctivitis
- **dermatologic**
  - keratoderma blennorrhagicum (hyperkeratotic skin lesions on palms and soles) and balanitis cinicata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- **gastrointestinal**
  - oral ulcers, diarrhea
- **urethritis and cervicitis**
  - sterile pyuria; presence not related to site of initiating infection

**Investigations**
- diagnosis is clinical plus laboratory
- blood work: normocytic, normochromic anemia, and leukocytosis
- sterile cultures
- serology: HLA-B27 positive

**Treatment**
- antibiotics for non-articular infections
- NSAIDs, physical therapy, exercise
- local therapy
  - joint protection
  - IA steroid injection
  - topical steroid for ocular involvement
- systemic therapy
  - corticosteroids, sulfasalazine, MTX (for peripheral joint involvement only)
  - TNF-α inhibitors for spinal inflammation

**Prognosis**
- self-limited, typically 3-5 mo, varies based on pathogen and patient’s genetic background
- chronic in 15-20% of cases

---

**Clinical Triad of Reactive Arthritis**
- Arthritis
- Conjunctivitis/uveitis
- Urethritis/cervicitis

**“Can’t See, Can’t Pee, Can’t Climb a Tree”**
Triad of conjunctivitis, urethritis, and arthritis is 99% specific (but 51% sensitive) for ReA

* 1st MTP = podagra
  *Ankle
  *Knee

© Jerry Won, after Linda Colati

**Figure 13** Common sites of involvement of gout (asymmetric joint involvement)
Crystal-Induced Arthropathies

Table 30  Gout vs. Pseudogout

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td>Age</td>
<td>Middle-aged males</td>
<td>Age &gt;60 yr</td>
</tr>
<tr>
<td>Age post-menopausal</td>
<td></td>
<td>Acute/insidious</td>
</tr>
<tr>
<td>Onset of Disease</td>
<td>Acute</td>
<td>Acute</td>
</tr>
<tr>
<td>Crystal Type</td>
<td>Monosodium urate</td>
<td>CPPD</td>
</tr>
<tr>
<td></td>
<td>Negative birefringence (yellow when</td>
<td>Positive birefringence (blue when</td>
</tr>
<tr>
<td></td>
<td>parallel to compensator filter, needle-</td>
<td>parallel), rhomboid shaped</td>
</tr>
<tr>
<td></td>
<td>shaped)</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>First MTP classically; also midfoot,</td>
<td>Knee, wrist; monoarticular, or</td>
</tr>
<tr>
<td></td>
<td>ankle, knee, or polarticular if chronic</td>
<td>polyarticular</td>
</tr>
<tr>
<td>Radiology (note findings are non-specific)</td>
<td>Erosions</td>
<td>Chondrocalcinosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DA (knee, wrist, 2nd and 3rd MCP)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Acute: NSAIDs, corticosteroids,</td>
<td>NSAIDs, corticosteroids</td>
</tr>
<tr>
<td></td>
<td>colchicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic: ± allopurinil, fuboxostat</td>
<td></td>
</tr>
</tbody>
</table>

Gout

**Definition**
- derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

**Etiology and Pathophysiology**
- uric acid can be obtained from the diet or made endogenously by xanthine oxidase, which converts xanthine to uric acid
- an excess of uric acid results in hyperuricemia
- uric acid can deposit in the tissues (tophi), synovium (microtophi) and bones, where they can crystalize to form monosodium urate crystals that lead to gout
- both modifiable and non-modifiable risk factors contribute to gout
- non-modifiable risk factors include: genetic mutations, male gender and advanced age
- modifiable risk factors include: diet (alcohol, purine rich foods such as meats and seafoods, fructose/sugar sweetened foods; see list of precipitants below)
- other risk factors: renal failure, metabolic syndrome, diuretics

**Signs and Symptoms**
- single episode progressing to recurrent episodes of acute inflammatory arthritis
- *acute gouty arthritis*
  - severe pain, redness, joint swelling, usually involving lower extremities
  - joint mobility may be limited
  - attack will subside spontaneously within several days to weeks; may recur
- *tophi*
  - urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
  - common sites: first MTP, ear helix, olecanon bursae, tendon insertions (common in Achilles tendon)
- *kidney*
  - gouty nephropathy
  - uric acid calculi

**Investigations**
- joint aspirate: >90% of joint aspirates show crystals of monosodium urate (negatively birefringent, needle-shaped)
- x-rays may show tophi as soft tissue swelling, punched-out lesions, erosion with “over-hanging”
- correlated with hyperuricemia in the blood
- may see elevated WBC and ESR (nonspecific)

**Treatment**
- *acute gout*
  - NSAIDs: high dose, then taper as symptoms improve
  - corticosteroids: IA, oral, or intra-muscular (if renal, cardiovascular or GI disease and/or if NSAIDs contraindicated or failed)
  - colchicine within first 12 h but effectiveness limited by narrow therapeutic range
  - allopurinol can worsen an acute attack (do not start during acute flare)
  - OA (knee, wrist, 2nd and 3rd MCP)
  - Knee, wrist; monoarticular, or polyarticular
  - Erosions Chondrocalcinosis
  - First MTP classically; also midfoot, ankle, knee, or polarticular if chronic
  - Erosions Chondrocalcinosis
  - DA (knee, wrist, 2nd and 3rd MCP)
  - Acute: NSAIDs, corticosteroids, colchicine
  - Chronic: ± allopurinol, fuboxostat

Precipitants of Gout

- Drugs are FACT
  - Furosemide
  - Aspirin® (low dose)/Alcohol
  - Cystinotic drugs (cyclosperine)
  - Thiazide diuretics
  - Foods are SALT
    - Seafood
    - Alcohol (beer and spirits)
    - Liver and kidney
    - Turkey (meat)

10 Recommendations on the Diagnosis and Management of Gout

1. Identification of monosodium urate crystals should be performed for a definitive diagnosis of gout.
2. Gout/hyperuricemia should prompt investigations of renal function and CV risk factors.
3. Acid-gout should be treated with colchicine, NSAIDs, and/or glucocorticoids.
4. Patients should be counselled about lifestyle.
5. Allopurinol is first line forurate lowering therapy, with uricosurics as second line.
6. Patients should be informed about the risk of acute-gout flare with initiation of urate lowering therapy; colchicine prophylaxis should be considered.
7. Allopurinol can be used in patients with mild/moderate renal impairment with slow titration and monitoring.
8. Treatment goal is urine <0.36 mM and absence of attacks and resolution of tophi.
9. Tophi should be treated medically by lowering serum urate to <0.3 mM. Surgery is only for select cases.
10. Prophylactic pharmacological management of asymptomatic hyperuricemia is not recommended.
• chronic gout
  • conservative
    ◆ avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
    ◆ avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)
  • medical
    ◆ antihyperuricemic drugs (allopurinol and febuxostat): decrease uric acid production by inhibiting xanthine oxidase
    ◆ uricosuric drugs (probenecid, sulfinpyrazone): very rarely used in combination with allopurinol or febuxostat in patients in whom hyperuricemia is not controlled with the latter
  • prophylaxis prior to starting antihyperuricemic drugs (colchicine/low-dose NSAID)
  • in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor Cr

• indications for treatment with antihyperuricemic medications include
  • recurrent attacks (more than 2-3/yr), tophi, bone erosions, urate kidney stones
  • perhaps in renal dysfunction with very high urate load (controversial)

### Pseudogout (Calcium Pyrophosphate Dihydrate Disease)

**Definition**
- joint inflammation caused by calcium pyrophosphate crystals

**Etiology and Pathophysiology**
- acute inflammatory arthritis due to phagocytosis of IgG-coated CPPD crystals by neutrophils and subsequent release of inflammatory mediators within joint space
- more frequently polyarticular
- slower in onset in comparison to gout, lasts up to 3 wk but is self-limited

**Risk Factors**
- old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), DM, hemochromatosis

**Signs and Symptoms**
- affects knees, wrists, MCPs, hips, shoulders, elbows, ankles, big toe
- multiple manifestations
- asymptomatic crystal deposition (seen on radiograph only)
- acute crystal arthritis (self-limited flares of acute inflammatory arthritis resembling gout)
- pseudo-OA (progressive joint degeneration, sometimes with episodes of acute inflammatory arthritis)
- pseudo-RA (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- acute may be triggered by dehydration, acute illness, surgery, trauma

**Investigations**
- must aspirate joint to rule out septic arthritis, gout
- CPPD crystals: present in 60% of patients, often only a few crystals, positive birefringence (blue) and rhomboid shaped
- x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

**Treatment**
- joint aspiration, rest, and protection
- NSAIDs: also used for maintenance therapy
- prophylactic colchicine PO (controversial)
- IA or oral steroids to relieve inflammation
Non-Articular Rheumatism

Definition
- disorders that primarily affect soft tissues or periarticular structures
- includes bursitis, tendinitis, tenosynovitis, fibromyalgia, and PMR

Polymyalgia Rheumatica

Definition
- characterized by pain and stiffness of the proximal extremities (girdle area)
- closely related to GCA (15% of patients with PMR develop GCA)
- no muscle weakness

Table 31. PMR Classification Criteria Scoring Algorithm*

<table>
<thead>
<tr>
<th>Points without</th>
<th>Points with Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>U/S (0-6)</td>
<td>U/S** (0-8)</td>
</tr>
</tbody>
</table>

- Morning stiffness duration > 45 min: 2 2
- Hip pain or limited ROM: 1 1
- Absence of RF or ACPA: 2 2
- Absence of other joint involvement: 1 1
- At least one shoulder with subdeltoid and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis on U/S: N/A 1
- Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or gleno-humeral synovitis on U/S: N/A 1

*Required criteria: age ≥ 50 yr, bilateral shoulder aching, and abnormal ESR/CRP
**A score of 4 or more is categorized as PMR in the algorithm without U/S and a score of 5 or more is categorized as PMR in the algorithm with U/S
***Optional U/S criteria

Epidemiology
- incidence 50 per 100,000 per year in those >50 yr
- age of onset typically >50 yr, F:M = 2:1

Signs and Symptoms
- constitutional symptoms prominent (fever, weight loss, malaise)
- pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs)
- gel phenomenon (stiffness after prolonged inactivity)
- physical exam reveals tender muscles, but no weakness or atrophy

Investigations
- blood work: often shows anemia, elevated platelets, elevated ESR and CRP, and normal CK; up to 5% of PMR reported with normal inflammatory markers

Treatment
- goal of therapy: symptom relief
- start with prednisone dose of 15-20 mg PO OD, reconsider diagnosis if no response within several days
- taper slowly over 1 yr period with closely monitoring
- relapses should be diagnosed and treated on clinical basis; do not treat a rise in ESR as a relapse
- treat relapses aggressively (50% relapse rate)
- monitor for steroid side effects, glucocorticoid-induced osteoporosis prevention, and follow for symptoms of GCA
Fibromyalgia

Definition
- chronic (>3 mo), widespread (axial, left- and right-sided, upper and lower segment), non-articular pain with characteristic tender points

Diagnosis

Table 32. 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widespread Pain Index = number of areas in which the patient had pain over the last week (max score = 19): L and R: shoulder girdle, upper arm lower arm, hip, upper leg, lower leg, jaw One Area: chest, abdomen, upper back, lower back, neck</td>
<td>A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met: 1. Widespread Pain Index (WPI) ≥ 7 and Symptom Severity (SS) scale score ≥ 5 or WPI 3–6 and SS scale score ≥ 9 2. Symptoms have been present at a similar level for at least 3 mo 3. The patient does not have a disorder that would otherwise explain the pain</td>
</tr>
<tr>
<td>Symptom Severity Score = sum of: a) severity of fatigue b) waking unrefreshed c) cognitive symptoms over the past week d) extent of somatic symptoms (IBS, H/A, abdominal pain/cramps, dry mouth, fever, hives, ringing in ears, vomiting, heartburn, dry eyes, SOB, loss of appetite, rash, hair loss, easy bruising, etc.) all (a-d) rated on 0-3 scale: 0 = no problem, 1 = mild 2 = moderate, 3 = severe</td>
<td></td>
</tr>
</tbody>
</table>

Epidemiology
- F:M = 3:1
- primarily ages 25–45 yr, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness

Signs and Symptoms
- widespread aching, stiffness
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent waking
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- neurologic symptoms of hyperalgesia, paresthesias
- associated with irritable bowel or bladder syndrome, migraines, tension H/As, restless leg syndrome, obesity, depression, and anxiety
- physical exam should reveal only tenderness with palpation of soft tissues, with no specificity for trigger/tender points

Investigations
- blood work: includes TSH and ESR; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

Differential Diagnosis
- diagnosis of exclusion
- rule out other disorders by history and physical exam (RA, SLE, PMR, myositis, hypothyroidism, hyperparathyroidism, neuropathies)
Common Medications

**Treatment**
- **non-pharmacological therapy**
  - education
  - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
  - stress reduction, CBT
- no evidence for alternative medicine such as biofeedback, meditation, acupuncture
- **pharmacological therapy**
  - low dose tricyclic antidepressant (e.g. amitriptyline)
  - for sleep restoration
  - select those with lower anticholinergic side effects
  - SNRI: duloxetine, milnacipran
  - anticonvulsant: pregabalin, gabapentin
  - analgesics may be beneficial for pain that interferes with sleep (NSAIDs, not narcotics)

**Prognosis**
- variable; usually chronic, unless diagnosed and treated early

---

**Table 33. Clinical Features of Inflammatory Myopathy vs. Polymyalgia Rheumatica vs. Fibromyalgia**

<table>
<thead>
<tr>
<th></th>
<th>Polymyositis</th>
<th>PMR</th>
<th>Fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>F &gt; M, 40-50 yrs</td>
<td>F &gt; M, &gt; 50 yrs</td>
<td>F &gt; M, 25-45 yrs</td>
</tr>
<tr>
<td><strong>Muscle Involvement</strong></td>
<td>Proximal muscle</td>
<td>Proximal muscle</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Weakness</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>Painless</td>
<td>Painful</td>
<td>Painful</td>
</tr>
<tr>
<td><strong>Stiffness</strong></td>
<td>Mild</td>
<td>Significant morning and gelling stiffness (shoulders, neck, hips)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Muscle biopsy, CK, EMG, R/O malignancy</td>
<td>ESR/CRP, R/O giant cell arteritis</td>
<td>Sleep assessment, TSH</td>
</tr>
<tr>
<td><strong>ESR/CRP</strong></td>
<td>Usually normal</td>
<td>Markedly elevated</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>High dose steroids, immunosuppressants</td>
<td>Low dose steroids</td>
<td>Exercise, TCA, SNRIs, anticonvulsants</td>
</tr>
</tbody>
</table>

---

**Table 34. Common Medications for Osteoarthritis**

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing (PO)</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
<td>acetaminophen</td>
<td>Tylenol®</td>
<td>500 mg tid q6h (3 g daily max)</td>
<td>1st line</td>
<td>Hepatotoxicity Overdose Potentiates warfarin</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>ibuprofen</td>
<td>Voltaren®</td>
<td>200-600 mg tid 25-50 mg tid 50-75/200 mg tid 125-300 mg bid 7.5-15 mg OD</td>
<td>2nd line</td>
<td>GI bleed Renal impairment Allergy to ASA, ASAIs Pregnancy (T3) Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>COX-2 INHIBITORS</td>
<td>celecoxib</td>
<td>Celebrex®</td>
<td>200 mg OD</td>
<td>High risk for GI bleed: age &gt;65 Hx of GI bleed, PUD</td>
<td>Renal impairment Sulf allergy (celecoxib) Cardiovascular disease Delayed ulcer healing Renal/hepatic impairment Rash</td>
<td></td>
</tr>
<tr>
<td>Other Treatments</td>
<td>Combination analgesics (acetaminophen + codeine, acetaminophen + NSAIDs)</td>
<td>Enhanced short-term effect compared to acetaminophen alone More adverse effects: sedation, constipation, nausea, GI upset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IA corticosteroid injection</td>
<td>Short-term (weeks-months) decrease in pain and improvement in function Used for management of an IA inflammatory process when infection has been ruled out</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IA hyaluronic acid q6mo</td>
<td>Used for mild-moderate OA of the knees, however little supporting evidence, and not considered to be effective Precaution with chicken/egg allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical NSAIDs</td>
<td>25% wt/vt topical diclofenac (Pennsaid®) May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capsaicin cream</td>
<td>Mild decrease in pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucosamine sulfate ± chondroitin</td>
<td>Limited clinical studies. No regulation by Health Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 35. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMMONLY USED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydroxychloroquine $</td>
<td>Plaquenil®</td>
<td>400 mg PO OD initially, 200-400 mg PO OD maintenance (8.5 mg/kg ideal body weight per day)</td>
<td>Retinal disease, G6PD deficiency</td>
<td>GI symptoms, skin rash, macular damage, neuromyopathy. Requires regular ophthalmological screening to monitor for retinopathy</td>
</tr>
<tr>
<td>sulfasalazine $</td>
<td>Salazopyrin® Azulfidine® (US)</td>
<td>1000 mg PO bid-tid</td>
<td>Sulf/ASA allergy, kidney disease, G6PD deficiency</td>
<td>GI symptoms, rash, H/A, leukopenia</td>
</tr>
<tr>
<td>methotrexate $</td>
<td>Rheumatrex® Folex/Mexate®</td>
<td>7.5-25 mg PO/IM/SC qweekly</td>
<td>Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EtOH abuse</td>
<td>Oral ulcers, GI symptoms, cirrhosis, myelosuppression, pneumonitis, tubular necrosis</td>
</tr>
<tr>
<td>leflunomide $</td>
<td>Arava®</td>
<td>10-20 mg PO OD</td>
<td>Liver disease</td>
<td>Alopecia, GI symptoms, liver dysfunction, pulmonary infiltrates</td>
</tr>
<tr>
<td><strong>NOT COMMONLY USED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine $</td>
<td>Neoral®</td>
<td>2.5-3 mg/kg/d divided and given in 2 doses PO</td>
<td>Kidney/liver disease, infection, HTN</td>
<td>HTN, decreased renal function, hair growth, tremors, b eeding</td>
</tr>
<tr>
<td>gold (injectable) $</td>
<td>Solganal® Myocrysine®</td>
<td>50 mg IM q1wk after gradual introduction</td>
<td>IBD, kidney/liver disease</td>
<td>Rash, mouth sores/ulcers, proteinuria, marrow suppression</td>
</tr>
<tr>
<td>azathioprine $</td>
<td>Imuran®</td>
<td>2/5 mg/kg/d PO once daily</td>
<td>Kidney/liver disease TPMT deficiency</td>
<td>Rash, pancytopenia (especially ↓ WBC, ↑ AST, ALT), biliary stasis, vomiting, diarrhea</td>
</tr>
<tr>
<td>cyclophosphamide $</td>
<td>Cytoxan®</td>
<td>1 g/m2/mo IV as per protocol</td>
<td>Kidney/liver disease</td>
<td>Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEWER DMARDs (Biologics)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>etanercept $$$$$</td>
<td>Enbrel®</td>
<td>25 mg biweekly or 50 mg weekly SC</td>
<td>Fusion protein of TNF receptor and Fc portion of IgG</td>
</tr>
<tr>
<td>infliximab $$$$$</td>
<td>Remicade®</td>
<td>3-5 mg/kg IV q8wk</td>
<td>Chimeric mouse/human monoclonal anti-TNF</td>
</tr>
<tr>
<td>adalimumab $$$$$</td>
<td>Humira®</td>
<td>40 mg SC q2wk</td>
<td>Monoclonal anti-TNF</td>
</tr>
<tr>
<td>golimumab $$$$$</td>
<td>Simponi®</td>
<td>50 mg SC qmo</td>
<td>Monoclonal anti-TNF</td>
</tr>
<tr>
<td>certolizumab $$$$$</td>
<td>Cimzia®</td>
<td>400 mg SC q2wk x3 then 200 mg SC q4wk</td>
<td>PEGylated monoclonal anti TNF</td>
</tr>
<tr>
<td>Apremilast $$$$$</td>
<td>Otezla®</td>
<td>Day 1: 10mg (AM), titrate up to 30mg BID by Day 6</td>
<td>Inhibitor of PDE4 which inhibits production of TNFα</td>
</tr>
<tr>
<td>abatacept $$$$$</td>
<td>Orencia®</td>
<td>IV infusion</td>
<td>Co-stimulation modulator of T-cell activation</td>
</tr>
<tr>
<td>rituximab $$$$$</td>
<td>Rituxan®</td>
<td>2 IV infusions, 2 wk apart</td>
<td>Causes B-cell depletion, binds to CD20</td>
</tr>
<tr>
<td>tocilizumab $$$$$</td>
<td>Actemra®</td>
<td>4-8 mg/kg IV q4wk</td>
<td>Interleukin-6 receptor antagonist</td>
</tr>
<tr>
<td>Tofacitinib $$</td>
<td>Xeljanz®</td>
<td>5mg BID</td>
<td>Inhibits the JAK enzyme and thus interferes with JAK-STAT signaling pathway</td>
</tr>
</tbody>
</table>

**Risks of Biologics**  
Reactivation of TB or hepatitis B. Patients require negative TB skin test, chest x-ray and negative hepatitis B virus serology prior to starting any of these medications. Increased risk of: serious infections, worsening heart failure, multiple sclerosis, and positive auto-antibodies.
# Landmark Rheumatology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RHEUMATOID ARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTTEST</td>
<td><em>Ann Rheum Dis</em> 2008;67:1086-103</td>
<td>Abatacept and infliximab have similar efficacy in RA patients who have failed MTX</td>
</tr>
<tr>
<td>ATTRACT</td>
<td>Lancet 1999;354:1932-9</td>
<td>Infliximab and MTX combined are more effective than MTX alone for patients with active RA</td>
</tr>
<tr>
<td>CIMESTRA</td>
<td><em>Arthritis Rheum</em> 2006;54:1401-9</td>
<td>Combination of MTX and sulfasalazine is superior to either alone</td>
</tr>
<tr>
<td>COMET</td>
<td>Lancet 2008;372:375-82</td>
<td>Etanercept add-on therapy increases rates of remission in early RA</td>
</tr>
<tr>
<td>ERA</td>
<td><em>NEJM</em> 2000;342:1586-93</td>
<td>Etanercept more rapidly decreases symptoms in early RA compared to MTX</td>
</tr>
<tr>
<td>European Leflunomide Study Group</td>
<td>Lancet 1999;353:259-66</td>
<td>Leflunomide is equal in efficacy to sulphasalazine and superior to placebo</td>
</tr>
<tr>
<td>FIN-RACo</td>
<td>Lancet 1999;353:1568-73</td>
<td>Combination therapy with DMARDs improves remission rates in early RA</td>
</tr>
<tr>
<td>Infliximab and MTX</td>
<td><em>NEJM</em> 2000;342:1594-602</td>
<td>Infliximab combined with MTX reduces joint damage in RA</td>
</tr>
<tr>
<td>Leflunomide Rheumatoid Arthritis Investigators Group</td>
<td><em>Arch Intern Med</em> 1999;159:2542-50</td>
<td>Leflunomide is equivalent to MTX therapy and superior to placebo</td>
</tr>
<tr>
<td>PREMIER</td>
<td><em>Arthritis Rheum</em> 2006;54:26-37</td>
<td>Combination therapy with adalimumab and MTX is superior to either alone in patients with early RA</td>
</tr>
<tr>
<td>Swefot</td>
<td><em>Lancet</em> 2008;374:459-66</td>
<td>Anti-TNF agents are more effective second line therapy than DMARDs in patients who fail MTX</td>
</tr>
<tr>
<td><strong>OSTEOARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAIT</td>
<td><em>NEJM</em> 2006;354:795-808</td>
<td>Glucosamine, chondroitin, and the combination of both are no more effective than placebo in treatment of knee OA</td>
</tr>
<tr>
<td>SLE Belimumab</td>
<td><em>Lancet</em> 2011;377:721-31</td>
<td>Treatment with belimumab reduces the incidence of BILAG A and B flares in patients with SLE compared to placebo</td>
</tr>
<tr>
<td>BILAG open-RCT</td>
<td><em>Rheumatology</em> 2010;49:723-32</td>
<td>Low dose cyclosporine and azathioprine are equivalent in efficacy as maintenance therapy for SLE</td>
</tr>
<tr>
<td>Mycophenylate mofetil or intravenous cyclophosphamide</td>
<td><em>NEJM</em> 2005;353:2219-28</td>
<td>Mycophenylate mofetil is more efficacious than cyclophosphamide in inducing remission of SLE nephritis</td>
</tr>
<tr>
<td><strong>CONNECTIVE TISSUE DISEASES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine or MTX maintenance for ANCA-associated vasculitis</td>
<td><em>NEJM</em> 2008;359:2790-803</td>
<td>MTX and azathioprine are equally safe and effective as maintenance agents in ANCA vasculitis</td>
</tr>
<tr>
<td>Cyclophosphamide in scleroderma lung disease</td>
<td><em>NEJM</em> 2006;354:2655-66</td>
<td>Cyclophosphamide therapy leads to transient improvements in lung function, skin scores, and overall health in patients with scleroderma</td>
</tr>
<tr>
<td>Etanercept plus standard therapy for granulomatosis with polyangiitis</td>
<td><em>NEJM</em> 2005;352:351-61</td>
<td>Etanercept is not effective in inducing remission in patients with ANCA vasculitis</td>
</tr>
<tr>
<td>Mycophenylate mofetil vs. azathioprine for maintenance in ANCA-associated vasculitis</td>
<td><em>JAMA</em> 2010;304:2381-8</td>
<td>Mycophenylate mofetil is less effective than azathioprine for maintaining disease in ANCA-associated vasculitis</td>
</tr>
<tr>
<td>Rituximab versus cyclophosphamide for ANCA-associated vasculitis</td>
<td><em>NEJM</em> 2010;363:221-32</td>
<td>Rituximab is not inferior to cyclophosphamide for induction of remission in ANCA vasculitis</td>
</tr>
<tr>
<td><strong>GOUT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febuxostat vs. allopurinol</td>
<td><em>NEJM</em> 2005;353:2450-61</td>
<td>Febuxostat is more effective than allopurinol at lowering serum urate, and has similar effectiveness on flare reduction</td>
</tr>
<tr>
<td><strong>ANKYLOSING SPONDYLITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td><em>Arthritis Rheum</em> 2006;54:2136-46</td>
<td>Adalimumab induced partial remission in 22% of AS patients</td>
</tr>
<tr>
<td>ASSERT (rituximab)</td>
<td><em>Arthritis Rheum</em> 2005;52:582-91</td>
<td>Sixty percent of patients treated with rituximab had a clinical response to the medication</td>
</tr>
<tr>
<td>ATLAS (adalimumab)</td>
<td><em>J Rheumatol</em> 2008;35:1346-53</td>
<td>Compared to placebo, adalimumab significantly reduces pain and fatigue in AS patients</td>
</tr>
<tr>
<td>Infliximab in AS</td>
<td>Lancet 2002;359:1187-93</td>
<td>Infliximab induces regression of symptoms in 50% of patients and is superior to placebo</td>
</tr>
<tr>
<td>SPINE (etanercept)</td>
<td><em>Ann Rheum Dis</em> 2011;70:799-804</td>
<td>Etanercept has short-term efficacy for patients with advanced AS and reduces disease severity</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td><em>Arthritis Rheum</em> 1995;38:618-27</td>
<td>Sulfasalazine is superior to placebo in treatment of patients with seronegative spondyloarthropathy</td>
</tr>
</tbody>
</table>
References
Kremer JM. Diagnosis and management of inflammatory polyarthritis. CMAJ 2000;162:1833-1838.
Reid G, Endale JM. Getting the most out of radiology. CMAJ 2000;162:1318-1325.
Shokany N. What laboratory tests are needed? CMAJ 2000;162:1157-1163.
Acronyms ....................................................... 2
Basic Anatomy Review ................................. 2
Urologic History ........................................... 3
Hematuria (Blood in the Urine) ....................... 4
Macroscopic (Gross) Hematuria
Microscopic Hematuria

Lower Urinary Tract Dysfunction ................. 5
Voiding
Urinary Incontinence

Lower Urinary Tract Symptoms (LUTS) ......... 6
Urinary Retention
Benign Prostatic Hyperplasia
Urethral Stricture
Neurogenic Bladder
Dysuria
Hydronephrosis
Post-Obstructive Diuresis

Overactive Bladder ........................................ 11

Infectious and Inflammatory Diseases ........... 12
Urinary Tract Infection
Recurrent/Chronic Cystitis
Interstitial Cystitis (Painful Bladder or
Bladder Pain Syndrome)
Acute Pyelonephritis
Prostatitis/Prostatodynia
Epididymitis and Orchitis
Urethritis

Stone Disease .............................................. 17
Approach to Renal Stones

Urological Neoplasms ................................. 20
Approach to Renal Mass
Benign Renal Neoplasms
Malignant Renal Neoplasms
Carcinoma of the Renal Pelvis and Ureter
Bladder Carcinoma
Prostate Cancer
Prostate Cancer Screening
Testicular Tumours
Penile Tumours

Scrotal Masses ............................................. 29

Penile Complaints ........................................ 30
Erectile Dysfunction

Trauma ....................................................... 32
Renal Trauma
Bladder Trauma
Urethral Injuries

Infertility ..................................................... 34
Female Factors
Male Factors

Pediatric Urology ......................................... 36
Congenital Abnormalities
Nephroblastoma (Wilms’ Tumour)
Cryptorchidism/Ectopic Testes
Disorders of Sexual Differentiation
Enuresis

Selected Urological Procedures ................. 40
Bladder Catheterization
Circumcision
Cystoscopy
Radical Prostatectomy
Transurethral Resection of the Prostate
Extracorporeal Shock Wave Lithotripsy

Common Medications .................................. 42

References ............................................... 44
Basic Anatomy Review

- recall that the anatomical position of the penis is erect; therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis.
Urologic History

- follow OPQRSTUVW approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
- inquire about risk factors: past urologic disease (e.g. UTI, stones, STI, cancers, anatomic abnormalities), family Hx, medications, lifestyle factors (smoking, alcohol, inactivity), trauma, previous surgical procedures
- urinary habits
  - frequency of voiding, incontinence, nocturia
  - specific urinary symptoms include
    - storage symptoms: frequency, nocturia, incontinence, urgency (rush to toilet), stress (leak with cough/laughter)
    - voiding symptoms: straining, hesitancy, dysuria, intermittency, post-void dribbling, reduced stream, feeling of incomplete voiding
  - hematuria: blood clots, red/pink tinged urine
- sexual function
  - scrotal mass: see Scrotal Mass, U29
  - ED: see Erectile Dysfunction, U30
  - infertility: see Infertility, U34
- associated symptoms
  - N/V
  - bowel dysfunction
- constitutional symptoms
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise, bone pain

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant vascular disease. If there is new onset ED, consider screening for DM and CAD risk factors.
Hematuria (Blood in the Urine)

Macroscopic (Gross) Hematuria

Definition
- blood in the urine that can be seen with the naked eye

Classification
- see Nephrology, NP21

Etiology

Table 1. Etiology by Age Group

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20</td>
<td>UTI, glomerulonephritis, congenital abnormalities</td>
</tr>
<tr>
<td>20-40</td>
<td>UTI, stones, bladder tumour, exercise</td>
</tr>
<tr>
<td>40-60</td>
<td>Male: bladder tumour, stones, UTI Female: UTI, stones, bladder tumour</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Male: BPH, bladder tumour, UTI, RCC Female: bladder tumour, UTI, RCC</td>
</tr>
</tbody>
</table>

Table 2. Etiology by Type

<table>
<thead>
<tr>
<th>Pseudohematuria</th>
<th>Infectious/ Inflammatory</th>
<th>Malignancy</th>
<th>Benign</th>
<th>Structural</th>
<th>Hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal bleeding</td>
<td>Pyelonephritis</td>
<td>RCC (mainly adults)</td>
<td>BPH Polyph</td>
<td>Stones</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Dyes (beets, rhodamine B in candy and juices)</td>
<td>Cystitis</td>
<td>UCC Wilm's tumour (mainly pediatric)</td>
<td>Exercise-exposed</td>
<td>Trauma Foreign body</td>
<td>Coagulation defects</td>
</tr>
<tr>
<td>Hemoglobin (hemolytic anemia)</td>
<td>Urethritis</td>
<td>Leukemia</td>
<td></td>
<td>Urinary stricture</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Myoglobin (rhabdomyolysis)</td>
<td>Glomerulonephritis</td>
<td>Arteriovenous malformation</td>
<td></td>
<td>Poly cystic kidneys</td>
<td>Thrombembolism</td>
</tr>
<tr>
<td>Drugs (rifampin, phenazopyridine, phenytoin)</td>
<td>Interstitial nephritis Tuberculosis</td>
<td>Infarct</td>
<td></td>
<td>Thromboembolism</td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
<td>Hydronephrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxatives (phenolphthalein)</td>
<td></td>
<td>Fistula</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

History
- timing of hematuria in urinary stream
  - initial: anterior urethra
  - terminal: bladder neck and prostatic urethra
  - total: bladder and/or above
- associated symptoms (storage and voiding)
  - pyuria, dysuria: UTI
  - flank pain, radiation: ureteral obstruction
- recent URTI: post-infectious glomerulonephritis, IgA nephropathy

Investigations
- CBC (rule out anemia, leukocytosis), electrolytes, Cr, BUN, INR, PTT
- urine studies
  - U/A, C&S, cytology
- imaging
  - CT contrast has largely replaced IVP to investigate upper tracts
  - consider contraindications: allergy, renal insufficiency, pregnancy
  - U/S alone may not be sufficient
  - cystoscopy to investigate lower tract (possible retrograde pyelogram)

Acute Management of Severe Bladder Hemorrhage
- manual irrigation via catheter with normal saline to remove clots
- Continuous Bladder Irrigation (CBI) using large (22-26 Fr) 3-way Foley to help prevent clot formation
- cystoscopy if active bleeding
  - identify resectable tumours
  - coagulate obvious sites of bleeding
- refractory bleeding
  - bilateral nephrostomy tube placement
  - hyperbaric oxygen
  - intravesical agents
  - continuous intravesical irrigation with 1% aluminum potassium sulfate solution as needed
  - intravesical instillation of 1% silver nitrate solution
  - intravesical instillation of 1-4% formalin (requires GA and pre-procedure cystogram to rule out reflux)
  - embolization or ligation of iliac branches
  - cystectomy and diversion (rarely performed)

Common Urologic Causes of Hematuria
 can be Classified as:

- TICS
  - Trauma/Tumour/Toxins
  - Infection/Inflammatory
  - Calculi/Cysts
  - Surgery/Sickle cell and other hematological causes

Upper Tract Imaging Options
- CT Urography (CTU): test of choice for renal parenchyma, calculi, and infections. Involves exposure to radiation and IV contrast (assess renal function and allergies)
- U/S: Superior to IVP for evaluation of renal parenchyma and renal cysts; limited sensitivity for UCC and small renal masses; U/S alone is insufficient for upper tract imaging
- Intravenous Pyelogram (IVP): Traditional option but rarely used (replaced by CTU); reasonable sensitivity for UCC, but poor sensitivity for RCC
**Microscopic Hematuria**

**Definition**
- blood in the urine that is not visible to the naked eye
- ≥2 RBCs/HPF on urinalysis of at least two separate samples

![Flowchart](image)

*Figure 6. Workup of asymptomatic microscopic hematuria*

Based on CUA Guidelines. Alternatively, the AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative workup is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists.

---

**Lower Urinary Tract Dysfunction**

- see Gynecology for relevant female topics
- the lower urinary tract consists of the bladder and urethra. LUTD frequently involves both parts

**Voiding**

- two phases of lower urinary tract function
  1. storage phase (bladder filling and urine storage)
     - accommodation and compliance
     - no involuntary contraction(s)
  2. voiding phase (bladder emptying)
     - coordinated detrusor contraction
     - synchronous relaxation of outlet sphincters
     - no anatomic obstruction
- voiding dysfunction can therefore be classified as
  - failure to store: due to bladder or outlet
  - failure to void: due to bladder or outlet
- three types of symptoms
  - storage (formerly known as irritative)
  - voiding (formerly known as obstructive)
  - post-voiding

**Urinary Incontinence**

**Definition**
- involuntary leakage of urine

**Etiology**
- urgency incontinence
  - detrusor overactivity
    - CNS lesion, inflammation/infection (cystitis, stone, tumour), bladder neck obstruction (tumour, stone), BPH, idiopathic
    - decreased compliance of bladder wall (inability to store urine)
  - CNS lesion, fibrosis
  - sphincter/urethral problem
• stress urinary incontinence (SUI)
  • common in women; seen in men after prostate cancer treatment or pelvic operations
  • urethral hypermobility
    • weakened pelvic floor and musculofascial urethral and vaginal supporting mechanisms allows bladder neck and urethra to descend with increased intra-abdominal pressure
  • urethra is pulled open by greater motion of posterior wall of outlet relative to anterior wall
  • associated with childbirth, pelvic surgery, aging, levator muscle weakness, obesity
  • intrinsic sphincter deficiency (ISD): weakness of the urethra and associated smooth and striated muscle elements
  • pelvic surgery, neurologic problem, aging and hypoestrogen state
  • ISD and urethral hypermobility frequently co-exist
  • mixed incontinence
  • combination of stress and urgency incontinence
  • overflow incontinence
  • is a term sometimes used to describe urinary incontinence associated with urinary retention; for causes of urinary retention see Table 4
  • use of the term should be accompanied by the associated pathophysiology (e.g. BPH with overflow incontinence)

**Epidemiology**
• variable prevalence in women: 25-45%
• F:M = 2:1
more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

**Table 3. Urinary Incontinence: Types and Treatments**

<table>
<thead>
<tr>
<th>Type</th>
<th>Urgency</th>
<th>Stress</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Involuntary leakage of urine preceded by a strong, sudden urge to void</td>
<td>Involuntary leakage of urine with sudden increases in intra-abdominal pressure</td>
<td>Urinary leakage associated with urgency and increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Etiology</td>
<td>Bladder (detrusor overactivity)</td>
<td>Urethra/sphincter weakness, post-partum pelvic muscle atony weakness</td>
<td>Combination of bladder and sphincter issues</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hx</td>
<td>Urodynamics</td>
<td>Hx</td>
</tr>
<tr>
<td></td>
<td>Urodynamics</td>
<td>Stress test (Valsalva/Cough)</td>
<td>Stress test</td>
</tr>
<tr>
<td>Therapy</td>
<td>Lifestyle changes (fluid alterations, diet, etc.)</td>
<td>Weight loss</td>
<td>Combination of management of urgency and stress incontinence</td>
</tr>
<tr>
<td></td>
<td>Bladder habit training</td>
<td>Kegel exercises</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticholinergics</td>
<td>Bulking agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ß-3-agonist</td>
<td>Surgery (slings, tension-free vaginal tape, retropubic urethroplasty, artificial sphincter)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurromodulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lower Urinary Tract Symptoms (LUTS)**

**Urinary Retention**

**Table 4. Etiology of Urinary Retention**

<table>
<thead>
<tr>
<th>Outflow Obstruction</th>
<th>Bladder Immersion</th>
<th>Pharmacologic</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurological (DSD)</td>
<td>Intracranial: CVA, tumour, Parkinson’s, cerebral palsy</td>
<td>Anticholinergics</td>
<td>GU: UTI, prostatitis abscess, genital herpes</td>
</tr>
<tr>
<td>Prostate: BPH, prostate cancer</td>
<td>Spinal cord: injury, disc herniation, MS</td>
<td>Narcotics</td>
<td>Infected foreign body</td>
</tr>
<tr>
<td>Urethra: stricture, phimosis, traumatic disruption</td>
<td>DM</td>
<td>Antihypertensives (ganglionic blockers, methyldopa)</td>
<td>Varicella zoster</td>
</tr>
<tr>
<td>Miscellaneous: constipation, pelvic mass</td>
<td>Post-abdominal or pelvic surgery</td>
<td>OTC cold medications containing ephedrine or pseudoephedrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychosomatic substances (e.g. ecstasy)</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Features**
• suprapubic pain (with acute retention), incomplete emptying, weak stream
• palpable and/or percussible bladder (suprapubic)
• possible purulent/bloody meatal discharge (with UTI)
• increased size of prostate or reduced anal sphincter tone on DRE
• neurological: presence of abnormal or absent deep tendon reflexes, reduced “anal wink”, saddle anesthesia
**Investigations**
- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

**Treatment**
- treat underlying cause
- catheterization
  - acute retention
    - immediate catheterization to relieve retention; leave Foley in to drain bladder; follow-up to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - intermittent catheterization by patient may be used; definitive treatment depends on etiology
- suprapubic catheter if obstruction precludes urethral catheter
- for post-operative patients with retention:
  - encourage ambulation
  - α-blockers to relax bladder neck outlet
  - may need catheterization
  - definitive treatment will depend on etiology

---

**Benign Prostatic Hyperplasia**

**Definition**
- periurethral hyperplasia of stroma and epithelium in prostatic transition zone
- prostatic smooth muscle cells play a role in addition to hyperplasia

**Etiology**
- unknown
  - DHT required (converted from testosterone by 5-α reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors

**Epidemiology**
- age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
- 25% of men will require treatment

**Clinical Features**
- result from outlet obstruction and compensatory changes in detrusor function
- voiding and storage symptoms
- DRE
  - prostate is smooth, rubbery, and may be symmetrically enlarged
- complications
  - retention
  - overflow incontinence
  - hydroureteronephrosis
  - renal insufficiency
  - infection
  - gross hematuria
  - bladder stones

**Investigations**
- Hx, assessing LUTS and impact on QOL
  - may include self-administered questionnaires (IPSS or AUA symptom index for severity, progression, and treatment response)
- P/E, including DRE
- U/A to exclude UTI
- Cr to assess renal function
- renal U/S to assess for hydroureteronephrosis
- PSA to rule out malignancy (see Prostate Cancer Screening, U26)
- uroflowmetry to measure flow rate (optional)
- PVR (optional)
- consider cystoscopy or bladder ultrasound prior to potential surgical management to evaluate outlet and prostate volume
- biopsy if suspicious for malignancy, i.e. elevated PSA or abnormal DRE

---

**Figure 7. Cross-section of prostate**

**Prostate size does not correlate well with symptoms in BPH**

**Approximate Prostate Sizes**
- 20 cc – chestnut
- 25 cc – plum
- 50 cc – lemon
- 75 cc – orange
- 100 cc – grapefruit

**AUA BPH Symptom Score**

**FUNWISE**
- Frequency
- Urgency
- Nocturia
- Weak stream
- Intermittency
- Straining
- Emptying, incomplete feeling of

Each symptom graded out of 5
- 0-7: Mildly symptomatic
- 8-18: Moderately symptomatic
- 20-35: Severely symptomatic

Note: dysuria not included in score but is commonly associated with BPH

Initial alpha-adrenergic antagonist monotherapy for score <20, combination therapy for score >20
Table 5. Treatment of BPH

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Conservative</th>
<th>Medical</th>
<th>Surgical</th>
<th>Minimally Invasive Surgical Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to use</td>
<td>Asymptomatic patients or symptomatic without bother</td>
<td>Moderate to severe symptoms that are distressing for patient</td>
<td>Significant symptom burden, acute urinary retention, refractory hematuria, recurrent infections</td>
<td>Patients who wish to avoid or may not tolerate surgery</td>
</tr>
<tr>
<td>Options</td>
<td>Watchful waiting: 50% of patients improve spontaneously</td>
<td>Lifestyle modifications (e.g. evening fluid restriction, planned voiding)</td>
<td>TURP (see U41)</td>
<td>Laser ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-adrenergic antagonists: reduce stromal smooth muscle tone</td>
<td>TURP (prostate &lt;30 g)</td>
<td>Open prostatectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-α reductase inhibitor: block conversion of testosterone to DHT; act to reduce prostate size</td>
<td>Microwave therapy</td>
<td>TUNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination is synergistic</td>
<td>Prostatic stent (not commonly used)</td>
<td></td>
</tr>
</tbody>
</table>

### Urethral Stricture

**Definition**
- decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

**Etiology**
- congenital
  - failure of normal canalization (i.e. posterior urethral valves)
- trauma
  - instrumentation/catheterization (most common)
  - external trauma (e.g. burns, straddle injury)
  - foreign body
- infection
  - long-term indwelling catheter
  - STI (gonococcal or chlamydial disease)
- inflammation
  - balanitis xerotica obliterans (BXO; lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal and urethral stenosis

**Clinical Features**
- voiding and storage symptoms
- urinary retention
- hydrotension
- related infections: recurrent UTI, secondary prostatitis/epididymitis

**Investigations**
- laboratory findings
  - flow rates <10 mL/s (normal ~20 mL/s) on uroflowmetry
  - urine culture usually negative, but U/A may show pyuria
- radiologic findings
  - RUG and VCUG will demonstrate location
  - cystoscopy

**Treatment**
- urethral dilatation
  - temporarily increases lumen size by breaking up scar tissue
  - healing will often reform scar tissue, recurrence of stricture
- visual internal urethrotomy (VIU)
  - endoscopically incise stricture
  - equal success rates to dilation with mid bulbar strictures <2 cm
  - high rate of recurrence (30-80%), avoid in younger patients
- open surgical reconstruction
  - complete stricture excision with anastomosis, ± urethroplasty depending on location and size of stricture

---

**Summary of Findings:**
- Men with planned cataract surgery should avoid starting β-adrenergic antagonists until after their surgery due to the risk of intraoperative floppy iris syndrome
- BPH Surgery
  - Absolute Indication
    - Renal failure with obstructive uropathy
    - Refractory urinary retention
  - Relative Indications
    - Recurrent UTI
    - Recurrent hematuria refractory to medical management
    - Renal insufficiency (rule out other causes)
    - Bladder stones

---

**Combination therapy vs. alpha blocker or SARI**

**Summary:**
- Men with baseline prostate volume ≥40mL and baseline PSA ≥1.5 ng/mL had greater reductions in RR of BPH-related surgery and RR of clinical progression on combined therapy compared to dutasteride monotherapy and than on tamsulosin monotherapy.

**Methods:** A 4 year combination of dutasteride and tamsulosin study was a multicentre double-blind RCT of outcomes in men ≥50 years old with symptomatic BPH, with PSA ≥1.5ng/mL and ≤10ng/mL, and prostate volume ≤30mL. Patients received tamsulosin, dutasteride or combination therapy. Primary endpoint was time to first acute urinary retention or BPH-related surgery; secondary endpoint was clinical progression of BPH/symptoms.

**Results:** Combination therapy resulted in significantly greater improvements in symptoms compared to dutasteride from 3 mo, and tamsulosin from 9 mo, and in BPH-related health status from 3 and 12 mo, respectively. There was a significant increase in ADE with combination therapy vs. monotherapies. However, withdrawal rates due to drug-related adverse events were similar across the treatment groups.

**Finasteride for Benign Prostatic Hyperplasia**

**Rationale:** To examine the effectiveness and safety of finasteride versus placebo or other active controls for the treatment of lower urinary tract symptoms.

**Summary of Findings:**
- 1. Finasteride improved urinary symptoms more than placebo in trials ≥1 yr duration and significantly lowered the risk of RUPH progression.
  - Compared with α-blockers, finasteride was less effective than either doxazosin or terazosin, but equally as effective as tamsulosin.
- 2. Symptom improvement with finasteride + doxazosin was equal to doxazosin alone.
- 3. Finasteride treatment resulted in an increased risk of ejaculation disorder, impotence and lowered libido compared with placebo.
- 4. Compared with doxazosin and terazosin, finasteride had a lower risk of orthostatic, dizziness, and postural hypotension.
Neurogenic Bladder

Definition
- dysfunction of the urinary bladder due to deficiency in some aspect of its innervation

Neurophysiology

Table 6. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply

<table>
<thead>
<tr>
<th>Nerve Fibres</th>
<th>Nerve Roots</th>
<th>Neurotransmitter/Receptor</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic</td>
<td>T10-L2</td>
<td>NA/Adrenergic</td>
<td>Trigone, internal sphincter, proximal urethra (α receptors) Bladder body (β receptors)</td>
</tr>
<tr>
<td>Somatic (Pudendal)</td>
<td>S2-4</td>
<td>ACh/Nicotinic</td>
<td>External sphincter</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>S2-4</td>
<td>ACh/Muscarinic (M2 M3)</td>
<td>Detrusor</td>
</tr>
</tbody>
</table>

- stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  - micturition
    - stimulation of parasympathetic neurons (bladder contraction)
    - inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  - urine storage
    - opposite of micturition
- voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
- cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem

Examples of Neurologic Voiding Dysfunction
- neurogenic detrusor overactivity (NDO) (formerly termed detrusor hyperreflexia)
  - lesion above PMC (e.g. stroke, tumour, MS, Parkinson’s disease)
  - loss of voluntary inhibition of voiding
  - intact pathway inferior to PMC maintains coordination of bladder and sphincter
- detrusor sphincter dysynergia (DSD)
  - suprasacral lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  - loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  - component of detrusor overactivity as well
- detrusor atony/areflexia
  - lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality, post abdominoperineal resection)
  - flaccid bladder which fails to contract
  - may progress to poorly compliant bladder with high pressures
- peripheral autonomic neuropathy
  - deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
- muscular lesion
  - can involve detrusor, smooth/striated sphincter

Neuro-Urologic Evaluation
- Hx and P/E (urologic and general neurologic)
- voiding diary
- catheterization volumes in patients with CIC
- U/A, renal profile
- imaging
  - U/S to rule out hydronephrosis and stones; occasionally CT scanning with or without contrast
  - cystoscopy
  - urodynamic studies
    - uroflowmetry to assess flow rate, pattern
    - filling CMG to assess capacity, compliance, detrusor overactivity
    - voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
    - video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
    - EMG and video ascertain presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

Treatment
- goals of treatment
  - prevent renal deterioration
  - prevent infections
  - achieve social continence

Microwave Thermotherapy for Benign Prostatic Hyperplasia

Purpose: To evaluate the efficacy and safety of microwave thermotherapy (TUMT) for men with symptomatic BPH with multiple comparison groups.

Selection Criteria: RCTs evaluating transurethral microwave therapy (TUMT) for men with symptomatic BPH with multiple comparison groups.

Results: 15 studies, 1,585 patients, mean age 66.8 yr, 3-6 mo duration. Mean urinary symptom scores decreased by 65% with TUMT and 77% with TURP. The pooled mean peak urinary flow increased by 70% with TUMT and 119% with TURP. Compared with TURP, TUMT was associated with decreased risks for retrograde ejaculation, treatment for strictures, hema uria, blood transfusions and transurethral resection syndrome, but increased risk of urinary retention and re-resection for BPH symptoms.

Conclusions: Overall, microwave thermotherapy techniques are effective alternatives to TURP and α-blockers for treating symptomatic BPH, although less effective than TURP in improving symptom score and urinary flow.

"Spinal shock", initially manifests as atonic bladder

Nerve roots in micturition: "S2-3-4 keeps the urine off the floor"
Lower Urinary Tract Symptoms (LUTS)

- clean intermittent catheterization (CIC)
- treatment options depend on status of bladder and urethra
  - bladder hyperactivity → anticholinergic medications to relax bladder (see Urinary Incontinence, U5)
    - refractory
      - botulinum toxin injections into bladder wall
      - occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance
        by grafting section of detubularized bowel onto the bladder)
      - occasionally urinary diversion (ileal conduit or continent diversion) in severe cases if bladder
        management unsuccessful
  - flaccid bladder → CIC

Dysuria

Definition
- painful urination

Etiology

Table 7. Differential Diagnosis of Dysuria

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perianal inflammation/infection, TB, vestibulitis</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Kidney, bladder, prostate, penis, vagina/vulva, BPH</td>
</tr>
<tr>
<td>Calculi</td>
<td>Bladder stone, urethral stone, ureteral stone</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis</td>
</tr>
<tr>
<td>Hormonal</td>
<td>Endometriosis, hypoestrogenism</td>
</tr>
<tr>
<td>Trauma</td>
<td>Catheter insertion post-coital cystitis (honeymoon cystitis)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Somatization disorder, depression, stress/anxiety disorder</td>
</tr>
<tr>
<td>Other</td>
<td>Contact sensitivity, foreign body, radiation/chemical cystitis, diverticulum</td>
</tr>
</tbody>
</table>

Investigations
- focused Hx and P/E to determine cause (fever, d/c, conjunctivitis, CVA tenderness, back/joint pain)
  - any d/c (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal d/c
  - U/A and urine C&S
  - if suspect infection, may start empiric ABx treatment (see Table 9, U12)
  - ± imaging of urinary tract (tumour, stones)

Hydronephrosis

- the upper urinary tract consists of the kidneys and ureters

Definition
- dilation of the renal pelvis and calyces caused by the impairment in antegrade urine flow

Etiology
- mechanical
  - congenital: see Congenital Abnormalities, U36
  - acquired
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral
      stricture, phimosis, previous urological surgery
    - extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies;
      lymphoma), aortic aneurysm, pregnancy (gravid uterus)
  - functional
    - neuropathic: neurogenic bladder, diabetic neuropathy, spinal cord disease
    - pharmacologic: α-adrenergic agonists
    - hormonal: pregnancy (progesterone decreases ureteral tone)

Investigations
- focused Hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, Hx of UTIs, calculi, PID, and urological surgery
- CBC, electrolytes, Cr, BUN, U/A, C&S
- imaging studies (U/S is >90% sensitive and specific)
- MAG3 diuretic renogram: evaluates differential renal function and demonstrates if functional
  obstruction exists

Treatment
- hydronephrosis can be physiologic
- treatment should be guided at improving symptoms, treating infections, or improving renal function
- urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure
overactive bladder

post-obstructive diuresis

definition
- polyuria resulting from relief of severe chronic obstruction
- >3 L/24 h or >200 cc/h over each of two consecutive hours

pathophysiology
- physiologic POD secondary to excretion of retained urea, Na⁺, and H₂O (high osmotic load) after relief of obstruction
  - self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
- pathologic POD is a Na⁺-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to:
  - decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  - increased medullary blood flow (solute washout)
  - increased flow and solute concentration in the distal nephrons

management
- admit patient and closely monitor hemodynamic status and electrolytes (Na⁺ and K⁺ q6-12h and replace prn; follow Cr and BUN to baseline)
- monitor U/O q2h and ensure total fluid intake <U/O by replacing every 1 mL U/O with 0.5 mL ½ NS IV (PO fluids if physiologic POD)
- avoid glucose-containing fluid replacement (iatrogenic diuresis)

overactive bladder

definition
- a symptom complex that includes urinary urgency with or without urgency incontinence, urinary frequency (voiding ≥8 times in a 24 hr period), and nocturia (awakening ONE or more times at night to void)

etiology
- multiple etiologies proposed
- symptoms usually associated with involuntary contractions of the detrusor muscle
- may be associated with other conditions such as SUI in women and BPH in men (see Table 8)
- may be neurogenic, myogenic or idiopathic

epidemiology
- F:M = 1:1
- prevalence increases with age. 42% in males ≥75 years; 31% in females ≥75 years

diagnosis
- the diagnostic process should document symptoms that define overactive bladder and exclude other disorders that could cause the patient's symptoms
- minimal requirements for the process consist of:
  - focused history including past genitourinary disorders and conditions outlined in Table 8, questionnaires of LUTS for women and diaries of urination frequency, volume and pattern
  - P/E including genitourinary, pelvic and rectal examination
  - U/A to rule out hematuria and infection
- in some patients, the following investigations could be considered
  - post-void residual
  - cystoscopy to rule out recurrent infections, carcinoma in situ and other intravesical abnormalities
  - urodynamics to rule out obstruction in older men

treatment
- non pharmacological: behaviour therapies such as bladder training, bladder control strategies, pelvic floor muscle training, fluid management, and avoidance of caffeine, alcohol
- pharmacological
  - anti-muscarinics: oxybutynin hydrochloride, tolterodine, solifenacin, fesoterodine, or trospium
  - β3-adrenoceptor agonist: mirabegron
- refractory patients may be treated with:
  - neuromuscular-junction inhibition: botulinum toxin bladder injection
- others
  - percutaneous tibial nerve stimulation (not used commonly in Canada)
  - sacral neuromodulation
Infectious and Inflammatory Diseases

Table 8. Conditions that Could Contribute to Symptoms of Overactive Bladder

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Urinary Tract</td>
<td>UTI, obstruction, impaired bladder contractility</td>
</tr>
<tr>
<td>Neurologic Conditions</td>
<td>Stroke, MS, dementia, diabetic neuropathy</td>
</tr>
<tr>
<td>Systemic Diseases</td>
<td>CHF, sleep disorders (primarily nocturia)</td>
</tr>
<tr>
<td>Functional and Behavioural</td>
<td>Excessive caffeine and alcohol, constipation, impaired mobility</td>
</tr>
<tr>
<td>Medication</td>
<td>Diuretics, anticholinergic agents, narcotics, calcium-channel blocker, cholinesterase inhibitors</td>
</tr>
</tbody>
</table>

Table 9. Antibiotic Treatment of Urological Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethritis</td>
<td>Non-Gonococcal: azithromycin (1 g PO) OR doxycycline (100 mg PO bid) OR ceftriaxone (250 mg IM) AND treat for Chlamydia trachomatis</td>
<td>x 1 d</td>
</tr>
<tr>
<td></td>
<td>Simple, Uncomplicated UTI: TMP-SMX (160 mg/800 mg PO bid) OR nitrofurantoin (100 mg PO bid)</td>
<td>3 d and 5 d</td>
</tr>
<tr>
<td></td>
<td>Complicated UTI: ciprofloxacin (1 g PO daily OR 400 mg IV q12h) OR ampicillin (1 g IV q6h) + gentamicin (1 mg/kg IV q8h) (used for relatively short courses because of toxicity) OR ceftriaxone (1-2 g IV q24h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td></td>
<td>Recurrent/Chronic Cystitis: Prophylactic Treatment Continuous: TMP-SMX (40 mg/200 mg PO qHS OR 3x/wk) OR nitrofurantoin (50-100 mg PO qHS) OR Post-Coital: TMP-SMX (40 mg/200 mg-80 mg/400 mg) OR nitrofurantoin (50-100 mg PO qd)</td>
<td>6-12 mo, 6-12 mo, within 2 h of coitus, within 2 h of coitus</td>
</tr>
<tr>
<td></td>
<td>Acute Prostatitis: ciprofloxacin (500-750 mg PO bid) OR TMP-SMX (160 mg/800 mg PO bid) OR IV therapy with gentamicin and ampicillin, penicillin with β-lactamase inhibitor, 3rd gen cephalosporin, OR a fluoroquinolone</td>
<td>2-4 wk</td>
</tr>
<tr>
<td></td>
<td>Chronic Prostatitis: ciprofloxacin (500 mg PO bid)</td>
<td>4-6 wk</td>
</tr>
<tr>
<td></td>
<td>Epididymitis/Orchitis: &lt;35 yr: ceftriaxone (200 mg IM) AND doxycycline (100 mg PO bid) OR ≥35 yr: ciprofloxacin (300 mg PO bid)</td>
<td>x 1 and 10 d</td>
</tr>
<tr>
<td></td>
<td>Acute Uncomplicated Pyelonephritis: ciprofloxacin (500 mg PO bid) OR ≥: ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV) OR IV therapy with a fluoroquinolone gentamicin and ampicillin, extended spectrum cephalosporin, extended spectrum penicillin, OR a carbapenem</td>
<td>7 d and x 1 and 14 d total (IV and oral step-down)</td>
</tr>
</tbody>
</table>

Infectious and Inflammatory Diseases

Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results.

Cystitis: Common Pathogens

KEEPS
- Klebsiella sp.
- E. coli (90%), other Gram-negatives
- Enterococci
- Proteus mirabilis, Pseudomonas
- S. saprophyticus

Acute uncomplicated pyelonephritis: suspected or confirmed Enterococcus infection requires treatment with ampicillin.

Urinary Tract Infection

- for UTIs during pregnancy, see Obstetrics, OB28

Definition
- symptoms suggestive of UTI + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy)

Classification
- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, male patients, immunocompromised, diabetic, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see Recurrent/Chronic Cystitis
**Risk Factors**
- stasis and obstruction
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cysto- ele, neurogenic bladder
- foreign body
- introduce pathogen or act as nidus of infection e.g. catheter, instrumentation
- decreased resistance to organisms
- DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors
  - trauma, anatomic abnormalities, female, sexual activity, menopause, fecal incontinence

**Clinical Features**
- storage symptoms: frequency, urgency, dysuria
- voiding symptoms: hesitancy, post-void dribbling, dysuria
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA, tenderness, flank pain)

**Organisms**
- typical organisms: KEEPS (E. coli 75-95%)
- atypical organisms
  - tuberculosis (TB)
  - Chlamydia trachomatis
  - Mycoplasma (Ureaplasma urealyticum)
  - fungi (Candida)

**Indications for Investigations**
- pyelonephritis
- persistence of pyuria/symptoms following adequate antibiotic therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- Hx of structural abnormalities/decreased flow

**Investigations**
- U/A, urine C&S
  - UA: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see Microscopic Hematuria, U5)
- U/S, CT scan if recurrent or treatment-resistant UTIs, suspected anatomic abnormalities, history indicates complicated cystitis

**Treatment**
- see Table 9, U12, Antibiotic Treatment of Urological Infections
- if febrile, consider admission with IV therapy and rule out obstruction

---

**Recurrent/Chronic Cystitis**

**Definition**
- ≥3 UTIs/yr

**Etiology**
- bacterial reinfection (80%) vs. bacterial persistence (relapse)
  - bacterial reinfection
    - recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  - bacterial persistence
    - same organism cultured within 2 wk of sensitivity-based therapy

**Investigations**
- assess predisposing factors
- investigations may include cystoscopy, U/S, CT

**Treatment**
- lifestyle changes (limit caffeine intake, increase fluid/H2O intake)
- ABx: continuous vs. post-coital
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

---

**Prevention of UTIs**
- Maintain good hydration (try cranberry juice)
- Wipe from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse
**Interstitial Cystitis**  
(Painful Bladder or Bladder Pain Syndrome)

**Definition**  
- bladder pain, chronic urgency and frequency without other reasonable causation

**Classification**  
- non-ulcerative (more common)  
- ulcerative

**Etiology**  
- unknown  
  - theories: increased epithelial permeability, autoimmune, neurogenic, defective GAG layer overlying mucosa

**Epidemiology**  
- prevalence: 20/100,000  
- 90% of cases are in females  
- mean age at onset is 40 yr (non-ulcerative tends to affect a younger to middle-aged population, while ulcerative tends to be seen in middle-aged to older)

**Clinical Features**  
- bladder pain, increase with filling and relief with emptying  
- glomerulations (submucosal petechiae) or Hunner’s lesions (ulcers) on cystoscopic examination  
- urinary urgency  
- negative U/A, urine C&S, and urine cytology

**Differential Diagnosis**  
- UTI, vaginitis, bladder tumour  
- radiation/chemical/eosinophilic/TB cystitis  
- eosinophilic/TB cystitis  
- bladder calculi

**Investigations**  
- Hx, P/E, urinalysis with microscopy

**Treatment**  
- first-line: patient empowerment (diet, lifestyle, stress management), pain management  
- second-line  
  - oral: pentosan polysulfate sodium, amitriptyline, cimetidine, hydroxyzine  
  - intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine  
- third-line: cystoscopy with bladder hydrodistention (traditionally diagnostic) under GA, treat Hunner’s lesions if present  
- other: neuromodulation, cyclosporine A, intradetrusor botulinum toxin  
- surgery (last resort): augmentation cystoplasty, or urinary diversion ± cystectomy

**Acute Pyelonephritis**

**Definition**  
- infection of the renal parenchyma with local and systemic manifestations  
- clinical diagnosis of flank pain, fever and elevated WBC

**Etiology**  
- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)  
- causative microorganisms  
  - gram positives: *Enterococcus faecalis, S. aureus, S. saprophyticus*  
  - gram negatives: *E. coli, Klebsiella, Proteus, Pseudomonas, Enterobacter*  
- common underlying causes of pyelonephritis  
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

**Clinical Features**  
- rapid onset (<24 h)  
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis  
- fever, chills, nausea, vomiting, myalgia, malaise  
- CVA tenderness and/or exquisite flank pain
Investigations
- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging indicated if suspicious of complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

Treatment
- hemodynamically stable
  - outpatient oral ABx treatment ± single initial IV dose (see Table 9, U12)
- severe or non-resolving
  - admit, hydrate, and treat with IV ABx (see Table 9, U12)
- emphysematous pyelonephritis
  - most patients receive nephrectomy after IV ABx started and patient stabilized
  - consider temporization with nephrostomy tubes
- renal obstruction
  - admit for emergent stenting or percutaneous nephrostomy tube

Prostatitis/Prostatodynia

Epidemiology
- most common urologic diagnosis in men <50 yr
- prevalence 2-12%

Classification

<table>
<thead>
<tr>
<th>Table 10. Comparison of the Three Types of Prostatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category I: Acute Bacterial Prostatitis</strong></td>
</tr>
</tbody>
</table>
| Etiology | Ascending urethral infection with KEEPS: 80% *E. coli*
| Clinical Features | Acute onset fever, chills, malaise, pelvic pain, LUTS |
| Investigations | P/E: abdomen, external genitalia, perineum, prostate U/A, Blood CBC, C&S, Transrectal U/S if non-resolving/suspect prostatic abscess |
| Treatment | Supportive measures PO or IV ABx depending how sick (see Table 9, U12), May consider catheterization in patients with severe obstructive LUTS or retention |

**Category II: Chronic Bacterial Prostatitis**
- Recurrent exacerbations of acute prostatitis-like signs and symptoms
- Recurrent UTI with same organism

**Category III: Chronic Pelvic Pain Syndrome (CPPS) (Abacterial)**
- Divided into inflammatory (IIIA) and non-inflammatory (IIIB)
- Intraprostatic reflux of urine ± urethral hypertonia
- Multifactorial (immunological, neuropathic, neuroendocrine, psychosocial)

**Clinical Features**
- Same as per Category I + pelvic pain, LUTS

**Investigations**
- E: as per Category I + pelvic floor Urine C&S: 4-glass test VB1 (voided bladder): in tial (urethra) P/VB2: midstream (bladder) EPS (expressed prostatic secretions): not usually performed VB3: post-massage/DRE

**Treatment**
- Supportive measures ABx (see Table 9, U12), Consider addition of an β-blocker

*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index*
Epididymitis and Orchitis

Etiology
- common infectious causes
  - <35 yr: N. gonorrhoeae or Chlamydia trachomatis
  - ≥35 yr or penetrative anal intercourse: GI organisms (especially E. coli)
- other causes
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)
- chemical: reflux of urine into ejaculatory ducts

Risk Factors
- UTI
- unprotected sexual contact
- instrumentation/catheterization
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis
- immunocompromise

Clinical Features
- sudden onset scrotal pain and swelling ± radiation along cord to flank
- scrotal erythema and tenderness
- fever
- storage symptoms, purulent d/c
- reactive hydrocele

Investigations
- U/A, urine C&S
- ± urethral d/c: Gram stain/culture
- if diagnosis uncertain, MUST rule out testicular torsion (U/S Doppler)

Treatment
- rule out torsion (see Investigations Table 24, U29)
- see Table 9, U12 for ABx therapy
- scrotal support, bed rest, ice, analgesia

Complications
- if severe → testicular atrophy
- 30% have persistent infertility problems

Urethritis

Etiology
- infectious or inflammatory (e.g. reactive arthritis)

Table 11. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

<table>
<thead>
<tr>
<th>Causative Organism</th>
<th>Gonococcal</th>
<th>Non-Gonococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Neisseria gonorrhoeae</td>
<td>Usually Chlamydia trachomatis</td>
</tr>
<tr>
<td>Hx of sexual contact, thick, profuse, yellow-grey purulent d/c, LUTS</td>
<td>Hx of sexual contact, mucoid whitish purulent d/c, ± storage LUTS</td>
<td></td>
</tr>
<tr>
<td>Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen</td>
<td>Gram stain demonstrates &gt;4 PMN/oil immersion field, no evidence of N. gonorrhoeae, urine PCR and/or culture from urethral specimen</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>See Table 9, U12</td>
<td>See Table 9, U12</td>
</tr>
</tbody>
</table>

Prehn’s Sign: pain may be relieved with elevation of testicles in epididymitis but not in testicular torsion (poor sensitivity, especially in children)

If unsure between diagnoses of epididymitis and torsion, always go to OR
Remember: torsion >6 h has poor prognosis

Reactive Arthritis (formerly known as Reiter’s syndrome)
Urethritis, uveitis (or conjunctivitis), and arthritis (can’t pee, can’t see, can’t climb a tree)

If culture negative or unresponsive to treatment consider: Ureaplasma urealyticum, Mycoplasma genitalium, Trichomonas vaginalis, HSV, or adenovirus
Stone Disease

Epidemiology
- prevalence: ~8% and increasing
- M:F = 2:1
- peak incidence 30-50 yr of age
- recurrence rate: 10% at 1 yr, 50% at 5 yr, 60-80% lifetime

Risk Factors
- hereditary: RTA, Glucose-6-phosphate dehydrogenase deficiency, cystinuria, xanthinuria, oxaluria, etc.
- lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
- medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, zonisamide, indinavir, acyclovir, sulfadiazine, triamterene
- medical conditions: UTI (with urea-splitting organisms: Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serrat a, S. aureus), myeloproliferative disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI >30)

Clinical Features
- urinary obstruction → upstream distention → pain
  - flank pain from renal capsular distention (non-colicky)
  - severe waxing and waning pain radiating from flank to groin, testis, or tip of penis from distended collecting system or ureter (ureteral colic)
  - writhing, persistent discomfort, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
- if fever, rule out concurrent pyelonephritis and/or obstruction

Table 12. Differential Diagnosis of Renal Colic

<table>
<thead>
<tr>
<th>GU</th>
<th>Abdominal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis</td>
<td>AAA</td>
<td>Radiculitis (L1): herpes zoster, nerve root compression</td>
</tr>
<tr>
<td>Ureteral obstruction from</td>
<td>Bowel ischemia</td>
<td></td>
</tr>
<tr>
<td>other cause:</td>
<td>Bowel ischemia</td>
<td></td>
</tr>
<tr>
<td>UPJ obstruction, clot</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>colic secondary to</td>
<td>Other acute abdominal</td>
<td></td>
</tr>
<tr>
<td>gross hematuria, sloughed</td>
<td>crisis (appendicitis,</td>
<td></td>
</tr>
<tr>
<td>papillae</td>
<td>cholecystitis d verticulitis)</td>
<td></td>
</tr>
<tr>
<td>Gynecological: ectopic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pregnancy, torsion/rupture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of ovarian cyst, PID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Location of Stones
- calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
- pelvis: tend to cause obstruction at UPJ, may cause persistent infection
- ureter: <5 mm diameter will pass spontaneously in 75% of patients

Stone Pathogenesis
- supersaturation of stone constituents (at appropriate temperature and pH)
- stasis, low flow, and low volume of urine (dehydration)
- crystal formation and stone nidus
- loss of inhibitory factors
  - citrate (forms soluble complex with calcium)
  - magnesium (forms soluble complex with oxalate)
  - pyrophosphate
  - Tamm-Horsfall glycoprotein
### Approach to Renal Stones

**Figure 8. Approach to renal stone**

#### Investigations

**Table 13. Investigations for Renal Stones**

<table>
<thead>
<tr>
<th>CBC, Uric Acid, U/A, Urine Crystals</th>
<th>KUB x-ray</th>
<th>CT Scan</th>
<th>Abdominal Ultrasound</th>
<th>Cystoscopy</th>
<th>PTH, 24 h urine x 2 for volume, Cr, Ca²⁺, Na⁺, PO₄³⁻, Mg²⁺, oxalate, citrate, ± cystine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who gets it?</strong></td>
<td>Everyone</td>
<td>Most</td>
<td>First episode renal colic</td>
<td>Pediatric cases or those concerning for obstruction</td>
<td>± Those concerning for bladder stone</td>
</tr>
<tr>
<td><strong>Why is it done?</strong></td>
<td>May show signs of infection, ± sensitivities</td>
<td>90% of stones are radiopaque</td>
<td>Distinguish radiolucent stone from soft tissue filling defect</td>
<td>Identify and follow-up stone without radiation exposure</td>
<td>Visualize bladder</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>—</td>
<td>—</td>
<td>Radiation (especially if female of childbearing age)</td>
<td>Must be a non-contrast scan</td>
<td>—</td>
</tr>
</tbody>
</table>

#### Treatment – Acute

- **medical**
  - analgesic ± antiemetic
  - NSAIDs help lower intra-ureteral pressure
  - medical expulsion therapy (MET)
    - α-blockers: increase rate of spontaneous passage in distal ureteral stones
    - ± Abx for bacteriuria
    - IV fluids if vomiting (note: IV fluids do NOT promote stone passage)
- **interventional**
  - required if obstruction endangers patient, e.g. sepsis, renal failure
  - first line: ureteric stent (via cystoscopy)
  - second line: image-guided percutaneous nephrostomy
  - admit if necessary
  - see *Indications for Admission to Hospital*

#### Treatment – Elective

- **medical**
  - likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
  - stones <5 mm especially likely to pass spontaneously
  - PO fluids to increase urine volume to >2 L/d (3-4 L if cystine) and MET
  - specific to stone type (see Table 14)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)

---

**Stones and Infection**

If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared.

**Indications for PCNL**

- Size >2 cm
- Staghorn
- UPJ obstruction with correction of obstruction
- Calyceal diverticulum
- Cystine stones (poorly fragmented with ESWL)
- Anatomical abnormalities
- Failure of less invasive modalities

**24 h urine collections must be done AFTER discontinuing stone preventing/promoting medications**

**Indications for Admission to Hospital**

- Intractable pain
- Intractable vomiting
- Fever (suggests infection)
- Compromised renal function (including single kidney, bilateral obstructing stone)
- Pregnancy

**Detailed metabolic studies are NOT recommended unless complex patient (recurrent stone formers, pregnancy, pediatrics, strong family history, underlying kidney or systemic disease, etc.)**

---

Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased GI oxalate absorption and higher urine levels of calcium oxalate.
• interventional
  • kidney
    • may stent prior to ESWL if stone is 1.5-2.5 cm
    • ESWL if stone <2 cm
    • PCNL if stone >2 cm
  • ureteral stones >10 mm
  • ESWL and URS are both first line treatment modalities for all locations
    – URS has significantly greater stone-free rates for stones at all locations in ureter, but also has higher complication rates (ureter perforation, stricture formation, etc.)
  • PCNL is second line treatment
  • laparoscopic or open stone removal (very rare)
  • bladder
    • transurethral stone removal or cystolitholapaxy
    • remove outflow obstruction (TURP or stricture dilatation)

Prevention
• dietary modification
  • increase fluid (>2 L/d), K+ intake
  • reduce animal protein, oxalate, Na*, sucrose, and fructose intake
  • avoid high-dose vitamin C supplements
• medications
  • thiazide diuretics for hypercalciuria
  • allopurinol for hyperuricosuria
  • potassium citrate for hypocitraturia, hyperuricosuria

Table 14. Stone Classification

<table>
<thead>
<tr>
<th>Type of Stone</th>
<th>Calcium (75-85%)</th>
<th>Uric Acid (5-10%)</th>
<th>Struvite (5-10%)</th>
<th>Cystine (1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Hypercalciuria</td>
<td>Hyperuricosuria</td>
<td>Infection with urea-splitting organisms</td>
<td>Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in urine (cystine, ornithine, lysine, arginine)</td>
</tr>
<tr>
<td></td>
<td>Hyperuricosuria (25% of patients with CaOx stones)</td>
<td>(Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)</td>
<td>and precipitation of struvite (magnesium ammonium phosphate)</td>
<td>and precipitation of struvite (magnesium ammonium phosphate)</td>
</tr>
<tr>
<td></td>
<td>Hyperoxaluria (&lt;5% of patients)</td>
<td>Hyperuricosuria alone</td>
<td>Perpetuates UTI because stone itself harbours organism</td>
<td>Aggressive stone disease seen in children and young adults</td>
</tr>
<tr>
<td></td>
<td>Hypocitraturia (12% of patients)</td>
<td>Drugs (ASA, thiazides)</td>
<td>Stone and all foreign bodies must be cleared to avoid recurrence</td>
<td>Recurrent stone formation, family Hx</td>
</tr>
<tr>
<td></td>
<td>Other causes:</td>
<td>Diet (urine rich red meats)</td>
<td>Associated with staghorn calculi</td>
<td>Often staghorn calculi</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia – associated with hyperoxaluria and hypocitraturia</td>
<td>Hyperuricosuria with hyperuricosuria</td>
<td>Positive urine dip and cultures</td>
<td>Fairly radiopaque on KUB</td>
</tr>
<tr>
<td></td>
<td>High dietary Na+</td>
<td>Gout</td>
<td>Note: E. coli infection does not cause struvite stones</td>
<td>Positive urine sodium nitroprusside test, urine chromatography for cystine</td>
</tr>
<tr>
<td></td>
<td>Decreased urinary proteins</td>
<td>High rate of cell turnover or cell death (leukemia, cytotoxic drugs)</td>
<td>M:F = 3:1, UTI more common in female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High urinary pH, low urine volume (e.g. GI water loss)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism, obesity, gout, DM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key Features

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Fluids to increase urine volume to &gt;2 L/d</th>
<th>Increased fluid intake</th>
<th>Complete stone clearance</th>
<th>Increased fluid intake (3-4 L of urine/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical if stone &lt;5 mm and no complications</td>
<td>For calcium stones: cellulose phosphate, orthophosphate for absorptive causes</td>
<td>Alkalization of urine to pH 6.5 to 7 (bicarbonate, p-tassium citrate) ± allopurinol</td>
<td>ABx for 6 wk</td>
<td>Alkalize urine (bicarbonate, potassium citrate), Penicillamine/S-MPG or Captopril (form complex with cystine)</td>
</tr>
<tr>
<td>Procedural/Surgical treatment if stone &gt;5 mm or presence of complications</td>
<td>Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol</td>
<td>Complete stone clearance</td>
<td>Regular follow-up urine cultures</td>
<td>ESWL not effective</td>
</tr>
<tr>
<td></td>
<td>Calcium struvite: ABx (stone must be removed to treat infection)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Purpose: To determine whether or not α-blockers compared with other pharmacological treatments or placebo improve stone clearance rates and other clinically relevant outcomes in patients presenting with symptoms of stones less than 10 mm confirmed by imaging.

Results/Conclusions: 32 RCTs, 5,184 participants. Although patients using α-blockers were more likely to experience stone clearance compared to standard therapy, stone-free rates were significantly higher in the α-blocker group (RR 1.48, 95% CI 1.33-1.64), expulsion time was 2.81 days shorter, and there was a reduction in the number of pain episodes (MD -0.49, 95% CI -0.94 to -0.01), the need for analgesic medication (MD -10.17, 95% CI -16.93 to -1.41), and hospitalization (RR 0.35, 95% CI 0.13-0.81). α-blockers should therefore be offered as a primary treatment modality for ureteral stones.
# Approach to Renal Mass

**Urological Neoplasms**

**Figure 9. Workup of a renal mass**

*Imaging modality may be different in cases of contrast allergy or elevated creatinine*

## Benign Renal Neoplasms

### CYSTIC KIDNEY DISEASE
- simple cysts: usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - Bosniak Classification is used to stratify for risk of malignancy based on cyst features from contrast CT
- polycystic kidney disease
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure, adult-onset
- medullary sponge kidney: cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- von Hippel-Lindau syndrome: multiple bilateral cysts or clear cell carcinomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

### Table 15. Bosniak Classification of Renal Cysts

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Features</th>
<th>Risk of Malignancy</th>
<th>Management Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Simple cyst</td>
<td>Round, no septations, no calcifications, no solid component</td>
<td>Near zero</td>
<td>Follow-up usually not required</td>
</tr>
<tr>
<td>II</td>
<td>Simple cyst</td>
<td>A few thin septa, no enhancement, well-margined, uniform high attenuation, &lt; 3 cm</td>
<td>Minimal</td>
<td>Follow-up usually not required</td>
</tr>
<tr>
<td>III</td>
<td>Minimally complex cyst with extra features that require follow-up</td>
<td>Still well-margined and non-enhancing but new multiple thin septa or some thickening/calcification of septa/wall, &gt; 3 cm</td>
<td>5-20%</td>
<td>Requires follow-up with imaging q6-12mo If the lesion evolves, may require surgical resection</td>
</tr>
<tr>
<td>III</td>
<td>Complex cyst</td>
<td>Thicker or more irregular walls with measurable enhancement</td>
<td>&gt; 50%</td>
<td>Requires surgical resection</td>
</tr>
<tr>
<td>IV</td>
<td>Clearly malignant</td>
<td>Class III + enhancing soft-tissue components</td>
<td>&gt; 80%</td>
<td>Requires surgical resection</td>
</tr>
</tbody>
</table>

There is controversy over optimal management of small renal masses

Percutaneous needle biopsies of cystic renal masses may lead to peritoneal seeding

Tuberous Sclerosis
- Syndrome characterized by mental retardation, epilepsy, and adenoma sebaceum
- 45-60% of patients also present with angiomyolipomas which are often multiple and bilateral
RENAL CELL CARCINOMA

Etiology
- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

Epidemiology
- 85% of primary malignant tumours in kidney
- M:F = 1.5:1
- peak incidence at 50-60 yr of age

Pathology
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobic (5-10%), collecting duct
- sarcomatoid elements in any subtype is a marker of poor prognosis

Risk Factors
- top 3 risk factors: smoking, HTN, obesity
- miscellaneous: horseshoe kidney, acquired renal cystic disease
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

Clinical Features
- usually asymptomatic; frequently diagnosed incidentally by U/S or CT
- indicators for poor prognosis: weight loss, weakness, anemia, bone pain
- classic “too late triad” found in 10-15%
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- metastases: seen in a 1/3 of new cases; additional 20-40% will go on to develop metastases (mostly in late presentations or large tumours)
  - bone, brain, lung and liver most common site
  - may invade renal veins and IVC lumen
- this may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

Investigations
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A
- renal U/S: solid vs. cystic lesion
- contrast-enhanced CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
- MRI: useful for evaluation of vascular extension
- renal biopsy: to confirm diagnosis if considering observation or other non-surgical therapy

Staging
- involves CT, CXR, liver enzymes and LFTs, bone/head imaging (if symptoms dictate)
Clinical Features

- gross/microscopic hematuria
- flank pain
- storage or voiding symptoms (dysuria only if lower urinary tract involved)
- flank mass ± hydronephrosis (10-20%)
Investigations
- IVP/CT urogram
- cystoscopy and retrograde pyelogram

Treatment
- radical nephroureterectomy with excision of ipsilateral bladder cuff
- distal ureterectomy for distal ureteral tumours with concomitant ureteral reimplant
- emerging role for endoscopic laser ablation in patients with low grade disease, poor baseline renal health

Bladder Carcinoma

Etiology
- unknown, but environmental risk factors include:
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior Hx of radiation treatment to the pelvis
  - *Schistosoma hematoobium* infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)
  - aristolochic acid: associated with Balkan Nephropathy (renal failure, upper tract urothelial cancer) and Chinese Herbal Nephropathy

Epidemiology
- 2nd most common urological malignancy
- M:F = 3:1, more common among whites than blacks
- mean age at diagnosis is 65 yr

Pathology
- classification
  - urothelial carcinoma (UC) >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis
  - non-muscle invasive (75%) → >80% overall survival
  - 15% of these will progress to invasive UC
  - majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5 yr survival
  - 85% have no prior history of superficial UC (i.e. *de novo*)
  - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
  - carcinoma *in situ* → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive UCC

Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumour (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider carcinoma *in situ*
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting, and diarrhea)

Investigations
- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast → look for filling defect
- cystoscopy with biopsy (gold standard) → establish diagnosis and to determine depth of penetration
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP)

Grading
- low grade: <10% invasive, 60% recur locally
- high grade: 50-80% are invasive or are expected to progress to invasive over time

Staging
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes (Ca²⁺, Mg²⁺, PO₄³⁻) (metastatic workup)

The ENTIRE urinary tract must be evaluated in patients with hematuria unless there is clear evidence of glomerular bleeding (e.g. red cell casts, dysmorphic RBCs, etc.)

Cystoscopy is the initial procedure of choice for the diagnosis and staging of urothelial malignancy

Unexplained hematuria in any individual >40 yr old must be investigated to rule out a malignancy

Tumour grade is the single most important prognostic factor for progression

Non-Muscle-Invasive Bladder Cancer (NMIBC) and BCG

AHRQ Publication 2015:15-EHC017-EF #153

**Summary:** BCG is the only intravesical therapy associated with decreased risk of bladder cancer progression; however, it is also associated with high rate of adverse events. More research is needed to define optimal dose/regimen.

**Methods:** Review of Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of SR, Health Technology Assessment, National Health Sciences Economic Evaluation, Database of Abstract of Reviews of Effects for studies on NMIBC interventions, including intravesical therapy.

**Results:** BCG is superior in prevention of bladder cancer recurrence compared to no intravesical therapy. BCG is superior to doxorubicin, epirubicin, and mitomycin in prevention of bladder cancer recurrence.
Table 18. 2010 TNM Classification of Bladder Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX: Primary tumour cannot be assessed</td>
<td>NX: Lymph nodes cannot be assessed</td>
<td>M0: No distant metastasis</td>
</tr>
<tr>
<td>T0: No evidence of primary tumour</td>
<td>N0: No lymph node metastasis</td>
<td>M1: Distant metastasis</td>
</tr>
<tr>
<td>Ta: Noninvasive papillary carcinoma</td>
<td>N1: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)</td>
<td></td>
</tr>
<tr>
<td>Tis: Carcinoma in situ: “flat tumour”</td>
<td>N2: Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)</td>
<td></td>
</tr>
<tr>
<td>T1: Tumour invades subepithelial connective tissue</td>
<td>N3: Lymph node metastasis to the common iliac lymph nodes</td>
<td></td>
</tr>
<tr>
<td>pT2a: Tumour invades superficial muscularis propria (inner half)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2b: Tumour invades deep muscularis propria (outer half)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2: Tumour invades perivesical tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3a: Microscopically</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3b: Macroscopically (extravesical mass)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3: Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a: Tumour invades prostatic stroma, uterus, vagina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b: Tumour invades pelvic wall, abdominal wall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment
- superficial (non-muscle invasive) disease: Tis, Ta T1
  - low-grade disease
  - TURBT ± intravesical chemotherapy (mitomycin C) to decrease recurrence rate
  - follow-up with cystoscopy and cytology
  - multifocal, or recurrent
  - TURBT ± intravesical chemio/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
  - T1 or CIS
  - repeat TURBT in 2-6 wk
  - maintenance with intravesical chemotherapy with BCG for 3 cycles every 3 mo, may be continued for 2-3 yr
- invasive disease: T2a, T2b, T3
  - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileal conduit, Indiana pouch, ileal neobladder) or TURBT + chemo-radiation (bladder sparing) for small tumours with non-obstructed ureters
  - neo-adjuvant chemotherapy prior to cystectomy may also be done
  - use of adjuvant chemotherapy after definitive local treatment is controversial
  - advanced/metastatic disease: T4a, T4b, N+, M+
    - initial combination of systemic chemotherapy ± irradiation ± surgery

Prognosis
- depends on stage, grade, size, number of lesions, recurrence and presence of CIS
  - T1: 90% 5 yr survival
  - T2: 55% 5 yr survival
  - T3: 30% 5 yr survival
  - T4/N+/M+: <5% 5 yr survival
Prostate Cancer

Etiology
- not known
- risk factors
  - age >50 yr, risk increases 1% per year after 65 yr
  - increased incidence in persons of African descent
  - high dietary fat (2x)
  - family Hx
    - 1st degree relative (2x)
    - 1st and 2nd degree relatives (9x)
  - positive BRCA mutation

Epidemiology
- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between ages of 60 and 85; mean age at diagnosis is 65

Pathology
- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma of the prostate (4.5%)
  - associated with UC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle

Anatomy (see Figure 7, U7)
- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

Clinical Features
- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see Prostate Cancer Screening, U26
- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
- metastatic disease
  - bony metastases to axial skeleton common
  - visceral metastases are less common (liver, lung, and adrenal gland most common sites)
  - leg pain and edema with nodal metastases obstructing lymphatic and venous drainage

Methods of Spread
- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

Investigations
- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan may be omitted in untreated CaP with PSA <10 ng/mL
- CT scanning to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsy and active surveillance

Table 19. 2010 TNM Classification of Prostate Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>T1b</td>
<td>T1c</td>
</tr>
<tr>
<td>T1: clinically undetectable tumour, normal DRE and TRUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a: tumour incidental histologic finding in &lt;5% of tissue resected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b: tumour incidental histologic finding in &gt;5% of tissue resected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c: tumour identified by needle biopsy (due to elevated PSA level)</td>
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<td></td>
</tr>
<tr>
<td>T2: palpable, confined to prostate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a: tumour involving ≤ one half of one lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b: tumour involving &gt; one half of one lobe, but not both lobes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2c: tumour involving both lobes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3: tumour extends through prostate capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a: extracapsular extension (unilateral or bilateral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b: tumour invading seminal vesicle(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4: tumour invades adjacent structures (besides seminal vesicles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1: spread to regional lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0: no regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NX: regional lymph nodes were not assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0: no distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1a: nonregional lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1b: bone(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1c: other site(s) with or without bone disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 20. Prostate Cancer Mortality Risk

<table>
<thead>
<tr>
<th>PSA</th>
<th>Low Risk (if any of following)</th>
<th>Intermediate Risk (if any of following)</th>
<th>High Risk (if any of following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>10-20</td>
<td>&gt;20</td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>7</td>
<td>8-10</td>
<td></td>
</tr>
<tr>
<td>T1-2a</td>
<td>T2c</td>
<td>T3a</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

- **T1/T2** (localized, low-risk)
  - if adequate life expectancy or no other significant comorbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - active surveillance for low risk, small volume Gleason 6 prostate cancer
  - no difference in cure or recurrence rates between definitive treatment modalities
  - in older population: watching waiting + palliative treatment for symptomatic progression
- **T1/T2** (intermediate or high-risk)
  - definitive therapy over active surveillance
- **T3, T4**
  - EBRT + androgen deprivation therapy or RP + adjuvant EBRT
  - N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bila er orchiectomy – decreases testosterone production by 90%
  - GnRH agonists (e.g. leuprolide, goserelin)
  - GnRH antagonist (e.g. degarelix)
  - estrogens (e.g. diethylstilbestrol [DES])
  - antiandrogens (e.g. bicalutamide, enzalutamide)
  - local irradiation of painful secondaries or half-body irradiation
  - hormone-refractory prostate cancer
  - chemotherapy: docetaxel, cabazitaxel, sipuleucel-T

**Prognosis**

- **T1-T2**: comparable to normal life expectancy
- **T3-T4**: 40–70% 10 yr survival
- **N**+ and/or **M**+ 4% 5 yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

**Table 21. Treatment Options for Localized Prostate Cancer**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Population Considered</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful Waiting</td>
<td>Short life expectancy (&lt;5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses</td>
<td>Disease progression</td>
</tr>
<tr>
<td>Active Surveillance (sRGB DRE and biopsies)</td>
<td>Low grade disease, good follow-up; is still considering more curative treatment if disease progresses</td>
<td>Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Low volume, low PSA (&lt;10), low grade</td>
<td>ED (50%), long-term effectiveness not well-established</td>
</tr>
<tr>
<td>EBRT</td>
<td>Locally advanced disease, older patients</td>
<td>Radiation proctitis (5%), ED (50%), risk of rectal cancer</td>
</tr>
<tr>
<td>RP</td>
<td>Young patients (&lt;75 yr), high-risk disease</td>
<td>Incontinence (10%), ED (30-50%)</td>
</tr>
</tbody>
</table>

*Other options include cryosurgery, HIFU, hormonal ablation

**Digital Rectal Exam**

- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

**Prostate Specific Antigen**

- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in setting of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cutpoint
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- PSA velocity, PSA density, and free:total PSA: all intended to increase sensitivity and specificity of serum PSA values
- decreased free:total PSA, elevated PSA velocity and elevated PSA density associated with increased CaP rates

**Screening Recommendations**

- conflicting evidence regarding mortality reduction with PSA-based screening and debate regarding overdiagnosis/overtreatment

---

1. 10 Year Outcomes After Monitoring, Surgery, or Radiotherapy for Localized Prostates Cancer  
   NEJM 2016;375(15):1415-1424  
   Summary: At 10 years, prostate-cancer-specific mortality was low regardless of the treatment, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastasis vs. active monitoring.  
   Methods: 1643 men randomized into active monitoring (45%), surgery (55%), and radiotherapy (5%)  
   - Primary outcome: prostate-cancer mortality at median 10 year follow-up.  
   - Secondary outcomes: rate of disease progression, metastases, and all-cause deaths.  
   Results: 1. Primary outcome: prostate-cancer-specific deaths overall; 8 in active-monitoring group, 5 in the surgery group, and 4 in the radiotherapy group; difference among the groups was not significant (p=0.4). No significant difference was seen among groups in numbers of deaths from any cause (189 deaths overall; p=0.87).  
   2. Secondary outcomes: metastases developed more in active monitoring group (33 men) vs. surgery group (13 men) or radiotherapy group (18 men) (overall p=0.004). Higher rates of disease progression in active-monitoring group (112 events) vs. surgery group (46 events) or radiotherapy group (46 events) (p<0.001 for the overall comparison).

---

2. Prostate Cancer Screening  
   Long-Term Follow-Up on PSA Screening  
   Lancet 2014;384(9959):2027-2035  
   Summary: With 13 yr follow-up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However, the number needed to screen to treat is decreasing, and is now below the number needed to screen observed in breast cancer trials.  
   Methods: multi-centre RCT with predefined central monitoring (545), surgery (553), and radiotherapy (545)  
   - Primary outcome: prostate-cancer mortality at 10 years follow-up in the intervention arm was compared to control arm.  
   - Secondary outcomes: rate of disease progression, metastases, and all-cause deaths.  
   Results: RR of PCa incidence between intervention and control arms was 1.91 after 9yr follow-up, 1.86 at 11yr follow-up, and 1.67 at 13yr follow-up.  
   - RR of PCa mortality was 0.85, 0.78, and 0.79, at 9, 11, 13 yr follow-up, respectively. RRR is 21%, and ARR from death is 1.28 per 1000 men.  
   - Causes of Increased PSA  
     BPH, prostatitis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy  
   - PSA is specific to the PROSTATE, but NOT to prostate cancer
• Long-Term Care and United States Preventative Services Task Force all recommend against PSA testing as a population wide screening tool
• however, serum PSA screening recommended in any man with >10 yr life-expectancy and any of the following
  - suspicious finding on DRE
  - moderate-severe LUTS
  - high risk individuals
  - investigating secondary carcinoma of unknown origin to rule out CaP as primary

**Canadian Urological Association Guidelines (2011) re: CaP Screening**
• harms and benefits of PSA testing must be explained to the patient and an informed, shared decision to test must be established
• initial screening should include both serum PSA and DRE
• all men should be offered screening at age 50 if >10 yr life-expectancy
• high-risk individuals (family Hx of CaP or African ancestry) should be offered screening at age 40 if >10 yr life-expectancy
• standard has been annual screening, but q2-4yr screening acceptable
• no strict cutpoint for when to biopsy; decision to biopsy should be based on more than a single PSA value
• AUA guidelines recommend against universal routine PSA screening for CaP

**Testicular Tumours**

**Etiology/Risk Factors**
• cryptorchidism, atrophy, sex hormones, HIV infection, infertility, family Hx, past Hx of testicular cancer

**Epidemiology**
• rare, but most common solid malignancy in young males 15-35 yr
• any solid testicular mass or acute hydrocoele in young patient – must rule out malignancy
• slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
• 2-3% bilateral (simultaneously or successively)

**Pathology**
• primary
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumours (all are malignant)
    - seminoma (35%) → classic, anaplastic, spermatocytic
    - NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<1%), mixed cell type (40%)
  - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
• secondary
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

**Clinical Features**
• painless testicular enlargement (painful if intratesticular hemorrhage or infarction)
• dull, heavy ache in lower abdomen, anal area or scrotum
• associated hydrocele (10%)
• coincidental trauma (10%)
• infertility (rarely presenting complaint)
• gynecomastia due to secretory tumour effects
• supraclavicular and inguinal lymphadenopathy
• abdominal mass (retroperitoneal lymph node mets)

**Methods of Spread**
• local spread follows lymphatics
  - right → medial, paracaval, anterior and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - “cross-over” metastases from right to left are fairly common, but no reports from left to right
  - hematogenous most commonly to lung, liver, bones, and kidney

**Investigations**
• diagnosis is established by pathological evaluation of specimen obtained by radical inguinal orchidectomy
• tumour markers (β-hCG, LDH, AFP)
  - β-hCG and AFP are positive in 85% of non-seminomatous tumours
  - elevated marker levels return to normal post-operatively if no metastasis
  - β-hCG positive in 7% of pure seminomas, AFP never elevated with seminoma
Urological Neoplasms

• testicular U/S (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
• evidence of testicular microlithiasis is not a risk factor for testicular cancer
• needle aspiration contraindicated

Staging
• clinical: CXR (lung mets), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)
  ▪ Stage I: disease limited to testis, epididymis, or spermatic cord
  ▪ Stage II: disease limited to the retroperitoneal nodes
  ▪ Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti:</td>
<td>intratubular germ cell neoplasia</td>
<td>N0: no regional lymph node metastasis</td>
</tr>
<tr>
<td>T1:</td>
<td>limited to testis and epididymis without vascular/lymphatic invasion</td>
<td>N1: Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2:</td>
<td>limited to testis and epididymis with vascular/lymphatic invasion</td>
<td>N2: Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3:</td>
<td>invasion of the spermatic cord ± vascular/lymphatics</td>
<td>N3: Metastasis with a lymph node mass more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4:</td>
<td>invasion of the scrotum ± vascular/lymphatics</td>
<td></td>
</tr>
</tbody>
</table>

Table 22. 2010 TNM Classification of Testicular Carcinoma

Management
• orchiectomy through inguinal ligament for all stages
• consider sperm banking, testicular prosthesis
• adjuvant therapies (see figure 13)

Prognosis
• 99% cured with stage I and II disease
• 70-80% complete remission with advanced disease

Penile Tumours

Epidemiology
• rare (<1% of cancer in males in U.S.)
• most common in 6th decade

Benign
• cyst, hemangioma, nevus, papilloma

Pre-Malignant
• balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

Pre-invasive Cancer
• carcinoma in situ
  ▪ Bowen's disease → crusted, red plaques on the shaft
  ▪ erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  ▪ treatment options: local excision, laser, radiation, topical 5-fluorouracil

Figure 13. Adjuvant management of testicular cancer post-orchiectomy

Adapted from Dr. MAS Jewett
Malignant
• risk factors
  ▪ chronic inflammatory disease
  ▪ STI
  ▪ phimosis
  ▪ uncircumcised penis
• 2% of all urogenital cancers
• SCC (>95%), basal cell, melanoma, Paget’s disease of the penis (extremely rare)
• definitive diagnosis requires full thickness biopsy of lesion
• lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

Treatment
• wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement)
  ± lymphadenectomy
• consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available

### Scrotal Masses

#### Table 23. Differentiating between Scrotal Masses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Palpation</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsion</td>
<td>+</td>
<td>Absent cremaster reflex, negative Prehn’s sign</td>
</tr>
<tr>
<td>Epididymitis (U16)</td>
<td>+</td>
<td>Present cremaster reflex, positive Prehn’s sign</td>
</tr>
<tr>
<td>Orchitis (U16)</td>
<td>+</td>
<td>Present cremaster reflex, positive Prehn’s sign</td>
</tr>
<tr>
<td>Hydrocele</td>
<td>–</td>
<td>No transillumination</td>
</tr>
<tr>
<td>Spermatocele</td>
<td>–</td>
<td>Transillumination</td>
</tr>
<tr>
<td>Varicocele</td>
<td>– (± if strangled)</td>
<td>Transillumination</td>
</tr>
<tr>
<td>Indirect Inguinal</td>
<td>– (± if strangulated)</td>
<td>No transillumination</td>
</tr>
<tr>
<td>Tumour</td>
<td>–</td>
<td>Hard lump/nodule</td>
</tr>
<tr>
<td>Generalized/</td>
<td>Diffuse swelling</td>
<td>Often post-operative or immobilized, check for liver dysfunction</td>
</tr>
<tr>
<td>Dependent edema</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 24. Benign Scrotal Masses

<table>
<thead>
<tr>
<th>Type</th>
<th>Varicocele</th>
<th>Spermatocele</th>
<th>Hydrocele</th>
<th>Testicular Torsion</th>
<th>Inguinal Hernia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Dilatation and tortuosity of pampiniform plexus</td>
<td>A benign, sperm-filled epididymal retention cyst</td>
<td>Collection of serous fluid that results from a defect or irritation in the tunica vaginalis</td>
<td>Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction</td>
<td>Protrusion of abdominal contents through the inguinal canal into the scrotum</td>
</tr>
<tr>
<td>Etiology</td>
<td>15% of men due to incompetent valves in the testicular veins 90% left sided</td>
<td>Multiple theories, including: Distal obstruction, Anorectal dilations of the epididymis, Agglutinated germ cells</td>
<td>Usually idiopathic Found in 5-10% testicular tumours Associated with trauma/infection Communicating: patent processus vaginalis, changes size during day (peds) Non communicating: non-patent processus vaginalis (adult)</td>
<td>Trauma Cryptorchidism “Bell clapper deformity” Many occur in sleep (50%) Necrosis of glands in 5-6 h</td>
<td>Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness</td>
</tr>
<tr>
<td>Hx/P/E</td>
<td>“Bag of worms” Often painless Pustules with Valsalva</td>
<td>Non-tender, cystic mass Transilluminates</td>
<td>Non-tender, intrascrotal mass Cystic Transilluminates</td>
<td>Acute onset severe scrotal pain, swelling GI upset cases Retracted and transverse testicle (horizontal lie) Negative Prehn’s sign Absent cremasteric reflex</td>
<td>A small bulge in the groin that may increase in size with Valsalva and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising</td>
</tr>
<tr>
<td>Investigations</td>
<td>P/E Valsalva</td>
<td>P/E U/S to rule out tumour</td>
<td>U/S to rule out tumour</td>
<td>U/S Doppler with probe over testicular artery Decrease uptake on 99mTc-pertechnetate scintillation scan (doughnut sign)</td>
<td>Hx and P/E Invagination of the scrotum Valsalva</td>
</tr>
<tr>
<td>Treatment</td>
<td>Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (balloon, sclerosing agents) Repair may improve sperm count/motility 50-75%</td>
<td>Conservative Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum</td>
<td>Conservative Needle drainage Surgical</td>
<td>Emergency surgical exploration and bilateral orchiectomy Definitive diagnosis NOT necessary to take to OR Orchiectomy if poor prognosis</td>
<td>Surgical repair</td>
</tr>
</tbody>
</table>
TORSION OF TESTICULAR APPENDIX
- twisting of testicular/epididymal vestigial appendix

Signs and Symptoms
- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
- "blue dot sign"
  - blue infarcted appendage seen through scrotal skin in children (can usually be palpated as small, tender lump)

Treatment
- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

HEMATOCELE
- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

Treatment
- ice packs, analgesics, surgical repair

Table 25. Penile Complaints

<table>
<thead>
<tr>
<th>Type</th>
<th>Peyronie’s Disease (Figure 14)</th>
<th>Priapism</th>
<th>Paraphimosis</th>
<th>Phimosis</th>
<th>Premature Ejaculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Acquired curvature of penile shaft secondary to fibrous thickening of tunica albuginea</td>
<td>Prolonged erection lasting &gt;4 h in the absence of sexual excitement/desire</td>
<td>Retracted foreskin (behind glans penis) that cannot be reduced</td>
<td>Inability to retract foreskin over glans penis</td>
<td>Ejaculation prior to when one or both partners desire it, either before or soon after penetration</td>
</tr>
<tr>
<td>Etiology</td>
<td>Etiology unknown</td>
<td>50% idiopathic Ischemic (common) Thromboembolic (sickle cell) Non-Ischemic Trauma Medications Neurorigenic</td>
<td>Iatrogenic (post cleaning/instrumentation) Trauma Infectious (balanitis, balanoposthitis)</td>
<td>Congenital (90%) Natural separation by age 3 Balanitis Poor Hygiene</td>
<td>Psychological factors Primary: no period of acceptable control Secondary: symptoms after a period of control, not associated with general medical condition</td>
</tr>
<tr>
<td>Hx/P/E</td>
<td>Penile curvature/shortening Pain with erection Poor erection distal to plaque</td>
<td>Painful erection ± signs of necrosis Note: non ischemic (high flow) priapism may present without pain</td>
<td>Painful, swollen glans penis, foreskin Constricting band proximal to corona Dysuria, decreased or normal stream in children</td>
<td>Limitation and pain when attempting to retract foreskin Balanoposthitis (infection of prepuce)</td>
<td>Ejaculatory latency &lt;1 min Inability to control or delay ejaculation Psychological distress</td>
</tr>
<tr>
<td>Investigations</td>
<td>Hx and P/E</td>
<td>Hx and P/E</td>
<td>Hx and P/E</td>
<td>Hx and P/E</td>
<td>Testosterone levels if in conjunction with impotence</td>
</tr>
<tr>
<td>Treatment</td>
<td>Watchful waiting (spontaneous resolution in up to 12%) Medical management: Intravascular or topical verapamil Surgical management: Incision/ excision of plaque Shortening of less affected side ± penile prosthesis</td>
<td>Treat reversible causes High-flow: Self-limited Consider arterial embolization Low-flow: Needle aspirated decompression Phenylephrine intracorporeal injection q3-5min Surgical shunt no response within 1 h</td>
<td>Manual pressure (with analgesia) Dorsal slit Circumcision (urgent or electively to prevent recurrence)</td>
<td>Proper hygiene Topical corticosteroids Dorsal slit Circumcision</td>
<td>Rule out medical condition Address psychiatric concerns, counselling Medication: SSRI or clomipramine Topical lidocaine-prilocaine</td>
</tr>
</tbody>
</table>

Erectile Dysfunction

Definition
- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

Physiology
- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic (dorsal penile/pudendal nerves [S2-4])
- erection (“POINT”)
  - parasympathetics → NO release → increased cGMP within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
• emission (“SHOOT”)
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
• ejaculation ("SHOOT")
  - bladder neck closure (sympathetic)
  - spasmodic contraction of bulbocavernosus and pelvic floor musculature (somatic)
• detumescence
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

Classification

Table 26. Classification of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Classification</th>
<th>Psychogenic*</th>
<th>Organic*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>10%</td>
<td>90%</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Gradual</td>
</tr>
<tr>
<td>Frequency</td>
<td>Sporadic</td>
<td>All circumstances</td>
</tr>
<tr>
<td>Variation</td>
<td>With partner and circumstance</td>
<td>No</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Organic Risk Factors (HTN, DM, dyslipidemia)</td>
<td>No organic factors</td>
<td>Risk factors present</td>
</tr>
<tr>
<td>Nocturnal/AM Erection</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

*Combination can co-exist

Etiology ("IMPOTENCE")

• Iatrogenic: pelvic surgery, pelvic radiation
• Mechanical: Peyronie’s, post-priapism
• Psychological: depression, stress, anxiety, PTSD, widower syndrome
• Occlusive: arterial HTN, DM, smoking, hyperlipidemia, PVD, impaired veno-occlusion
• Trauma: penile/pelvic, bicycling
• Extra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
• Neurogenic: CNS (e.g. Parkinson’s, MS, spinal cord injury, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
• Chemical: antihypertensives, sedatives, antidepressants, anxiolytics, anticholinergics, antihistamines, anti-androgens (including 5-a reductase inhibitors), statins, GnRH agonists, illicit drugs
• Endocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

Diagnosis

• complete Hx (include sexual, medical, and psychosocial aspects)
• self administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
• focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
• lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
• specialized testing including nocturnal penile tumescence monitoring usually unnecessary
• evaluation of penile vasculature only relevant with past history of trauma (i.e. pelvic fracture)

Treatment

• can often be managed by family doctor, see sidebar for when to refer
• must fully inform patient/partner of options, benefits and complications
• non-invasive
  - lifestyle changes (alcohol, smoking), psychological (sexual counselling and education)
  - change precipitating medications
  - treat underlying causes (DM, CVD, HTN, endocrinopathies)
• minimally invasive
  - oral medication (see Common Medications, U42)
    - sildenafil, tadalafil, vardenafil, avanafil (not available in Canada): inhibits PDE-5 to increase intracavernosal cyclic GMP levels
    - all four have similar effectiveness, difference in onset of action is not clinically significant
      - tadalafil has longer half-life, no cyanopsia, and can be taken on empty or full stomach
    - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis
    - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra
• invasive
  - intracavernous vasodilator injection/self-injection
    - triple therapy (papaverine, phentolamine, PGE1) or PGE1 alone
    - complications: priapism (overdose), fibrosis of tunica albuginea at site of repeated injections (Peyronie's plaque) and injection site injuries (pain, hematoma, etc.)
• surgical
  - penile implant (last resort): malleable or inflatable
  - penile artery reconstruction (in young men with isolated vascular lesion – investigational)
**Trauma**

- see Emergency Medicine, ER7

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**Renal Trauma**

**Classification According to Severity**

- minor
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

**Etiology**

- 80% blunt MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

**Clinical Features**

- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

**Investigations**

- U/A
  - hematuria: requires workup but degree does not correlate with the severity of injury
- imaging
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

**Staging (does not necessarily correlate well with clinical status)**

- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: laceration causing urinary extravasation and/or main arterial or vein injury with contained hematoma
- V: shattered kidney or avulsion of pedicle

**Treatment**

- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization
  - absolute indications
    - hemorrhage and hemodynamic instability
  - relative indications
    - non-viable tissue and major laceration
    - urinary extravasation
    - vascular injury
    - expanding or pulsating peri-renal mass
    - laparotomy for associated injury
  - follow-up with U/S or CT before discharge, and at 6 wk

**Complications**

- HTN in 5% of renal trauma

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**Bladder Trauma**

**Classification**

- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures involve anterior or lateral bladder wall in full bladder

**Etiology**

- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases
Clinical Features
- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

Investigations
- U/A: gross hematuria in 90%
- imaging (including CT cystogram and post-drainage films for extravasation)

Treatment
- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications
- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

Urethral Injuries

Etiology
- posterior urethra
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra
  - straddle injury can crush bulbar urethra against pubic rami
- other causes
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

Clinical Features
- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder

Investigations
- must perform RUG or cystoscopy prior to catheterization

Treatment
- simple contusions
  - no treatment
- partial urethral disruption
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment
- periodic flow rates/urethromps to evaluate for stricture formation
- complete disruption
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

Complications
- stricture
Infertility

Definition

- failure to conceive after one year of frequent, unprotected and properly timed intercourse
- incidence
  - 15% of all couples (35–40% female, 20% male, 25–30% combined)

Female Factors

- see Gynecology GY23

Male Factors

Male Reproduction

- hypothalamic-pituitary-testicular axis (HPTA)
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

Etiology

- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumour
  - congenital (Klinefelter’s triad: small, firm testes, gynecomastia, and azoospermia)
  - post-infectious (epididymo-orchitis, STIs, mumps)
  - uncorrected torsion
  - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery; see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
  - bilateral ejaculatory duct obstruction, epididymal obstructions
  - Kartagener’s syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see Endocrinology E45)
  - HPTA (2-3%) e.g. Kallmann’s syndrome congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery
  - medications
  - prior exposure to chemotherapy or pelvic radiation
  - drugs: marijuana, cocaine, tobacco, alcohol
  - increased testicular temperature (sauna, hot baths, tight pants or underwear)
  - chronic disease: e.g. liver, renal

History

- age of both partners
- medical: past illnesses, DM, trauma, CF, genetic syndromes, STIs, cryptorchidism
- surgical: vasectomy, herniorrhaphy, orchidopexy, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- family Hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social Hx: alcohol, tobacco, cocaine, marijuana, school performance/learning disabilities (suggestive of Klinefelter syndrome)
- occupational exposures: radiation, heavy metals

Physical Exam

- general appearance: sexual development, gynecomastia, obesity, pubic hair
- scrotal exam: size, consistency, and nodularity of testicles; palpation of cord for presence of vas deferens; DRE; valsalva for varicocele
Investigations
- semen analysis (SA) at least 2 specimens, collected 1-2 wk apart
- hormonal evaluation
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
- serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation
  - chromosomal studies (Klinefelter’s syndrome - XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

Treatment
- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections
- surgical
  - varicocelectomy (if indicated)
  - vasovasostomy (vasectomy reversal) or epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART)
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - in vitro fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

Figure 15. Infertility workup
Pediatric Urology

Congenital Abnormalities

- not uncommon; 1/200 have congenital abnormalities of the GU tract
  six common presentations of congenital urological abnormalities

1. ANTENATAL HYDRONEPHROSIS

Epidemiology
- 1-5% fetal U/S, some detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

Differential Diagnosis
- UPJ or UVJ obstruction
- multi-cystic dysplastic kidney
- VUR
- PUVs (only in boys)
- duplication anomalies
- ureterocele
- ectopic ureter

Treatment
- antenatal in utero intervention rarely indicated unless evidence of lower urinary tract obstruction with oligohydramnios

2. POSTERIOR URETHRAL VALVES

Epidemiology
- the most common congenital obstructive urethral lesion in male infants

Pathophysiology
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

Clinical Presentation
- dependent on age
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), urinary ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive; rule out pyloric stenosis, which may present similarly
  - toddlers: UTIs or voiding dysfunction
  - school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

Investigations
- most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened bladder, dilated posterior urethra ("keyhole sign"), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

Treatment
- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

3. URETEROPELVIC JUNCTION OBSTRUCTION

Etiology
- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, aberrant blood vessels
- can rarely be secondary to tumour, stone, etc. in children

Epidemiology
- the most common congenital defect of the ureter
  - M:F = 2:1
  - up to 40% bilateral, which may be associated with worse prognosis
Clinical Presentation
- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
- in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl's crisis)

Investigations
- antenatal: serial U/S most common, and renal scan ± furosemide

Treatment
- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

4. VESICOURETERAL REFLUX

Definition
- retrograde passage of urine from the bladder, through the UVJ, into the ureter

Classification
- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neuropathic) bladder dysfunction

Epidemiology
- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition

Investigations
- focused Hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for infections (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to relatively high incidence of renal scarring
  - height, weight, blood pressure
  - serum Cr
  - U/A, C&S
  - renal U/S
  - DMSA renal scan if at high risk (greater sensitivity in detecting structural defects associated with dysplasia, renal scarring or pyelonephritis; entails radiation exposure)
  - sibling family screening is controversial

Treatment
- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment
  - medical treatment: daily ABx prophylaxis at half the treatment dose for acute infection (see Table 9, U12 - TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
  - surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (Deflux® or Macroplastique®)
    - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux
  - defer circumcision in patients with hypospadias

5. HYPOSPADIAS

Definition
- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream, having intercourse or depositing sperm in vagina

Epidemiology
- very common; 1/300 live male births
- distal hypospadias more common than proximal
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia
Treatment
- early surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

6 EXSTROPHY-EPISPADIAS COMPLEX

Definition
- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
- bladder exstrophy: congenital defect of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
- cloacal exstrophy
  - exposed bladder and bowel with imperforate anus
  - associated with spina bifida in >50%
- epispadias (least severe)
  - urethra opens on dorsal aspect of the penis, often associated with penile curvature

Etiology
- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

Epidemiology
- rare: incidence 1/30,000, M:F = 3:1 predominance
- high morbidity → multiple reconstructive surgeries, incontinence, infertility, reflux

Treatment
- surgical correction at birth
- later corrections for incontinence, VUR, and low bladder capacity may be needed

Nephroblastoma (Wilms’ Tumour)

Etiology
- arises from abnormal proliferation of metanephric blastema

Epidemiology
- 5-5-10: 5% of all childhood cancers, 5% bilateral, 10% associated with congenital malformation syndromes
- most common primary malignant renal tumour of childhood
- average age of incidence is 3 yr

Clinical Features
- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness (30-40%)
- microscopic hematuria (12-25%)
- nausea/vomiting

Treatment
- always investigate contralateral kidney and renal vein (for tumour thrombus)
- unilateral disease: radical nephrectomy ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

Prognosis
- 5 yr survival 80%

Cryptorchidism/Ectopic Testes

Definition
- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- Denis Browne pouch (between external oblique fascia and Scarpa’s fascia) most common
- differential diagnosis:
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

Epidemiology
- 2.7% of full term newborns
- 0.7-0.8% at 1 yr
**Treatment**
- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

**Prognosis**
- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility
  - paternity rates: 53%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intraabdominal > inguinal
  - surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)

---

**Disorders of Sexual Differentiation**

**Definition**
- formerly known as intersex disorders: considered social emergency
- abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females

**Classification**
1. 46 XY DSD
   - defect in testicular synthesis of androgens
   - androgen resistance in target tissues
   - palpable gonad
2. 46 XX DSD
   - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
   - undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)
3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   - presence of Y chromosome → partial testis determination to varying degrees

**Diagnosis**
- thorough family Hx noting any consanguinity
- maternal Hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
- P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
- laboratory tests
  - plasma 17-OH-progesterone (after 36 h of life) → increased in CAH
  - plasma 11-deoxycorticisol → increased in 11-β-hydroxylase deficiency
  - basal adrenal steroid levels
  - serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/d for 4 d)
  - serum electrolytes
  - chromosomal evaluation including sex karyotype
- U/S of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and gen tography of urogenital sinus

**Treatment**
- steroid supplementation as indicated (e.g. CAH)
- sex assignment after extensive family consultation
  - must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
- reconstruction of external genitalia between 6 and 12 mo
- long-term psychological guidance and support for both patient and family

---

**Enuresis**
- see Pediatrics, P9
Selected Urological Procedures

Bladder Catheterization

• catheter size measured by the French (Fr) scale – circumference in mm
  each 1 mm increase in diameter = approximately 3 Fr increase (standard size 14-18 Fr)
  should be removed as soon as possible to reduce the risk of UTI

Continuous Catheterization

• indications
  • accurate monitoring of U/O
  • relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  • temporary therapy for urinary incontinence
  • perineal wounds
  • clot prevention (22-24 Fr) for CBI
  • intra- and post-operative
  • comfort for end of life care

Alternatives to Continuous Catheterization

• intermittent catheterization
  • PVR measurement
  • to obtain sterile diagnostic specimens for U/A, urine C&S
  • management of neurogenic bladder or chronic urinary retention
  • condom catheter
  • suprapubic catheter

Causes of Difficult Catheterizations and Treatment

• patient discomfort → use sufficient lubrication (± xylocaine)
• collapsing catheter → lubrication as above ± firmer or larger catheter (silastic catheter)
• meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
• BPH → use coudé catheter as angled tip can help navigate around enlarged prostate
• urethral disruption/obstruction → filling of and followers or suprapubic catheterization
• anxious patient → anxiolytic medication

Complications of Catheterization

• infection: UTI, bladder fistula, bladder perforation (rare)
• meatal/urethral trauma

Contraindications

• trauma: blood at the urinary meatus, scrotal hematoma, pelvic fracture, and/or high riding prostate

Circumcision

Definition

• removal of some or all of the foreskin from the penis

Epidemiology

• 30% worldwide
• frequency varies with geography, religious affiliation, socioeconomic status

Medical Indications

• phimosis and recurrent paraphimosis
• recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
• balanitis xerotica obliterans or other chronic inflammatory conditions

Contraindications

• unstable or sick infant
• congenital genital abnormalities (hypospadias)
• family Hx of bleeding disorders warrants laboratory investigation prior to circumcision

Complications

• bleeding
• infection
• preputial entrapment, skin bridges
• fistula
• glans injury
• penile sensation deficits

Figure 18. Transurethral (Foley) catheters

Main Circumcision for Prevention of Heterosexual Acquisition of HIV in Men


Purpose: To evaluate the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.

Me hods: The analyzed data is from three randomized controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa.

Results: Medical male circumcision reduces the acquisition of HIV by heterosexual men (38-66% over 24 mo).

Circumcision Status and Risk of HIV and Sexually Transmitted Infections among Men who have Sex with Men: A Meta-Analysis

JAMA 2012;308:1680-1685

Purpose: To describe the association between male circumcision and HIV infection and other sexually transmitted infections (STIs) among men who have sex with men (MSM).

Methods: Meta-analysis of 15 studies (n=53,567)

Results: The associations between circumcision and HIV infection and STIs were not statistically significant. Male circumcision had a protective association with HIV in a subset of MSM conducted before the introduction of highly active anti-retroviral therapy.

Conclusions: There is insufficient evidence to support that male circumcision protects against HIV infection or other STIs.

Male Circumcision

Pediatrics 2012;30:756-785

Study: Guidelines by the American Academy of Pediatrics (AAP)

Recommendations: The American Academy of Pediatrics radically changed their position on male circumcision in 2012. The report from the AAP now states that the preventive health benefits outweigh the risks of the procedure and that the procedure is well-tolerated with adequate pain management and sterility. Stated benefits include the prevention of urinary tract infection, penile cancer, transmission of sexually transmitted infections, including HIV. There is believed to be no effect on penile sexual function, sensitivity or sexual satisfaction. Acute complications are rare and more common if the procedure is done by an untrained provider.

Note: The Canadian Pediatric Society (CPS) has not yet updated their position on male circumcision since 1998, which stated that the CPS is opposed to routine circumcision. A new statement is expected soon.
Cystoscopy

Objective
- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
- scopes can be flexible or rigid

Indications
- gross hematuria
- LUTS (storage or voiding)
- urethral and bladder neck strictures
- bladder stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

Complications
- during procedure
  - bleeding
  - anesthetic related
  - perforation (rare)
- post procedure (short-term)
  - infections (antibiotic prophylaxis recommended)
  - urinary retention
  - post-procedure (long-term)
  - stricture

Radical Prostatectomy

Objective
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (depend on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also partially or completely removed

Indications
- treatment for localized prostate cancer

Complications
- immediate (intraoperative)
  - blood loss
  - rectal injury (extremely rare)
  - ureteral injury (extremely rare)
- perioperative
  - lymphocele formation if concurrent pelvic lymphadenectomy performed
- late
  - moderate to severe urinary incontinence (3-10%)
  - mild urinary incontinence (20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

Transurethral Resection of the Prostate (TURP)

Objective
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination

Indications
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy
Complications

- acute
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called “post-TURP syndrome”)
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinuses, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture

Extracorporeal Shock Wave Lithotripsy

Objective

- to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
- shockwaves focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications

- potential first-line therapy for renal and ureteral calculi <2.5 cm
- individuals with calculi in solitary kidney
- individuals with HTN, DM or renal insufficiency
*patient preference and wait-times play a large role in stone management

Contraindications

- acute UTI or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- obstruction distal to stone (ESWL can be used after stent or nephrostomy inserted)

Complications

- bacteriuria
- bacteremia
- post-procedure hematuria
- ureteric obstruction (by stone fragments)
- peri-nephric hematoma

Common Medications

Table 27. Erectile Dysfunction Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil</td>
<td>Phosphodiesterase 5 inhibitor</td>
<td>Selective inhibition of PDE5 (enzyme which degrades cGMP) Leads to sinusoidal smooth muscle relaxation, increased blood flow and erection</td>
<td>Severe hypotension (very rare) Flushing, headaches, dyspepsia Contraindicated if Hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycthemia, sickle cell disease) Contraindicated with nitrates</td>
</tr>
<tr>
<td>tadalafil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vardenafil (PDE5s for use when some erection present)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alprostadil (MUSE®), PGE: + phentolamine + papaverine mixture</td>
<td>Prostaglandin E1</td>
<td>Activation of cAMP, relaxing sinusoidal smooth muscle Local release (urethral suppository)</td>
<td>Penile pain Presyncpoe</td>
</tr>
<tr>
<td>alprostadil, papaverine (intracavernosal injection)</td>
<td></td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>triple therapy also used: papaverine, phentolamine, PGE:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 28. Benign Prostatic Hyperplasia Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>terazosin</td>
<td>α-blockers</td>
<td>α-adrenergic antagonists reduce stromal smooth muscle tone</td>
<td>Presyncope</td>
</tr>
<tr>
<td>doxazosin</td>
<td></td>
<td>Reduce dynamic component of bladder outlet obstruction</td>
<td>Leg edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Retrograde ejaculation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nasal congestion</td>
</tr>
<tr>
<td>tamsulosin</td>
<td>α1A selective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alfuzosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>silodosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>finasteride</td>
<td>5-α reductase</td>
<td>Blocks conversion of testosterone to DHT</td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>dutasteride</td>
<td>inhibitor</td>
<td>Reduces static component of bladder outlet obstruction</td>
<td>PSA decreases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces prostatic volume</td>
<td></td>
</tr>
</tbody>
</table>

### Table 29. Prostatic Carcinoma Medications (N>0, M>0)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>leuprolide, goserelin</td>
<td>GnRH agonist</td>
<td>Initially stimulates LH, increasing testosterone and causing “flare” (initially increases bone pain) Later causes low testosterone</td>
<td>Hot flashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased libido</td>
</tr>
<tr>
<td><em>cyproterone acetate</em></td>
<td>Steroidal antiandrogen</td>
<td>Competes with DHT for intracellular receptors: 1. Prevent flare produced by GnRH agonist 2. Use for complete androgen blockade 3. May preserve potency</td>
<td></td>
</tr>
<tr>
<td>flutamide, bicalutamide</td>
<td>Non-steroidal antiandrogen</td>
<td>As above</td>
<td>Hepatotoxic: AST/ALT monitoring</td>
</tr>
<tr>
<td>abiraterone</td>
<td>Non-steroidal antiandrogen</td>
<td>Irreversible CYP17 inhibition, blocking synthesis of androgens in tumour, testis, and adrenal glands</td>
<td>Adrenal insufficiency (concurrent treatment with steroids often required) Hypertinglyceridemia Peripheral edema</td>
</tr>
<tr>
<td>enzalutamide</td>
<td>Non-steroidal antiandrogen</td>
<td>Androgen receptor signaling inhibitor (full antagonist)</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatigue and weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hot flashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Very rarely used</strong></td>
</tr>
</tbody>
</table>

### Table 30. Continence Agents and Overactive Bladder Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxybutynin</td>
<td>Antispasmodic</td>
<td>Inhibits action of ACh on smooth muscle</td>
<td>Overactive bladder</td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases frequency of uninhibited detrusor contraction</td>
<td>Urge incontinence + urgency + frequency</td>
<td>Blurred vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diminishes initial urge to void</td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suprapruventricular tachycardia</td>
</tr>
<tr>
<td>oxybutynin, tolterodine, trospium, solifenacin, darifenacin, fesoterodine</td>
<td>Anticholinergic</td>
<td>Muscarinic receptor antagonist Selective for bladder Increases bladder volume Decreases detrusor pressure</td>
<td>Overactive bladder</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urge incontinence + urgency + frequency</td>
<td></td>
</tr>
<tr>
<td>mirabegron</td>
<td>β3 agonist</td>
<td>Beta sympathetic receptor blocker in the bladder; relaxes bladder during storage phase</td>
<td>Overactive bladder</td>
<td>Blood pressure should be monitored</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urge incontinence + urgency + frequency</td>
<td></td>
</tr>
<tr>
<td>imipramine</td>
<td>Tricyclic antidepressant</td>
<td>Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation</td>
<td>Stress and urge incontinence</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prolonged PR interval</td>
</tr>
<tr>
<td>Botulinum toxin A</td>
<td>Neurotoxin</td>
<td>Prevents the release of neurotransmitters</td>
<td>Refractory OAB incontinence both neurogenic and non-neurogenic</td>
<td>Urinary retention, UTI</td>
</tr>
</tbody>
</table>

Note: All anti-cholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long-acting formulations are lacking.
References

General Information

Common Presenting Problems
Teichman JMR. Acute renal colic from ureteral calculi. NEJM 2004;350:694-693.

Overactive Bladder

Benign Renal Neoplasm

Urologic Emergencies

Medications

EBM
Acronyms ........................................ 2

Peripheral Arterial Disease (PAD) ........... 2
Acute Arterial Ischemia
Chronic Arterial Occlusion/Insufficiency

Aortic Disease ................................. 4
Aortic Dissection
Aortic Aneurysm

Carotid Stenosis ............................... 6

Peripheral Venous Disease .................... 7
Deep Venous Thromboembolism
Varicose Veins
Chronic Venous Insufficiency

Lymphedema .................................. 8

References ................................. 9
Peripheral Arterial Disease (PAD)

Acute Arterial Ischemia

**Definition**
- acute occlusion of a peripheral artery, usually without a history of claudication
- urgent management required
  - skeletal muscle can tolerate 6 h of ischemia before irreversible damage and myonecrosis; exception is in acute-on-chronic occlusion, where previously developed collaterals allow more time
  - tends to be lower extremity > upper extremity; femoropopliteal > aortoiliac
  - paralysis and neuromuscular compromise are signs of late ischemia

**Etiology and Risk Factors**
- embolism vs. thrombosis
  - examples of conditions that predispose to embolism are: arrhythmias, endocarditis, and arterial aneurysms
  - existing atherosclerotic plaques (i.e. chronic PAD) can rupture causing thrombosis
  - previous vascular grafts/reconstructions can fail and thrombose leading to acute presentation
  - hypercoagulable states can contribute to arterial thrombosis

**Clinical Features**

**Table 1. Arterial Embolism vs. Thrombosis**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Embolus</th>
<th>Thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Progressive, acute-on-chronic</td>
</tr>
<tr>
<td>Loss of Function/Sensation</td>
<td>Prominent</td>
<td>Less profound (due to underlying collaterals)</td>
</tr>
<tr>
<td>Hx of Claudication</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Atrophic Changes</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Contralateral Limb Pulses</td>
<td>Classically normal</td>
<td>Decreased or absent</td>
</tr>
</tbody>
</table>

**Investigations**
- history and physical exam are essential: depending on degree of ischemia one may have to forego investigations and go straight to the operating room
- ABI: extension of physical exam, easily performed at bedside
- ECG: troponin: rule out recent MI or arrhythmia
- CBC: ruled out leukocytosis, thrombocytosis or recent drop in platelets in patients receiving heparin (may suggest HIT/S)
- PT/INR, PTT: patient anticoagulated/sub-therapeutic INR
- Echo: identify wall motion abnormalities, intracardiac thrombus, valvular disease, aortic dissection (Type A)
- CT angiogram: underlying atherosclerosis, aneurysm, aortic dissection
- conventional catheter based angiography: can be obtained in OR; prelude to thrombolytics, as part of endovascular intervention or for planning treatment

**Treatment**
- immediate heparinization with 5000 IU bolus (80 Units/kg) and continuous infusion to titrate PTT to 70-90 s
- if impa red neurovascular status: emergent revascularization
- if intact neurovascular status: time for workup (including angiogram-CTA)
- definitive treatment
Peripheral Arterial Disease (PAD)

Reperfusion Complications
- compartment syndrome (see Orthopedic Surgery, OR9) with prolonged ischemia; requires 4-compartment (anterior/lateral/superficial and deep posterior) fasciotomy
- risk of arrhythmia and death with reperfusion injury
- renal failure and multi-organ failure due to toxic metabolites from ischemic muscle

Prognosis
- 12-15% mortality rate
- 5-40% morbidity rate (amputation)

Chronic Arterial Occlusion/Insufficiency

Definition
- chronic ischemia due to inadequate arterial supply to meet cellular metabolic demands (during walking (Claudication) or at rest (limb threat/critical limb ischemia))

Etiology and Risk Factors
- predominantly due to atherosclerosis (for pathogenesis, see Cardiology and Cardiac Surgery, C26); primarily occurs in the lower extremities
- major risk factors: smoking, DM older age
- minor risk factors: HTN, hyperlipidemia, obesity, sedentary lifestyle, PMHx or FMHx CAD/CVD

Clinical Features
- claudication: must differentiate vascular from neurogenic claudication or MSK
  1. pain with exertion: usually in calves or any exercising muscle group
  2. relieved by short rest: 2-5 min, and no postural changes necessary
  3. reproducible: same distance or time to elicit pain, same location of pain, same amount of rest to relieve pain
- critical limb ischemia (CLI)
  1. includes rest pain, night pain, tissue loss (ulceration or gangrene)
  2. pain most commonly over the forefoot, waking person from sleep, and often relieved by hanging foot off bed
  3. ankle pressure <40 mmHg, toe pressure <30 mmHg, ABI <0.40
    - pulses may be absent at some locations, bruits may be present
    - signs of poor perfusion: hair loss, hypertrophic nails, atrophic muscle, ulcerations and infections, slow capillary refill, prolonged pallor on dependency, venous through (collapse of superficial veins of foot)

Investigations
- non-invasive
- routine blood work fasting metabolic profile
- ABI: take highest brachial and highest ankle (dorsalis pedis artery or posterior tibial artery) pressures for each side generally (see Table 2) (may be falsely normal or elevated in those with calcified vessels e.g. diabetics)
- CTA and MRA
  - excellent for large arteries (aorta, iliac, femoral, popliteal) but may have difficulty with tibial arteries (especially in the presence of disease)
  - require IV injection of nephrotoxic contrast (iodinated contrast for CT, gadolinium for MR)
  - used primarily for planning interventions
- invasive
  - arteriography: superior resolution to CTA/MRA, better for tibial arteries, can be done intraoperatively or as part of endovascular intervention

Table 2. Ankle-Brachial Indices

<table>
<thead>
<tr>
<th>ABI Recording</th>
<th>Degree of Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.20</td>
<td>Suspect wall calcification (most common in diabetics)</td>
</tr>
<tr>
<td>&gt;0.95</td>
<td>Normal/no ischemia</td>
</tr>
<tr>
<td>0.50-0.80</td>
<td>Claudication range</td>
</tr>
<tr>
<td>&lt;0.40</td>
<td>Possible critical ischemia</td>
</tr>
</tbody>
</table>
Aortic Disease

Treatment
• conservative
  ▪ risk factor modification (smoking cessation, HbA1c control, treatment of HTN, hyperlipidemia (sta in), antiplatelet therapy [ECASA])
  ▪ exercise program (30 min 3x/wk): improves collateral circulation and oxygen extraction at the muscle level
  ▪ foot care (especially in DM): keep wounds clean/dry, avoid trauma and pressure on wounds
• pharmacotherapy
  ▪ antiplatelet agents (e.g. ECASA, clopidogrel)
  ▪ cilostazol (cAMP-phosphodiesterase inhibitor with antiplatelet and vasodilatory effects): improves walking distance for some patients with claudication (not available in Canada)
• surgical/endovascular
  ▪ indications: severe lifestyle impairment, vocational impairment, critical ischemia
  ▪ endovascular (angioplasty ± stenting)
  ▪ endarterectomy: removal of plaque and repair with patch (usually distal aorta or common/ profunda femoral)
  ▪ bypass graft sites: aortofemoral, axillofemoral, femoropopliteal, distal arterial – graft choices: vein graft (reversed or in situ), synthetic (polytetrafluoroethylene graft (e.g. Gore-Tex®) or Dacron®)
  ▪ amputation: if not suitable for revascularization, persistent serious infections/gangrene, unremitted rest pain poorly controlled with analgesics

Prognosis
• claudication: conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 yr, <4% will require amputation
• for patients with CLI, at 2 yr: 25% risk of mortality, 25% risk of bilateral limb amputation, 25% risk of unilateral limb amputation, 25% without complications. 33% 5 yr survival rate

Aortic Disease

Aortic Dissection

Definition
• tear in aortic intima allowing blood to dissect into the media
• Stanford classification: Type A (involve the ascending aorta) vs. Type B (do not)
• acute <2 wk (initial mortality 1% per hr for Type A dissections)
• chronic >2 wk

Etiology
• most common: HTN
• other: connective tissue disease (e.g. Marfans, Ehlers-Danlos), cystic medial necrosis, atherosclerosis, congenital conditions (e.g. coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection (e.g. syphilis), trauma, arteritis (e.g. Takayasus)

Epidemiology
• M:F = 3:1
• small increased incidence in African-Canadians (related to higher incidence of HTN); lowest incidence in Asians
• peak incidence 50-65 yr old; 20-40 yr old with connective tissue diseases

Clinical Features
• sudden onset tearing chest pain that radiates to back with:
  ▪ hypertension with asymmetric BPs and pulses between arms (>30 mmHg difference indicates poor prognosis)
  ▪ ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotids (ischemic stroke, Horner’s syndrome), splanchic (mesenteric ischemia), renal (AKI), peripheral (ischemic leg), intercostal vessels (spinal cord ischemia)
  ▪ “unseating” of aortic valve cusps (new diastolic murmur in 20-30%) in Type A dissection
  ▪ rupture into pleura (dyspnea, hemoptysis) or retroperitoneum (hypotension, shock) or pericardium (cardiac tamponade)
  ▪ syncope
• aortic dissection is considered a ‘great imitator’ of other conditions, thus increased risk to patient and MD (medicolegal)

Investigations
• CTA is the mainstay of both diagnosis and determining the extent of dissection
• ECG and troponin to rule out other causes: (LVH ± ischemic changes, pericarditis, heart block)
• CXR: pleural cap (pleural effusion in lung apices), widened mediastinum, left pleural effusion with extravasation of blood
• TEE: can visualize aortic valve and thoracic aorta but not abdominal aorta
• consider: lactate (elevated in ischemic gut, shock), amylase (rule out pancreatitis), troponin (rule out MI)
Aortic Disease

Treatment

- Type A dissection needs referral to cardiac surgeon for urgent repair
  - resection of segment with intimal tear; reconstitution of flow through true lumen; replacement of the affected aorta with prosthetic graft
  - post-operative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
  - 2/3 of patients die of operative or post-operative complications
  - initial mortality rate without surgery is 3% per hr for first 24 h, 30% 1 wk, 80% 2 wk

- Type B dissection is managed medically
  - acute therapy is typically with intravenous antihypertensives titrated to BP measured by arterial line in critical care setting
  - may transition to oral meds after initial control
  - β-blocker to lower BP and decrease cardiac contractility (nondihydropyridine CCB if clear contraindications to β-blockers)
  - ACEI and/or other vasodilators if insufficient BP or HR control
  - selective intervention (endovascular or surgical) for complications or refractory symptoms/progression despite medical therapy
  - may be a subset of patients who could be well treated with early aortic stent-grafting after initial medical stabilization – evolving area of the literature

Aortic Aneurysm

Definition

- localized dilatation of an artery having a diameter at least 1.5x that of the expected normal diameter
  - true aneurysm: involving all vessel wall layers (intima, media, adventitia)
  - false aneurysm (also known as pseudo-aneurysm): disruption of the aortic wall or the anastomotic site between vessel and graft with containment of blood by a fibrous capsule made of surrounding tissue
  - aneurysms can rupture, thrombose, embolize, erode, and fistulize

Classification

- thoracic aortic aneurysm (TAA): ascending, transverse arch, descending
- abdominal aortic aneurysm (AAA): 90-98% are infrarenal
- suprarenal: involves one or more visceral arteries, but does not involve the chest
- pararenal: renal arteries arise from aneurysmal aorta, but the SMA origin is not aneurysmal
- juxtarenal: the renal arteries originate from normal aorta, but are immediately adjacent to aneurysmal aorta (there is no nonaneurysmal aorta distal to the origin of the renal arteries)
- infrarenal: the aneurysm originates distal to the renal arteries (there is nonaneurysmal aorta distal to the origins of the renal arteries)

Etiology and Risk Factors

- risk factors: smoking, HTN, PVD, CAD, CVD, age >70, family history
- degenerative
- traumatic
- mycotic (Salmonella, Staphylococcus, usually suprarenal aneurysms)
- connective tissue disorder (Marfan syndrome, Loeys-Dietz Syndrome, Ehlers Danlos syndrome)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic aneurysms are associated with bicuspid aortic valve

Clinical Features

- 75% asymptomatic
- most commonly in the abdominal aorta
- common presentation: due to acute expansion or rupture
  - syncope
  - pain (chest, abdominal, flank, back)
  - hypotension
  - palpable pulsatile mass above the umbilicus
  - airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis (indicates thoracic or thoracoabdominal aortic aneurysm)
  - distal pulses may be intact

Investigations

- blood work: CBC, electrolytes, urea, creatinine, PTT, INR, type and cross
- abdominal U/S (approaching 100% sensitivity, up to ±0.6 cm accuracy in size determination) – useful for screening and surveillance
- CT with contrast (accurate visualization, size determination, EVAR planning)
- peripheral arterial Doppler/duplex (rule out aneurysms elsewhere, e.g. popliteal)

ACC/AHA 2005 Guidelines define an AAA when the minimum AP diameter of abdominal aorta ≥3.0 cm

True Aneurysm

- Saccular
- Fusiform

Pseudo-Aneurysm

Classic Triad of Ruptured AAA

- Hypotension/collapse
- Back/abdominal pain
- Palpable, pulsatile abdominal mass (caution in patients with raised BMI)

CCS PAD Guidelines 2006 Recommend AAA Screening Among:

- Men aged 65-74 yr
- Women aged 65 yr with cardiovascular disease and positive family history of AAA
- Men aged 50 yr and above with a positive family history
Treatment
- conservative (for asymptomatic aneurysms that do not meet the size threshold for repair)
  - cardiovascular risk factor reduction: smoking cessation; control of HTN, DM, hyperlipidemia, regular exercise, watchful waiting, U/S surveillance with frequency depending on size and location
- surgical
  - indications
    - ruptured
    - symptomatic
    - size >5-5.9 cm
    - ascending thoracic aortic aneurysms
      - symptomatic, enlarging, diameter >6 cm or >2x normal lumen size, >4.5 cm and aortic regurgitation (annuloaortic ectasia); >4.5-5 cm in Marfan syndrome
  - risk of rupture depends on: size, family history of rupture, rate of enlargement (>1 cm/yr in diameter), symptoms, and comorbidities (HTN, COPD, dissection), smoking
  - elective AAA repair mortality 2-5% for open repair (1-2% for EVAR); elective TAA repair mortality <10% (highest with proximal aortic and thoracoabdominal repairs)
- surgical options
  - open surgery (laparotomy or retroperitoneal) with graft replacement
    - complications
      - early: renal failure, spinal cord injury (paraparesis or paraplegia), impotence, arterial thrombosis, anastomotic rupture or bleeding, peripheral emboli
      - late: graft infection/thrombosis, aortoenteric fistula, anastomotic (pseudo) aneurysm
  - endovascular aneurysm repair (EVAR)
    - newer procedure; high success rates in patients with suitable anatomy
    - advantages: preferred to open surgery in ruptured AAA for patients with suitable anatomy, decreased morbidity and mortality, procedure time, need for transfusion, ICU admissions, length of hospitalization, and recovery time
    - disadvantages: endoleak rates as high as 20-30%, device failure increasing as longer follow-up periods are achieved, re-intervention rates 10-30%, cost-effectiveness is an issue, radiation exposure (especially in younger patients due to need for life-long follow-up)
    - complications
      - early: immediate conversion to open repair (<1%), groin hematoma, arterial thrombosis, iliac artery rupture, and thromboemboli
      - late: endoleak, graft kinking, migration, thrombosis, rupture of aneurysm

Carotid Stenosis

Definition
- narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids

Risk Factors
- for atherosclerosis: HTN, smoking, DM, CVD or CAD, dyslipidemia, older age

Clinical Features
- may be asymptomatic
- if symptomatic – hemispheric or ocular presentation

Investigations
- CBC, PT/INR, PTT (hypercoagulable states)
- fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)
- auscultation over carotid bifurcation for bruits (do not correlate with degree of stenosis)
- carotid duplex: determines severity of disease (mild/moderate/severe stenosis or occlusion) ± cross sectional imaging with CT or MR

Treatment
- risk factor modification for all patients to control HTN, lipids, DM
- pharmacological - antiplatelet agents (ASA ± dipyridamole, clopidogrel) ~25% relative risk reduction
- surgical - carotid endarterectomy (generally if symptomatic and >70% stenosis) or endovascular angioplasty ± stenting

Prevention of Disability and Fatal Strokes by Successful Carotid Endarterectomy in Patients Without Recent Neurological Symptoms: Randomized Controlled Trial
Lancet 2004;363:1491-1502
Study: Asymptomatic Carotid Surgery Trial (ACST), a RCT with follow-up at 5 yr.
Patients: 3,120 asymptomatic patients with significant carotid artery stenosis were randomized equally between immediate carotid endarterectomy (CEA) and indefinite deferral of CEA and were followed for up to 5 yr (mean 3.4 yr).
Main Outcome: Any stroke (including fatal or disabling).
Conclusions: In asymptomatic patients with significant carotid artery stenosis, immediate CEA reduced the net 5-yr stroke risk from about 12% to about 8%. Half of this 5-yr benefit involved disabling or fatal strokes.
Peripheral Venous Disease

Deep Venous Thromboembolism

• see Hematology, H35

Varicose Veins

Definition
• distention of tortuous superficial veins resulting from incompetent valves in the deep, superficial, or perforator systems

Etiology
• primary (99% of cases) varicosities: venous valve incompetence or obstruction
  ■ contributing factors: increasing age, systemic hormonal contraceptive use, prolonged standing, pregnancy, obesity
• secondary varicosities: DVT, malignant pelvic tumours with venous compression, congenital anomalies, arteriovenous fistulae, trauma

Epidemiology
• primary varicose veins are the most common form of venous disorder of lower extremity
  65% of north American adult population gets some degree of venous insufficiency

Clinical Features (often the degree of symptoms do not correlate with the clinical findings)
• diffuse aching, fullness/tightness, nocturnal cramping
  ■ aggravated by prolonged standing (end of day), premenstrual
• visible long, dilated and tortuous superficial veins along thigh and leg (great or small saphenous veins and tributaries)
• ulceration, hyperpigmentation, and induration (i.e. lipodermatosclerosis)

Complications
• recurrent superficial thrombophlebitis/superficial vein thrombosis
• features of chronic venous insufficiency: ulceration, eczema, lipodermatosclerosis, stasis dermatitis and hyperpigmentation
• bleeding or hematoma secondary to trauma

Treatment
• largely a cosmetic problem
• conservative: elastic compression stockings
• indications for surgery: failure of conservative treatment, symptomatic varix (pain, bleeding, recurrent thrombophlebitis), tissue changes (hyperpigmentation, ulceration), cosmetic
• surgical: high ligation and stripping of the long saphenous vein and its tributaries, ultrasound-guided foam sclerotherapy, endovenous laser therapy
• 10 year post-operative recurrence of 20%

Chronic Venous Insufficiency

Definition
• venous insufficiency and skin damage

Etiology
• calf muscle pump dysfunction and valvular incompetence (reflux) due to phlebitis, varicosities, or DVT
• venous obstruction

Clinical Features
• pain (most common), ankle and calf edema – relieved by foot elevation
• pruritus, brownish hyperpigmentation (hemosiderin deposits)
• stasis dermatitis, subcutaneous fibrosis if chronic (lipodermatosclerosis)
• ulceration: shallow, above medial malleolus, weeping (wet), painless, irregular outline
• signs of DVT/varicose veins/thrombophlebitis

Investigations
• not required if conservative treatment only
• Doppler U/S (most commonly used in pre-operative assessment)
Lymphedema

Treatment
- conservative
  - elastic compression stockings, ambulation, periodic rest elevation, avoid prolonged standing
  - ulcers: multilayer compression bandage, antibiotics prn
- surgical
  - if conservative measures fail, or if recurrent/large ulcers to reduce the risk of recurrence
  - surgical ligation of perforators in region of ulcer (GSV/LSV ligation and stripping)
  - endovenous: laser or radiofrequency ablation or foam sclerotherapy

Definition
- obstruction of lymphatic drainage resulting in edema with high protein content

Etiology
- primary
  - Milroy’s syndrome: congenital hereditary lymphedema
  - lymphedema praecox (75% of cases): starts in adolescence
  - lymphedema tarda: starts >35 yr
- secondary
  - infection: filariasis (#1 cause worldwide)
  - malignant infiltration: axillary, groin or intrapelvic
  - radiation/surgery (axillary, groin lymph node removal): #1 cause in North America

Clinical Features
- classically non-pitting edema
- impaired limb mobility, discomfort/pain, psychological distress

Treatment
- avoid limb injury (can precipitate or worsen lymphedema)
- cellulitis: treat early to avoid further lymphatic damage
- skin hygiene
  - daily skin care with moisturizers
  - early medical assessment and treatment for infection (topical for fungal infection; systemic for bacterial infection)
- external support
  - intensive: compression bandages
  - maintenance: compression garment
- exercise
  - gentle daily exercise of affected limb, gradually increasing ROM
  - must wear a compression sleeve/bandages when doing exercises
- massage: manual lymph drainage therapy
References

Guidelines


Vascular Surgery


Irritable Bowel Syndrome; G23
Ischemic Heart Disease; C25
Ischemic Stroke; N50
“tiss” Imaging; M115
IV Fluids; A14

**J**
Jaundice; P64, G6
Jejunum; G3
Joint Pain; ER24, FM37, RH3
Joint Pathology; RH2
Juvenile Idiopathic Arthritis; P85

**K**
Kawasaki Disease; P87
Kayser-Fleischer Ring; OP18
Keloids; D7
Keratoconjunctivitis Sicca; OP10
Keratoacanthoma; D35
Keloids; D7
Kayser-Fleischer Ring; OP18
Kawasaki Disease; P87
Juvenile Idiopathic Arthritis; P85
Joint Pathology; RH2
Joint Pain; ER24, FM37, RH3
Juvenile Idiopathic Arthritis; P85

**L**
Labour; OB30
Complications of Labour and Delivery; OB37
Lacerations; OB42
Lacral Apparatus; OP10
Lactose Intolerance; P36
Lambert-Eaton Myasthenic Syndrome; N39
Language Delay; P23
Large Bowel; G3
Bowel Obstruction; GS29
Genomic Changes; MG5
Vessel Disease; NP28
Vessel Vasculitis; RH20
Laryngomalacia; OT45
Lead Poisoning; H17
Legg-Calvé-Perthes Disease; OR43
Len; OP20
Leopold’s Maneuvers; OB6
Lens; OP20
Legg-Calvé-Perthes Disease; OR43
Leukemia; P44
Leukemia; P44
Leukemia; P44
Lymphoma; D10
Liver; G28, G3
Liver Abscesses; GS43
Liver Cysts; GS43
Liver Disease; H32
Liver Transplantation; GS45
Local Anesthetic Agents; A22
Local Edema; C4
Local Infiltration; A23
Loss of Consciousness; C4
Loss of Vision; OP3
Low Back Pain; FM38
Lower Gastrointestinal Bleeding; G27
Lower GI Bleed; G5
Lower Limb Ulcers; PL16
Lower Respiratory T act Diseases; P80
Lower Urinary Tract Dysfunction; U5
Lower Urinary Tract Symptoms; U6
Low High-Density Lipoprotein; E4
Lumbar Disc Syndrome; NS26
Lumbar Puncture; N9
Lumbar Spinal Stenosis; NS28
Lund-Browder Diagram; PL19
Lung Abnormalities; M16
Lung Cancer; R28
Lung Cancer Screening; FM4
Luteinizing Hormone; E17
Lyme Disease; PR6
Lyme Disease; ID23
Lymphadenopathy; H12, P43
Lymphedema; V58
Lymphocytosis; H10
Lymphoid Malignancies; H44
Lymphomas; H45 P44
Lymphopenia; H11
Lymphoplasmacytic Lymphoma; H51
Macrocytic Anemia; H23
Macroglossia; OB19
Malignant Bone Tumours; OR47
Malignant Clonal Proliferations of Mature B-Cells; OR47
Malignant Hyperthermia; A28
Malignant Melanoma; D35
Malignant Melanoma; D35
Malignant Melanoma; D35
Malignant (Necrotizing) Otitis Externa; OT16
Malignant Skin Lesions; PL5
Malignant Skin Lesions; PL5
Malignant Skin Lesions; PL5
Malignant Vulvar Lesions; GY47
Mallampati Classification; A3
Mallory-Weiss Tear; G26
Malnutrition; GM6
Malpresentation; OB21
Malrotation; GS63
Mammalian Bites; ER47
Mammography; FM4, M130
Mandibular Fractures; PL31
Mastitis; FM50
Mastoiditis; OT18
Mastopexy; PL36
Maternal Physiologic Adaptations to Pregnancy; OB3
Maxillary Fractures; PL32
Mechell’s Diverticulum; GS62
Meconium; OB40
Mediastinal Abnormalities; M19
Mediastinal Masses; R21
Mediastinitis; R21
Medical Complications of Pregnancy; OB25
Medium Vessel Disease; NP29
Medium Vessel Vasculitis; RH19
Medullary Sponge Kidney; NP36
Melasma; D9
Ménière’s Disease; OT13
Meningioma; NS13
Meningitis; ID18, P54
Menses; OR33
Menopausal Cycle; GY4
Mental Status; N2
Mental Status Exam; PS3
Mesoétheliolema; R25
Metabolic Acidosis; NP16
Metabolic Alkalosis; NP17
Metabolic Bone Disease; E40, M124
Metabolic Bone Disease Medications; ES1
Metabolic Diseases; MG8
Metastatic Bone Tumours; M123
Metastatic Tumours; NS12
Metatarsal Fracture; OR40
Microangiopathic Hemolytic Anemia
Thrombotic Microangiopathy; H22
Microbiology; ID2
Microcytic Anemia; H13
Migraine Headaches; N45
Molinecrestin; D6
Mild Neurocognitive Disorder; N21
Mild Traumatic Brain Injury; ER9, FM20, N28
Milk Allergy; P36
Mineralocorticoids; C30
Modulated Glasgow Coma Score; ER57
Miosis; OP30
Modified Glasgow Coma Score; ER57
Medullary Sponge Kidney; OB40
Monitoring; A6
Monoclonal Gammopathy of Unknown Significance; H51
Monteggia Fracture; OB19
Mood Disorders; PS9, PS36
Mood Episodes; PS9
Mood Stabilizers; PS47
Motor Exam; N4
Motor Neuron Disease; N35
Movement Disorders; N29, N31, NS39
Multi-Fetal Gestation; OB21
Multiple Endocrine Neoplasm; H39
Multiple Myeloma; H49, NP33
Multiple Sclerosis; M20, N52, OP34
Mumps; P55
Muscle Relaxants; A17
Musculoskeletal System; MI21
Mycology; ID5
Mydriasis; OP30
Myelodysplastic Syndromes; H39
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