Dedication

To the contributors to this and past editions, who took time to share their knowledge, insight, and humor for the benefit of students and physicians everywhere.
Donate for good in bitcoin
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**GUIDE TO EFFICIENT EXAM PREPARATION**

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Preface

With the 28th edition of *First Aid for the USMLE Step 1*, we continue our commitment to providing students with the most useful and up-to-date preparation guide for the USMLE Step 1. This edition represents an outstanding revision in many ways, including:

- 35 entirely new high-yield topics reflecting evolving trends in the USMLE Step 1.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of more than 40 medical student and resident physician authors who excelled on their Step 1 examinations and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- A new section on learning and memory science in Section I, Guide to Efficient Exam Preparation.
- Updated with 35+ new full-color photos to help visualize various disorders, descriptive findings, and basic science concepts. Additionally, revised imaging photos have been labeled and optimized to show both normal anatomy and pathologic findings.
- Updated study tips on the opening page of each chapter.
- Improved integration of clinical images and illustrations to better reinforce and learn key anatomic concepts.
- Improved organization of text, figures, and tables throughout for quick review of high-yield topics.
- Updated with 50+ new and revised diagrams and illustrations as part of our ongoing collaboration with USMLE-Rx (MedIQ Learning, LLC).
- Reorganized Rapid Review section to present high-yield concepts by topic and with page numbers to the corresponding text.
- Revitalized coverage of current, high-yield print and digital resources in Section IV with clearer explanations of their relevance to USMLE Step 1 review.
- Real-time Step 1 updates and corrections can be found exclusively on our blog, www.firstaidteam.com.

We invite students and faculty to share their thoughts and ideas to help us continually improve *First Aid for the USMLE Step 1* through our blog and collaborative editorial platform. (See How to Contribute, p. xvii.)

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Special Acknowledgments

This has been a collaborative project from the start. We gratefully acknowledge the thousands of thoughtful comments, corrections, and advice of the many medical students, international medical graduates, and faculty who have supported the authors in our continuing development of *First Aid for the USMLE Step 1*.

We provide special acknowledgment and thanks to the following individuals who made exemplary contributions to this edition through our voting, proofreading, and crowdsourcing platform: Huzaifa Ahmad, Ram Baboo, Kashif Badar, Nwamaka Bob-Ume, Paige Estave, Nathaniel Fitch, Panagiotis Kaparaliotis, Elaine Luther, Sarah Hamid Mian, Prashank Shree Neupane, Keyhan Piranviseh, Cindy Tsui, and Ankeet Vakharia.

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We are also very grateful to Dr. Fred Howell and Dr. Robert Cannon of Textensor Ltd for providing us extensive customization and support for their powerful Annotate.co collaborative editing platform (www.annotate.co), which allows us to efficiently manage thousands of contributions. Thanks to Dr. Richard Usatine and Dr. Kristine Krafts for their outstanding image contributions. Thanks also to Jean-Christophe Fournet (www.humpath.com), Dr. Ed Uthman, and Dr. Frank Gaillard (www.radiopaedia.org) for generously allowing us to access some of their striking photographs. Thank you to Dr. Brenda Zureick for her ophthalmology review. For faculty contributions, we thank Dr. Aditya Bardia, Dr. Christina Ciaccio, Dr. Stuart Flynn, Dr. Vicki Park, Dr. Jeannine Rahimian, Dr. Joseph Schindler, and Dr. Stephen Thung.

For exceptional editorial leadership, enormous thanks to Christine Diedrich, Emma Underdown, and Catherine Johnson. Thank you to our USMLE-Rx/ScholarRx team of editors, Linda Davoli, Jacqueline Mahon, Janene Matragrano, Erika Nein, Isabel Nogueira, Sally Rineker, Rebecca Stigall, Ashley Vaughn, and Hannah Warnshuis. Many thanks to Tara Price for page design and all-around InDesign expertise. Thank you to Ruthie Whittaker for assistance in reorganizing the Rapid Review section. Special thanks to our indexer Dr. Anne Fifer. We are also grateful to our medical illustrator, Hans Neuhart, for his creative work on the new and updated illustrations. Lastly, tremendous thanks to Rainbow Graphics, especially David Hommel and Donna Campbell, for remarkable ongoing editorial and production support under time pressure.

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General Acknowledgments

Each year we are fortunate to receive the input of thousands of medical students and graduates who provide new material, clarifications, and potential corrections through our website and our collaborative editing platform. This has been a tremendous help in clarifying difficult concepts, correcting errata from the previous edition, and minimizing new errata during the revision of the current edition. This reflects our long-standing vision of a true, student-to-student publication. We have done our best to thank each person individually below, but we recognize that errors and omissions are likely. Therefore, we will post an updated list of acknowledgments at our website, www.firstaidteam.com/bonus/. We will gladly make corrections if they are brought to our attention.

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How to Contribute

This version of *First Aid for the USMLE Step 1* incorporates thousands of contributions and improvements suggested by student and faculty advisors. We invite you to participate in this process. Please send us your suggestions for:

- Study and test-taking strategies for the USMLE Step 1
- New facts, mnemonics, diagrams, and clinical images
- High-yield topics that may appear on future Step 1 exams
- Personal ratings and comments on review books, question banks, apps, videos, and courses

For each new entry incorporated into the next edition, you will receive up to a **$20 Amazon.com gift card** as well as personal acknowledgment in the next edition. Significant contributions will be compensated at the discretion of the authors. Also, let us know about material in this edition that you feel is low yield and should be deleted.

All submissions including potential errata should ideally be supported with hyperlinks to a dynamically updated Web resource such as UpToDate, AccessMedicine, and ClinicalKey.

We welcome potential errata on grammar and style if the change improves readability. Please note that *First Aid* style is somewhat unique; for example, we have fully adopted the AMA *Manual of Style* recommendations on eponyms (“We recommend that the possessive form be omitted in eponymous terms”) and on abbreviations (no periods with eg, ie, etc).

The preferred way to submit new entries, clarifications, mnemonics, or potential corrections with a valid, authoritative reference is via our website: [www.firstaidteam.com](http://www.firstaidteam.com).

This website will be continuously updated with validated errata, new high-yield content, and a new online platform to contribute suggestions, mnemonics, diagrams, clinical images, and potential errata.

Alternatively, you can email us at: [firstaidteam@yahoo.com](mailto:firstaidteam@yahoo.com).

Contributions submitted by **May 15, 2018**, receive priority consideration for the 2019 edition of *First Aid for the USMLE Step 1*. We thank you for taking the time to share your experience and apologize in advance that we cannot individually respond to all contributors as we receive thousands of contributions each year.
NOTE TO CONTRIBUTORS

All contributions become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. Contributions should be supported by at least two high-quality references.

Check our website first to avoid duplicate submissions. In the event that similar or duplicate entries are received, only the first complete entry received with valid, authoritative references will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

JOIN THE FIRST AID TEAM

The First Aid author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated medical students and physicians. Internships range from a few months (e.g., a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular First Aid series.

For 2018, we are actively seeking passionate medical students and graduates with a specific interest in improving our medical illustrations, expanding our database of medical photographs, and developing the software that supports our crowdsourcing platform. We welcome people with prior experience and talent in these areas. Relevant skills include clinical imaging, digital photography, digital asset management, information design, medical illustration, graphic design, and software development.

Please email us at firstaidteam@yahoo.com with a CV and summary of your interest or sample work.
How to Use This Book

CONGRATULATIONS: You now possess the book that has guided nearly two million students to USMLE success for over 25 years. With appropriate care, the binding should last the useful life of the book. Keep in mind that putting excessive flattening pressure on any binding will accelerate its failure. If you purchased a book that you believe is defective, please immediately return it to the place of purchase. If you encounter ongoing issues, you can also contact Customer Service at our publisher, McGraw-Hill Education, at https://www.mheducation.com/contact.html.

START EARLY: Use this book as early as possible while learning the basic medical sciences. The first semester of your first year is not too early! Devise a study plan by reading Section I: Guide to Efficient Exam Preparation, and make an early decision on resources to use by checking Section IV: Top-Rated Review Resources. Note that First Aid is neither a textbook nor a comprehensive review book, and it is not a panacea for inadequate preparation.

CONSIDER FIRST AID YOUR ANNOTATION HUB: Annotate material from other resources, such as class notes or comprehensive textbooks, into your book. This will keep all the high-yield information you need in one place. Other tips on keeping yourself organized:

- For best results, use fine-tipped ballpoint pens (eg, BIC Pro+, Uni-Ball Jetstream Sports, Pilot Drawing Pen, Zebra F-301). If you like gel pens, try Pentel Slicci, and for markers that dry almost immediately, consider Staedtler Triplus Fineliner, Pilot Drawing Pen, and Sharpies.

- Consider using pens with different colors of ink to indicate different sources of information (eg, blue for USMLE-Rx Step 1 Qmax, green for UWorld Step 1 Qbank).

- Choose highlighters that are bright and dry quickly to minimize smudging and bleeding through the page (eg, Tombow Kei Coat, Sharpie Gel).

- Many students de-spine their book and get it 3-hole-punched. This will allow you to insert materials from other sources, including curricular materials.

INTEGRATE STUDY WITH CASES, FLASH CARDS, AND QUESTIONS: To broaden your learning strategy, consider integrating your First Aid study with case-based reviews (eg, First Aid Cases for the USMLE Step 1), flash cards (eg, First Aid Flash Facts), and practice questions (eg, the USMLE-Rx Step 1 Qmax). Read the chapter in the book, then test your comprehension by using cases, flash cards, and questions that cover the same topics. Maintain access to more comprehensive resources (eg, First Aid for the Basic Sciences: General Principles and Organ Systems and First Aid Express videos) for deeper review as needed.

PRIME YOUR MEMORY: Return to your annotated Sections II and III several days before taking the USMLE Step 1. The book can serve as a useful way of retaining key associations and keeping high-yield facts fresh in your memory just prior to the exam. The Rapid Review section includes high-yield topics to help guide your studying.

CONTRIBUTE TO FIRST AID: Reviewing the book immediately after your exam can help us improve the next edition. Decide what was truly high and low yield and send us your comments. Feel free to send us scanned images from your annotated First Aid book as additional support. Of course, always remember that all examinees are under agreement with the NBME to not disclose the specific details of copyrighted test material.
## Selected USMLE Laboratory Values

* = Included in the Biochemical Profile (SMA-12)

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<th>Reference Range</th>
<th>SI Reference Intervals</th>
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</thead>
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<td>*Alanine aminotransferase (ALT, GPT at 30°C)</td>
<td>8–20 U/L</td>
<td>8–20 U/L</td>
</tr>
<tr>
<td>Amylase, serum</td>
<td>25–125 U/L</td>
<td>25–125 U/L</td>
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<tr>
<td>*Aspartate aminotransferase (AST, GOT at 30°C)</td>
<td>8–20 U/L</td>
<td>8–20 U/L</td>
</tr>
<tr>
<td>Bilirubin, serum (adult)</td>
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<td></td>
</tr>
<tr>
<td>Total // Direct</td>
<td>0.1–1.0 mg/dL // 0.0–0.3 mg/dL</td>
<td>2–17 µmol/L // 0–5 µmol/L</td>
</tr>
<tr>
<td>*Calcium, serum (Total)</td>
<td>8.4–10.2 mg/dL</td>
<td>2.1–2.8 mmol/L</td>
</tr>
<tr>
<td>*Cholesterol, serum (Total)</td>
<td>Rec: &lt; 200 mg/dL.</td>
<td>&lt; 5.2 mmol/L</td>
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<tr>
<td>*Creatinine, serum (Total)</td>
<td>0.6–1.2 mg/dL</td>
<td>53–106 µmol/L</td>
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<tr>
<td>Electrolytes, serum</td>
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<tr>
<td>Sodium (Na⁺)</td>
<td>136–145 mEq/L</td>
<td>136–145 mmol/L</td>
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<tr>
<td>Chloride (Cl⁻)</td>
<td>95–105 mEq/L</td>
<td>95–105 mmol/L</td>
</tr>
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<td>*Potassium (K⁺)</td>
<td>3.5–5.0 mEq/L</td>
<td>3.5–5.0 mmol/L</td>
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<tr>
<td>Bicarbonate (HCO₃⁻)</td>
<td>22–28 mEq/L</td>
<td>22–28 mmol/L</td>
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<tr>
<td>Magnesium (Mg²⁺)</td>
<td>1.5–2 mEq/L</td>
<td>0.75–1.0 mmol/L</td>
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<tr>
<td>Gases, arterial blood (room air)</td>
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<tr>
<td>PO₂</td>
<td>75–105 mm Hg</td>
<td>10.0–14.0 kPa</td>
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<tr>
<td>PCO₂</td>
<td>33–45 mm Hg</td>
<td>4.4–5.9 kPa</td>
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<tr>
<td>pH</td>
<td>7.35–7.45</td>
<td>[H⁺] 36–44 mmol/L</td>
</tr>
<tr>
<td>*Glucose, serum</td>
<td>Fasting: 70–110 mg/dL</td>
<td>3.8–6.1 mmol/L</td>
</tr>
<tr>
<td></td>
<td>2-h postprandial: &lt; 120 mg/dL</td>
<td>&lt; 6.6 mmol/L</td>
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<tr>
<td>Growth hormone – arginine stimulation</td>
<td>Fasting: &lt; 5 ng/mL</td>
<td>&lt; 5 µg/L</td>
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<tr>
<td></td>
<td>provocative stimuli: &gt; 7 ng/mL</td>
<td>&gt; 7 µg/L</td>
</tr>
<tr>
<td>Osmolality, serum</td>
<td>275–295 mOsm/kg</td>
<td>275–295 mOsm/kg</td>
</tr>
<tr>
<td>*Phosphatase (alkaline), serum (p-NPP at 30°C)</td>
<td>20–70 U/L</td>
<td>20–70 U/L</td>
</tr>
<tr>
<td>*Phosphorus (inorganic), serum</td>
<td>3.0–4.5 mg/dL</td>
<td>1.0–1.5 mmol/L</td>
</tr>
<tr>
<td>Prolactin, serum (hPRL)</td>
<td>&lt; 20 ng/mL</td>
<td>&lt; 20 µg/L</td>
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<tr>
<td>*Proteins, serum</td>
<td></td>
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<tr>
<td>Total (recumbent)</td>
<td>6.0–7.8 g/dL</td>
<td>60–78 g/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5–5.5 g/dL</td>
<td>35–55 g/L</td>
</tr>
<tr>
<td>Globulins</td>
<td>2.3–3.5 g/dL</td>
<td>23–35 g/L</td>
</tr>
<tr>
<td>*Urea nitrogen, serum (BUN)</td>
<td>7–18 mg/dL</td>
<td>1.2–3.0 mmol/L</td>
</tr>
<tr>
<td>*Uric acid, serum</td>
<td>3.0–8.2 mg/dL</td>
<td>0.18–0.48 mmol/L</td>
</tr>
</tbody>
</table>

(continues)
<table>
<thead>
<tr>
<th>Cerebrospinal Fluid</th>
<th>Reference Range</th>
<th>SI Reference Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>40–70 mg/dL</td>
<td>2.2–3.9 mmol/L</td>
</tr>
</tbody>
</table>

**Hematologic**

<table>
<thead>
<tr>
<th>Erythrocyte count</th>
<th>Male: 4.3–5.9 million/mm³</th>
<th>4.3–5.9 × 10¹²/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female: 3.5–5.5 million/mm³</td>
<td>3.5–5.5 × 10¹²/L</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (Westergen)</td>
<td>Male: 0–15 mm/h</td>
<td>0–15 mm/h</td>
</tr>
<tr>
<td></td>
<td>Female: 0–20 mm/h</td>
<td>0–20 mm/h</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Male: 41–53%</td>
<td>0.41–0.53</td>
</tr>
<tr>
<td></td>
<td>Female: 36–46%</td>
<td>0.36–0.46</td>
</tr>
<tr>
<td>Hemoglobin, blood</td>
<td>Male: 13.5–17.5 g/dL</td>
<td>2.09–2.71 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Female: 12.0–16.0 g/dL</td>
<td>1.86–2.48 mmol/L</td>
</tr>
<tr>
<td>Hemoglobin, plasma</td>
<td>1–4 mg/dL</td>
<td>0.16–0.62 µmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukocyte count and differential</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count</td>
<td>4,500–11,000/mm³</td>
<td>4.5–11.0 × 10⁹/L</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>54–62%</td>
<td>0.54–0.62</td>
</tr>
<tr>
<td>Band forms</td>
<td>3–5%</td>
<td>0.03–0.05</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1–3%</td>
<td>0.01–0.03</td>
</tr>
<tr>
<td>Basophils</td>
<td>0–0.75%</td>
<td>0–0.0075</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>25–33%</td>
<td>0.25–0.33</td>
</tr>
<tr>
<td>Monocytes</td>
<td>3–7%</td>
<td>0.03–0.07</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>25.4–34.6 pg/cell</td>
<td>0.39–0.54 fmol/cell</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>80–100 µm³</td>
<td>80–100 fL</td>
</tr>
<tr>
<td>Partial thromboplastin time (activated)</td>
<td>25–40 seconds</td>
<td>25–40 seconds</td>
</tr>
<tr>
<td>Platelet count</td>
<td>150,000–400,000/mm³</td>
<td>150–400 × 10⁹/L</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>11–15 seconds</td>
<td>11–15 seconds</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>0.5–1.5% of red cells</td>
<td>0.005–0.015</td>
</tr>
</tbody>
</table>

**Sweat**

| Chloride                           | 0–35 mmol/L              | 0–35 mmol/L      |

**Urine**

| Creatine clearance                 | Male: 97–137 mL/min      |                   |
|                                    | Female: 88–128 mL/min    |                   |
| Osmolality                          | 50–1,400 mOsm/kg H₂O    |                   |
| Proteins, total                     | < 150 mg/24 h            | < 0.15 g/24 h     |
# First Aid Checklist for the USMLE Step 1

This is an example of how you might use the information in Section I to prepare for the USMLE Step 1. Refer to corresponding topics in Section I for more details.

## Years Prior
- [ ] Select top-rated review resources as study guides for first-year medical school courses.
- [ ] Ask for advice from those who have recently taken the USMLE Step 1.

## Months Prior
- [ ] Review computer test format and registration information.
- [ ] Register six months in advance. Carefully verify name and address printed on scheduling permit. Call Prometric or go online for test date ASAP.
- [ ] Define goals for the USMLE Step 1 (eg, comfortably pass, beat the mean, ace the test).
- [ ] Set up a realistic timeline for study. Cover less crammable subjects first. Review subject-by-subject emphasis and clinical vignette format.
- [ ] Simulate the USMLE Step 1 to pinpoint strengths and weaknesses in knowledge and test-taking skills.
- [ ] Evaluate and choose study methods and materials (eg, review books, question banks).

## Weeks Prior
- [ ] Simulate the USMLE Step 1 again. Assess how close you are to your goal.
- [ ] Pinpoint remaining weaknesses. Stay healthy (exercise, sleep).
- [ ] Verify information on admission ticket (eg, location, date).

## One Week Prior
- [ ] Remember comfort measures (loose clothing, earplugs, etc).
- [ ] Work out test site logistics such as location, transportation, parking, and lunch.
- [ ] Call Prometric and confirm your exam appointment.

## One Day Prior
- [ ] Relax.
- [ ] Lightly review short-term material if necessary. Skim high-yield facts.
- [ ] Get a good night’s sleep.
- [ ] Make sure the name printed on your photo ID appears EXACTLY the same as the name printed on your scheduling permit.

## Day of Exam
- [ ] Relax. Eat breakfast. Minimize bathroom breaks during the exam by avoiding excessive morning caffeine.
- [ ] Analyze and make adjustments in test-taking technique.

## After the Exam
- [ ] Celebrate, regardless.
- [ ] Send feedback to us on our website at [www.firstaidteam.com](http://www.firstaidteam.com).
SECTION I

Guide to Efficient Exam Preparation

“I don’t love studying. I hate studying. I like learning. Learning is beautiful.”
—Natalie Portman

“Finally, from so little sleeping and so much reading, his brain dried up and he went completely out of his mind.”
—Miguel de Cervantes Saavedra, Don Quixote

“Sometimes the questions are complicated and the answers are simple.”
—Dr. Seuss

“He who knows all the answers has not been asked all the questions.”
—Confucius

“It’s what you learn after you know it all that counts.”
—John Wooden

“A goal without a plan is just a wish.”
—Antoine de Saint-Exupéry

“I was gratified to be able to answer promptly, and I did. I said I didn’t know.”
—Mark Twain
INTRODUCTION

Relax.

This section is intended to make your exam preparation easier, not harder. Our goal is to reduce your level of anxiety and help you make the most of your efforts by helping you understand more about the United States Medical Licensing Examination, Step 1 (USMLE Step 1). As a medical student, you are no doubt familiar with taking standardized examinations and quickly absorbing large amounts of material. When you first confront the USMLE Step 1, however, you may find it all too easy to become sidetracked from your goal of studying with maximal effectiveness. Common mistakes that students make when studying for Step 1 include the following:

- Starting to study (including First Aid) too late
- Starting to study intensely too early and burning out
- Starting to prepare for boards before creating a knowledge foundation
- Using inefficient or inappropriate study methods
- Buying the wrong resources or buying too many resources
- Buying only one publisher’s review series for all subjects
- Not using practice examinations to maximum benefit
- Not understanding how scoring is performed or what the score means
- Not using review books along with your classes
- Not analyzing and improving your test-taking strategies
- Getting bogged down by reviewing difficult topics excessively
- Studying material that is rarely tested on the USMLE Step 1
- Failing to master certain high-yield subjects owing to overconfidence
- Using First Aid as your sole study resource
- Trying to prepare for it all alone

In this section, we offer advice to help you avoid these pitfalls and be more productive in your studies.

USMLE STEP 1—THE BASICS

The USMLE Step 1 is the first of three examinations that you must pass in order to become a licensed physician in the United States. The USMLE is a joint endeavor of the National Board of Medical Examiners (NBME) and the Federation of State Medical Boards (FSMB). The USMLE serves as the single examination system for US medical students and international medical graduates (IMGs) seeking medical licensure in the United States.
The Step 1 exam includes test items drawn from the following content areas:\(^1\):

**DISCIPLINE**
- Aging
- Anatomy
- Behavioral Sciences
- Biochemistry
- Biostatistics and Epidemiology
- Genetics
- Immunology
- Microbiology
- Molecular and Cell Biology
- Nutrition
- Pathology
- Pharmacology
- Physiology

**ORGAN SYSTEM**
- Behavioral Health & Nervous Systems/Special Senses
- Biostatistics & Epidemiology/
- Population Health/
- Social Sciences
- Blood & Lymphoreticular System
- Cardiovascular System
- Endocrine System
- Gastrointestinal System
- General Principles of Foundational Science
- Immune System
- Multisystem Processes & Disorders
- Musculoskeletal, Skin, & Subcutaneous Tissue
- Renal/Urinary System
- Reproductive System
- Respiratory System

**How Is the Computer-Based Test (CBT) Structured?**

The CBT Step 1 exam consists of one “optional” tutorial/simulation block and seven “real” question blocks of up to 40 questions per block with no more than 280 questions in total, timed at 60 minutes per block. A short 11-question survey follows the last question block. The computer begins the survey with a prompt to proceed to the next block of questions.

Once an examinee finishes a particular question block on the CBT, he or she must click on a screen icon to continue to the next block. Examinees cannot go back and change their answers to questions from any previously completed block. However, changing answers is allowed within a block of questions as long as the block has not been ended and if time permits.

**What Is the CBT Like?**

Given the unique environment of the CBT, it’s important that you become familiar ahead of time with what your test-day conditions will be like. In fact, you can easily add up to 15 minutes to your break time! This is because the 15-minute tutorial offered on exam day may be skipped if you are already familiar with the exam procedures and the testing interface. The 15 minutes is then added to your allotted break time of 45 minutes for a total of 1 hour of potential break time. You can download the tutorial from the USMLE website and do it before test day. This tutorial interface is very similar to the one you will use in the exam; learn it now and you can skip taking it during the exam, giving you up to 15 extra minutes of break time. You can also gain experience...
with the CBT format by taking the 120 practice questions (3 blocks with 40 questions each) available online or by signing up for a practice session at a test center.

For security reasons, examinees are not allowed to bring any personal electronic equipment into the testing area. This includes both digital and analog watches, iPods, tablets, calculators, cell phones, and electronic paging devices. Examinees are also prohibited from carrying in their books, notes, pens/pencils, and scratch paper. Food and beverages are also prohibited in the testing area. The testing centers are monitored by audio and video surveillance equipment. However, most testing centers allot each examinee a small locker outside the testing area in which he or she can store snacks, beverages, and personal items.

Questions are typically presented in multiple choice format, with 4–5 possible answer options. There is a countdown timer on the lower left corner of the screen as well. There is also a button that allows the examinee to mark a question for review. If a given question happens to be longer than the screen (which occurs very rarely), a scroll bar will appear on the right, allowing the examinee to see the rest of the question. Regardless of whether the examinee clicks on an answer choice or leaves it blank, he or she must click the “Next” button to advance to the next question.

The USMLE features a small number of media clips in the form of audio and/or video. There may even be a question with a multimedia heart sound simulation. In these questions, a digital image of a torso appears on the screen, and the examinee directs a digital stethoscope to various auscultation points to listen for heart and breath sounds. The USMLE orientation materials include several practice questions in these formats. During the exam tutorial, examinees are given an opportunity to ensure that both the audio headphones and the volume are functioning properly. If you are already familiar with the tutorial and planning on skipping it, first skip ahead to the section where you can test your headphones. After you are sure the headphones are working properly, proceed to the exam.

The examinee can call up a window displaying normal laboratory values. In order to do so, he or she must click the “Lab” icon on the top part of the screen. Afterward, the examinee will have the option to choose between “Blood,” “Cerebrospinal,” “Hematologic,” or “Sweat and Urine.” The normal values screen may obscure the question if it is expanded. The examinee may have to scroll down to search for the needed lab values. You might want to memorize some common lab values so you spend less time on questions that require you to analyze these.

The CBT interface provides a running list of questions on the left part of the screen at all times. The software also permits examinees to highlight or cross out information by using their mouse. There is a “Notes” icon on the top part of the screen that allows students to write notes to themselves for review at a later time. Finally, the USMLE has recently added new functionality including text magnification and reverse color (white text on black background). Being

- **Keyboard shortcuts:**
  - A, B, etc.—letter choices
  - Enter or spacebar—move to next question
  - Esc—exit pop-up Lab and Exhibit windows
  - Alt-T—countdown timers for current session and overall test

- **Heart sounds are tested via media questions.** Make sure you know how different heart diseases sound on auscultation.

- **Be sure to test your headphones during the tutorial.**

- **Familiarize yourself with the commonly tested lab values (eg, Hgb, WBC, platelets, Na⁺, K⁺).**

- **Illustrations on the test include:**
  - Gross specimen photos
  - Histology slides
  - Medical imaging (eg, x-ray, CT, MRI)
  - Electron micrographs
  - Line drawings

- **Be sure to test your headphones during the tutorial.**
familiar with these features can save time and may help you better view and organize the information you need to answer a question.

For those who feel they might benefit, the USMLE offers an opportunity to take a simulated test, or “CBT Practice Session” at a Prometric center. Students are eligible to register for this three-and-one-half-hour practice session after they have received their scheduling permit.

The same USMLE Step 1 sample test items (120 questions) available on the USMLE website, www.usmle.org, are used at these sessions. **No new items will be presented.** The practice session is available at a cost of $75 and is divided into a short tutorial and three 1-hour blocks of ~40 test items each. Students receive a printed percent-correct score after completing the session. **No explanations of questions are provided.**

You may register for a practice session online at www.usmle.org. A separate scheduling permit is issued for the practice session. Students should allow two weeks for receipt of this permit.

**How Do I Register to Take the Exam?**

Prometric test centers offer Step 1 on a year-round basis, except for the first two weeks in January and major holidays. The exam is given every day except Sunday at most centers. Some schools administer the exam on their own campuses. Check with the test center you want to use before making your exam plans.

US students can apply to take Step 1 at the NBME website. This application allows you to select one of 12 overlapping three-month blocks in which to be tested (eg, April–May–June, June–July–August). Choose your three-month eligibility period wisely. If you need to reschedule outside your initial three-month period, you can request a one-time extension of eligibility for the next contiguous three-month period, and pay a rescheduling fee. The application also includes a photo ID form that must be certified by an official at your medical school to verify your enrollment. After the NBME processes your application, it will send you a scheduling permit.

The scheduling permit you receive from the NBME will contain your USMLE identification number, the eligibility period in which you may take the exam, and two additional numbers. The first of these is known as your “scheduling number.” You must have this number in order to make your exam appointment with Prometric. The second number is known as the “candidate identification number,” or CIN. Examinees must enter their CINs at the Prometric workstation in order to access their exams. However, you will not be allowed to bring your permit into the exam and will be asked to copy your CIN onto your scratch paper. Prometric has no access to the codes. **Do not lose your permit!** You will not be allowed to take the exam unless you present this permit along with an unexpired, government-issued photo ID that includes your signature (such as a driver’s license or passport). Make sure the name on your photo ID exactly matches the name that appears on your scheduling permit.
Once you receive your scheduling permit, you may access the Prometric website or call Prometric’s toll-free number to arrange a time to take the exam. You may contact Prometric two weeks before the test date if you want to confirm identification requirements. Although requests for taking the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a “first-come, first-served” basis, it is recommended that you contact Prometric as soon as you receive your permit. After you’ve scheduled your exam, it’s a good idea to confirm your exam appointment with Prometric at least one week before your test date. Prometric will provide appointment confirmation on a print-out and by email. Be sure to read the 2018 USMLE Bulletin of Information for further details.

What If I Need to Reschedule the Exam?

You can change your test date and/or center by contacting Prometric at 1-800-MED-EXAM (1-800-633-3926) or www.prometric.com. Make sure to have your CIN when rescheduling. If you are rescheduling by phone, you must speak with a Prometric representative; leaving a voicemail message will not suffice. To avoid a rescheduling fee, you will need to request a change at least 31 calendar days before your appointment. Please note that your rescheduled test date must fall within your assigned three-month eligibility period.

When Should I Register for the Exam?

You should plan to register as far in advance as possible ahead of your desired test date (eg, six months), but, depending on your particular test center, new dates and times may open closer to the date. Scheduling early will guarantee that you will get either your test center of choice or one within a 50-mile radius of your first choice. For most US medical students, the desired testing window is in June, since most medical school curricula for the second year end in May or June. Thus, US medical students should plan to register before January in anticipation of a June test date. The timing of the exam is more flexible for IMGs, as it is related only to when they finish exam preparation. Talk with upperclassmen who have already taken the test so you have real-life experience from students who went through a similar curriculum, then formulate your own strategy.

Where Can I Take the Exam?

Your testing location is arranged with Prometric when you call for your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit www.prometric.com.
How Long Will I Have to Wait Before I Get My Scores?

The USMLE reports scores in three to four weeks, unless there are delays in score processing. Examinees will be notified via email when their scores are available. By following the online instructions, examinees will be able to view, download, and print their score report online for ~120 days after score notification, after which scores can only be obtained through requesting an official USMLE transcript. Additional information about score timetables and accessibility is available on the official USMLE website.

What About Time?

Time is of special interest on the CBT exam. Here’s a breakdown of the exam schedule:

- Tutorial (skip if familiar with test format and features)
- Seven 60-minute question blocks
- Break time (includes time for lunch)

The computer will keep track of how much time has elapsed on the exam. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly (at a rate of approximately one question per 90 seconds).

The computer does not warn you if you are spending more than your allotted time for a break. You should therefore budget your time so that you can take a short break when you need one and have time to eat. You must be especially careful not to spend too much time in between blocks (you should keep track of how much time elapses from the time you finish a block of questions to the time you start the next block). After you finish one question block, you’ll need to click to proceed to the next block of questions. If you do not click within 30 seconds, you will automatically be entered into a break period.

Break time for the day is 45 minutes, but you are not required to use all of it, nor are you required to use any of it. You can gain extra break time (but not extra time for the question blocks) by skipping the tutorial or by finishing a block ahead of the allotted time. Any time remaining on the clock when you finish a block gets added to your remaining break time. Once a new question block has been started, you may not take a break until you have reached the end of that block. If you do so, this will be recorded as an “unauthorized break” and will be reported on your final score report.

Finally, be aware that it may take a few minutes of your break time to “check out” of the secure resting room and then “check in” again to resume testing, so plan accordingly. The “check-in” process may include fingerprints, pocket checks, and metal detector scanning. Some students recommend pocketless clothing on exam day to streamline the process.
If I Freak Out and Leave, What Happens to My Score?

Your scheduling permit shows a CIN that you will need to enter to start your exam. Entering the CIN is the same as breaking the seal on a test book, and you are considered to have started the exam when you do so. However, no score will be reported if you do not complete the exam. In fact, if you leave at any time from the start of the test to the last block, no score will be reported. The fact that you started but did not complete the exam, however, will appear on your USMLE score transcript. Even though a score is not posted for incomplete tests, examinees may still get an option to request that their scores be calculated and reported if they desire; unanswered questions will be scored as incorrect.

The exam ends when all question blocks have been completed or when their time has expired. As you leave the testing center, you will receive a printed test-completion notice to document your completion of the exam. To receive an official score, you must finish the entire exam.

What Types of Questions Are Asked?

All questions on the exam are one-best-answer multiple choice items. Most questions consist of a clinical scenario or a direct question followed by a list of five or more options. You are required to select the single best answer among the options given. There are no “except,” “not,” or matching questions on the exam. A number of options may be partially correct, in which case you must select the option that best answers the question or completes the statement. Additionally, keep in mind that experimental questions may appear on the exam, which do not affect your score.

How Is the Test Scored?

Each Step 1 examinee receives an electronic score report that includes the examinee’s pass/fail status, a three-digit test score, and a graphic depiction of the examinee’s performance by discipline and organ system or subject area. The actual organ system profiles reported may depend on the statistical characteristics of a given administration of the examination.

The USMLE score report is divided into two sections: performance by discipline and performance by organ system. Each of the questions (minus experimental questions) is tagged according to any or all relevant content areas. Your performance in each discipline and each organ system is represented by a line of X’s, where the width of the line is related to the confidence interval for your performance, which is often a direct consequence of the total number of questions for each discipline/system. If any lines have an asterisk (*) at the far right, this means your performance was exemplary in that area—not necessarily representing a perfect score, but often close to it (see Figure 1).

The NBME provides a three-digit test score based on the total number of items answered correctly on the examination, which corresponds to a
particular percentile (see Figure 2). Your three-digit score will be qualified by the mean and standard deviation of US and Canadian medical school first-time examinees. The translation from the lines of X's and number of asterisks you receive on your report to the three-digit score is unclear, but higher three-digit scores are associated with more asterisks.

Since some questions may be experimental and are not counted, it is possible to get different scores for the same number of correct answers. In 2016, the mean score was 228 with a standard deviation of 21.

A score of 192 or higher is required to pass Step 1. The NBME does not report the minimum number of correct responses needed to pass, but estimates that it is roughly 60–70%. The NBME may adjust the minimum passing score in the future, so please check the USMLE website or www.firstaidteam.com for updates.

According to the USMLE, medical schools receive a listing of total scores and pass/fail results plus group summaries by discipline and organ system. Students can withhold their scores from their medical school if they wish. Official USMLE transcripts, which can be sent on request to residency programs, include only total scores, not performance profiles.
Consult the USMLE website or your medical school for the most current and accurate information regarding the examination.

What Does My Score Mean?

The most important point with the Step 1 score is passing versus failing. Passing essentially means, “Hey, you’re on your way to becoming a fully licensed doc.” As Table 1 shows, the majority of students pass the exam, so remember, we told you to relax.

TABLE 1. Passing Rates for the 2015–2016 USMLE Step 1. 2

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th></th>
<th>2016</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Tested</td>
<td>% Passing</td>
<td>No. Tested</td>
<td>% Passing</td>
</tr>
<tr>
<td>Allopathic 1st takers</td>
<td>20,213</td>
<td>96%</td>
<td>20,122</td>
<td>96%</td>
</tr>
<tr>
<td>Repeaters</td>
<td>898</td>
<td>68%</td>
<td>1,000</td>
<td>64%</td>
</tr>
<tr>
<td>Allopathic total</td>
<td>21,111</td>
<td>94%</td>
<td>21,122</td>
<td>94%</td>
</tr>
<tr>
<td>Osteopathic 1st takers</td>
<td>3,185</td>
<td>93%</td>
<td>3,398</td>
<td>94%</td>
</tr>
<tr>
<td>Repeaters</td>
<td>37</td>
<td>65%</td>
<td>56</td>
<td>75%</td>
</tr>
<tr>
<td>Osteopathic total</td>
<td>3,222</td>
<td>93%</td>
<td>3,454</td>
<td>93%</td>
</tr>
<tr>
<td>Total US/Canadian</td>
<td>24,333</td>
<td>94%</td>
<td>24,576</td>
<td>94%</td>
</tr>
<tr>
<td>IMG 1st takers</td>
<td>15,030</td>
<td>78%</td>
<td>15,031</td>
<td>78%</td>
</tr>
<tr>
<td>Repeaters</td>
<td>2,719</td>
<td>38%</td>
<td>2,575</td>
<td>39%</td>
</tr>
<tr>
<td>IMG total</td>
<td>17,749</td>
<td>72%</td>
<td>17,606</td>
<td>72%</td>
</tr>
<tr>
<td>Total Step 1 examinees</td>
<td>42,082</td>
<td>85%</td>
<td>42,182</td>
<td>88%</td>
</tr>
</tbody>
</table>
Beyond that, the main point of having a quantitative score is to give you a sense of how well you’ve done on the exam and to help schools and residencies rank their students and applicants, respectively.

**Official NBME/USMLE Resources**

The NBME offers a Comprehensive Basic Science Examination (CBSE) for practice that is a shorter version of the Step 1. The CBSE contains four blocks of 50 questions each and covers material that is typically learned during the basic science years. Scores range from 45 to 95 and correlate with a Step 1 equivalent (see Table 2). The standard error of measurement is approximately 3 points, meaning a score of 80 would estimate the student’s proficiency is somewhere between 77 and 83. In other words, the actual Step 1 score could be predicted to be between 218 and 232. Of course, these values do not correlate exactly, and they do not reflect different test preparation methods. Many schools use this test to gauge whether a student is expected to pass Step 1. If this test is offered by your school, it is usually conducted at the end of regular didactic time before any dedicated Step 1 preparation. If you do not encounter the CBSE before your dedicated study time, you need not worry about taking it. Use the information to help set realistic goals and timetables for your success.

The NBME also offers six forms of Comprehensive Basic Science Self-Assessment (CBSSA). Students who prepared for the exam using this web-based tool reported that they found the format and content highly indicative of questions tested on the actual exam. In addition, the CBSSA is a fair predictor of USMLE performance (see Table 3). The test interface, however, does not match the actual USMLE test interface, so practicing with these forms alone is not advised.

The CBSSA exists in two formats: standard-paced and self-paced, both of which consist of four sections of 50 questions each (for a total of 200 multiple choice items). The standard-paced format allows the user up to 65 minutes to complete each section, reflecting time limits similar to the actual exam. By contrast, the self-paced format places a 4:20 time limit on answering all multiple choice questions. Every few years, a new form is released and an older one is retired, reflecting changes in exam content. Therefore, the newer exams tend to be more similar to the actual Step 1, and scores from these exams tend to provide a better estimation of exam day performance.

Keep in mind that this bank of questions is available only on the web. The NBME requires that users log on, register, and start the test within 30 days of registration. Once the assessment has begun, users are required to complete the sections within 20 days. Following completion of the questions, the CBSSA provides a performance profile indicating the user’s relative strengths and weaknesses, much like the report profile for the USMLE Step 1 exam. The profile is scaled with an average score of 500 and a standard deviation of 100. In addition to the performance profile, examinees will be informed of the number of questions answered incorrectly. You will have the ability to review the text of the incorrect question with the correct answer. Explanations for

---

**Table 2. CBSE to USMLE Score Prediction.**

<table>
<thead>
<tr>
<th>CBSE Score</th>
<th>Step 1 Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 94</td>
<td>≥ 260</td>
</tr>
<tr>
<td>92</td>
<td>255</td>
</tr>
<tr>
<td>90</td>
<td>250</td>
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<td>48</td>
<td>145</td>
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<td>46</td>
<td>140</td>
</tr>
<tr>
<td>≤ 44</td>
<td>≤ 135</td>
</tr>
</tbody>
</table>

*Practice questions may be easier than the actual exam.*
TABLE 3. CBSSA to USMLE Score Prediction.

<table>
<thead>
<tr>
<th>CBSSA Score</th>
<th>Approximate USMLE Step 1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>155</td>
</tr>
<tr>
<td>200</td>
<td>165</td>
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<tr>
<td>250</td>
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<td>750</td>
<td>280</td>
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<tr>
<td>800</td>
<td>290</td>
</tr>
</tbody>
</table>

The NBME scoring system is weighted for each assessment exam. While some exams seem more difficult than others, the score reported takes into account these inter-test differences when predicting Step 1 performance. Also, while many students report seeing Step 1 questions “word-for-word” out of the assessments, the NBME makes special note that no live USMLE questions are shown on any NBME assessment.

Lastly, the International Foundations of Medicine (IFOM) offers a Basic Science Examination (BSE) practice exam at participating Prometric test centers for $200. Students may also take the self-assessment test online for $35 through the NBME’s website. The IFOM BSE is intended to determine an examinee’s relative areas of strength and weakness in general areas of basic science—not to predict performance on the USMLE Step 1 exam—and the content covered by the two examinations is somewhat different. However, because there is substantial overlap in content coverage and many IFOM items were previously used on the USMLE Step 1, it is possible to roughly project IFOM performance onto the USMLE Step 1 score scale. More information is available at http://www.nbme.org/ifom/.

DEFINING YOUR GOAL

It is useful to define your own personal performance goal when approaching the USMLE Step 1. Your style and intensity of preparation can then be matched to your goal. Furthermore, your goal may depend on your school’s requirements, your specialty choice, your grades to date, and your personal assessment of the test’s importance. Do your best to define your goals early so that you can prepare accordingly.

The value of the USMLE Step 1 score in selecting residency applicants remains controversial, and some have called for less emphasis to be placed on the score when selecting or screening applicants. For the time being, however, it continues to be an important part of the residency application, and it is not uncommon for some specialties to implement filters that screen out applicants who score below a certain cutoff. This is more likely to be seen in competitive specialties (e.g., orthopedic surgery, ophthalmology, dermatology, otolaryngology). Independent of your career goals, you can maximize your future options by doing your best to obtain the highest score possible (see Figure 3). At the same time, your Step 1 score is only one of a number of factors that are assessed when you apply for residency. In fact, many residency programs value other criteria such as letters of recommendation, third-year clerkship grades, honors, and research experience more than a high score on Step 1. Fourth-year medical students who have recently completed the residency application process can be a valuable resource in this regard.

Some competitive residency programs place more weight on Step 1 scores when choosing candidates to interview.

Fourth-year medical students have the best feel for how Step 1 scores factor into the residency application process.
Many students feel overwhelmed during the preclinical years and struggle to find an effective learning strategy. Table 4 lists several learning strategies you can try and their estimated effectiveness for Step 1 preparation based on the literature (see References). These are merely suggestions, and it’s important to take your learning preferences into account. Your comprehensive learning approach will contain a combination of strategies (eg, elaborative interrogation followed by practice testing, mnemonics review using spaced repetition, etc). Regardless of your choice, the foundation of knowledge you build during your basic science years is the most important resource for success on the USMLE Step 1.

**HIGH EFFICACY**

**Practice Testing**

Also called “retrieval practice,” practice testing has both direct and indirect benefits to the learner. Effortful retrieval of answers does not only identify weak spots—it directly strengthens long-term retention of material. The more effortful the recall, the better the long-term retention. This advantage has been shown to result in higher test scores and GPAs. In fact, research has shown a positive correlation between the number of boards-style practice questions completed and Step 1 scores among medical students.

Practice testing should be done with “interleaving” (mixing of questions from different topics in a single session). Question banks often allow you to intermingle topics. Interleaved practice helps learners develop their ability to focus on the relevant concept when faced with many possibilities. Practicing topics in massed fashion (eg, all cardiology, then all dermatology) may seem intuitive, but there is strong evidence that interleaving correlates with longer-term retention.
term retention and increased student achievement, especially on tasks that involve problem solving.\textsuperscript{5}

In addition to using question banks, you can test yourself by arranging your notes in a question-answer format (e.g., via flash cards). Testing these Q&As in random order allows you to reap the benefit of interleaved practice. Bear in mind that the utility of practice testing comes from the practice of information retrieval, so simply reading through Q&As will attenuate this benefit.

**Distributed Practice**

Also called “spaced repetition,” distributed practice is the opposite of massed practice or “cramming.” Learners review material at increasingly spaced out intervals (days to weeks to months). Massed learning may produce more short-term gains and satisfaction, but learners who use distributed practice have better mastery and retention over the long term.\textsuperscript{5,9}

Flash cards are a simple way to incorporate both distributed practice and practice testing. Studies have linked spaced repetition learning with flash cards
to improved long-term knowledge retention and higher exam scores.\textsuperscript{6,8,10} Apps with automated spaced-repetition software (SRS) for flash cards exist for smartphones and tablets, so the cards are accessible anywhere. Proceed with caution: there is an art to making and reviewing cards. The ease of quickly downloading or creating digital cards can lead to flash card overload (it is unsustainable to make 50 flash cards per lecture!). Even at a modest pace, the thousands upon thousands of cards are too overwhelming for Step 1 preparation. Unless you have specific high-yield cards (and have checked the content with high-yield resources), stick to pre-made cards by reputable sources that curate the vast amount of knowledge for you.

If you prefer pen and paper, consider using a planner or spreadsheet to organize your study material over time. Distributed practice allows for some forgetting of information, and the added effort of recall over time strengthens the learning.

**MODERATE EFFICACY**

**Mnemonics**

A “mnemonic” refers to any device that assists memory, such as acronyms, mental imagery (eg, keywords with or without memory palaces), etc. Keyword mnemonics have been shown to produce superior knowledge retention when compared with rote memorization in many scenarios. However, they are generally more effective when applied to memorization-heavy, keyword-friendly topics and may not be broadly suitable.\textsuperscript{5} Keyword mnemonics may not produce long-term retention, so consider combining mnemonics with distributed, retrieval-based practice (eg, via flash cards with SRS).

Self-made mnemonics may have an advantage when material is simple and keyword friendly. If you can create your own mnemonic that accurately represents the material, this will be more memorable. When topics are complex and accurate mnemonics are challenging to create, pre-made mnemonics may be more effective, especially if you are inexperienced at creating mnemonics.\textsuperscript{11}

**Elaborative Interrogation/Self-Explanation**

Elaborative interrogation (“why” questions) and self-explanation (general questioning) prompt learners to generate explanations for facts. When reading passages of discrete facts, consider using these techniques, which have been shown to be more effective than rereading (eg, improved recall and better problem-solving/diagnostic performance).\textsuperscript{5,12,13}

**Concept Mapping**

Concept mapping is a method for graphically organizing knowledge, with concepts enclosed in boxes and lines drawn between related concepts.
Creating or studying concept maps may be more effective than other activities (eg, writing or reading summaries/outlines). However, studies have reached mixed conclusions about its utility, and the small size of this effect raises doubts about its authenticity and pedagogic significance.\textsuperscript{14}

**LOW EFFICACY**

**Rereading**

While the most commonly used method among surveyed students, rereading has not been shown to correlate with grade point average.\textsuperscript{9} Due to its popularity, rereading is often a comparator in studies on learning. Other strategies that we have discussed (eg, practice testing) have been shown to be significantly more effective than rereading.

**Highlighting/Underlining**

Because this method is passive, it tends to be of minimal value for learning and recall. In fact, lower-performing students are more likely to use these techniques.\textsuperscript{9} Students who highlight and underline do not learn how to actively recall learned information and thus find it difficult to apply knowledge to exam questions.

**Summarization**

While more useful for improving performance on generative measures (eg, free recall or essays), summarization is less useful for exams that depend on recognition (eg, multiple choice). Findings on the overall efficacy of this method have been mixed.\textsuperscript{5}

**TIMELINE FOR STUDY**

**Before Starting**

Your preparation for the USMLE Step 1 should begin when you enter medical school. Organize and commit to studying from the beginning so that when the time comes to prepare for the USMLE, you will be ready with a strong foundation.

**Make a Schedule**

After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, the difficulty of your ongoing coursework, and your family and social commitments (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in
preparing for standardized examinations (eg, SAT, MCAT). Talk to students at your school who have recently taken Step 1. Ask them for their study schedules, especially those who have study habits and goals similar to yours.

Typically, US medical schools allot between four and eight weeks for dedicated Step 1 preparation. The time you dedicate to exam preparation will depend on your target score as well as your success in preparing yourself during the first two years of medical school. Some students reserve about a week at the end of their study period for final review; others save just a few days. When you have scheduled your exam date, do your best to adhere to it. Studies show that a later testing date does not translate into a higher score, so avoid pushing back your test date without good reason.

Make your schedule realistic, and set achievable goals. Many students make the mistake of studying at a level of detail that requires too much time for a comprehensive review—reading Gray’s Anatomy in a couple of days is not a realistic goal! Have one catch-up day per week of studying. No matter how well you stick to your schedule, unexpected events happen. But don’t let yourself procrastinate because you have catch-up days; stick to your schedule as closely as possible and revise it regularly on the basis of your actual progress. Be careful not to lose focus. Beware of feelings of inadequacy when comparing study schedules and progress with your peers. Avoid others who stress you out. Focus on a few top-rated resources that suit your learning style—not on some obscure books your friends may pass down to you. Accept the fact that you cannot learn it all.

You will need time for uninterrupted and focused study. Plan your personal affairs to minimize crisis situations near the date of the test. Allot an adequate number of breaks in your study schedule to avoid burnout. Maintain a healthy lifestyle with proper diet, exercise, and sleep.

Another important aspect of your preparation is your studying environment. Study where you have always been comfortable studying. Be sure to include everything you need close by (review books, notes, coffee, snacks, etc). If you’re the kind of person who cannot study alone, form a study group with other students taking the exam. The main point here is to create a comfortable environment with minimal distractions.
Year(s) Prior

The knowledge you gained during your first two years of medical school and even during your undergraduate years should provide the groundwork on which to base your test preparation. Student scores on NBME subject tests (commonly known as “shelf exams”) have been shown to be highly correlated with subsequent Step 1 scores. Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam.

We also recommend that you buy highly rated review books early in your first year of medical school and use them as you study throughout the two years. When Step 1 comes along, these books will be familiar and personalized to the way in which you learn. It is risky and intimidating to use unfamiliar review books in the final two or three weeks preceding the exam. Some students find it helpful to personalize and annotate *First Aid* throughout the curriculum.

Months Prior

Review test dates and the application procedure. Testing for the USMLE Step 1 is done on a year-round basis. If you have disabilities or special circumstances, contact the NBME as early as possible to discuss test accommodations (see the Section I Supplement at www.firstaidteam.com/bonus).

Use this time to finalize your ideal schedule. Consider upcoming breaks and whether you want to relax or study. Work backward from your test date to make sure you finish at least one question bank. Also add time to redo missed or flagged questions (which may be half the bank). This is the time to build a structured plan with enough flexibility for the realities of life.

Begin doing blocks of questions from reputable question banks under “real” conditions. Don’t use tutor mode until you’re sure you can finish blocks in the allotted time. It is important to continue balancing success in your normal studies with the Step 1 test preparation process.

Weeks Prior (Dedicated Preparation)

Your dedicated prep time may be one week or two months. You should have a working plan as you go into this period. Finish your schoolwork strong, take a day off, and then get to work. Start by simulating a full-length USMLE Step 1 if you haven’t yet done so. Consider doing one NBME CBSSA and the free questions from the NBME website. Alternatively, you could choose 7 blocks of randomized questions from a commercial question bank. Make sure you get feedback on your strengths and weaknesses and adjust your studying accordingly. Many students study from review sources or comprehensive programs for part of the day, then do question blocks. Also, keep in mind that reviewing a question block can take upward of two hours. Feedback from CBSSA exams and question banks will help you focus on your weaknesses.
One Week Prior

Make sure you have your CIN (found on your scheduling permit) as well as other items necessary for the day of the examination, including a current driver’s license or another form of photo ID with your signature (make sure the name on your ID exactly matches that on your scheduling permit). Confirm the Prometric testing center location and test time. Work out how you will get to the testing center and what parking and traffic problems you might encounter. Drive separately from other students taking the test on the same day, and exchange cell phone numbers in case of emergencies. If possible, visit the testing site to get a better idea of the testing conditions you will face. Determine what you will do for lunch. Make sure you have everything you need to ensure that you will be comfortable and alert at the test site. It may be beneficial to adjust your schedule to start waking up at the same time that you will on your test day. And of course, make sure to maintain a healthy lifestyle and get enough sleep.

One Day Prior

Try your best to relax and rest the night before the test. Double-check your admissions and test-taking materials as well as the comfort measures discussed earlier so that you will not have to deal with such details on the morning of the exam. At this point it will be more effective to review short-term memory material that you’re already familiar with than to try to learn new material. The Rapid Review section at the end of this book is high yield for last-minute studying. Remember that regardless of how hard you have studied, you cannot know everything. There will be things on the exam that you have never even seen before, so do not panic. Do not underestimate your abilities.

Many students report difficulty sleeping the night prior to the exam. This is often exacerbated by going to bed much earlier than usual. Do whatever it takes to ensure a good night’s sleep (eg, massage, exercise, warm milk, no back-lit screens at night). Do not change your daily routine prior to the exam. Exam day is not the day for a caffeine-withdrawal headache.

Morning of the Exam

On the morning of the Step 1 exam, wake up at your regular time and eat a normal breakfast. If you think it will help you, have a close friend or family member check to make sure you get out of bed. Make sure you have your scheduling permit admission ticket, test-taking materials, and comfort measures as discussed earlier. Wear loose, comfortable clothing. Plan for a variable temperature in the testing center. Arrive at the test site 30 minutes before the time designated on the admission ticket; however, do not come too early, as doing so may intensify your anxiety. When you arrive at the test site, the proctor should give you a USMLE information sheet that will explain critical factors such as the proper use of break time. Seating may be assigned, but ask to be reseated if necessary; you need to be seated in an area that...
will allow you to remain comfortable and to concentrate. Get to know your testing station, especially if you have never been in a Prometric testing center before. Listen to your proctors regarding any changes in instructions or testing procedures that may apply to your test site.

Finally, remember that it is natural (and even beneficial) to be a little nervous. Focus on being mentally clear and alert. Avoid panic. When you are asked to begin the exam, take a deep breath, focus on the screen, and then begin. Keep an eye on the timer. Take advantage of breaks between blocks to stretch, maybe do some jumping jacks, and relax for a moment with deep breathing or stretching.

After the Test

After you have completed the exam, be sure to have fun and relax regardless of how you may feel. Taking the test is an achievement in itself. Remember, you are much more likely to have passed than not. Enjoy the free time you have before your clerkships. Expect to experience some “reentry” phenomena as you try to regain a real life. Once you have recovered sufficiently from the test (or from partying), we invite you to send us your feedback, corrections, and suggestions for entries, facts, mnemonics, strategies, resource ratings, and the like (see p. xvi, How to Contribute). Sharing your experience will benefit fellow medical students and IMGs.

STUDY MATERIALS

Quality Considerations

Although an ever-increasing number of review books and software are now available on the market, the quality of such material is highly variable. Some common problems are as follows:

- Certain review books are too detailed to allow for review in a reasonable amount of time or cover subtopics that are not emphasized on the exam.
- Many sample question books were originally written years ago and have not been adequately updated to reflect recent trends.
- Some question banks test to a level of detail that you will not find on the exam.

Review Books

In selecting review books, be sure to weigh different opinions against each other, read the reviews and ratings in Section IV of this guide, examine the books closely in the bookstore, and choose carefully. You are investing not only money but also your limited study time. Do not worry about finding the “perfect” book, as many subjects simply do not have one, and different students prefer different formats. Supplement your chosen books with personal notes from other sources, including what you learn from question banks.
There are two types of review books: those that are stand-alone titles and those that are part of a series. Books in a series generally have the same style, and you must decide if that style works for you. However, a given style is not optimal for every subject.

You should also find out which books are up to date. Some recent editions reflect major improvements, whereas others contain only cursory changes. Take into consideration how a book reflects the format of the USMLE Step 1.

**Apps**

With the explosion of smartphones and tablets, apps are an increasingly popular way to review for the Step 1 exam. The majority of apps are compatible with both iOS and Android. Many popular Step 1 review resources (eg, UWorld, USMLE-Rx) have apps that are compatible with their software. Many popular web references (eg, UpToDate) also now offer app versions. All of these apps offer flexibility, allowing you to study while away from a computer (eg, while traveling).

**Practice Tests**

Taking practice tests provides valuable information about potential strengths and weaknesses in your fund of knowledge and test-taking skills. Some students use practice examinations simply as a means of breaking up the monotony of studying and adding variety to their study schedule, whereas other students rely almost solely on practice. You should also subscribe to one or more high-quality question banks. In addition, students report that many current practice-exam books have questions that are, on average, shorter and less clinically oriented than those on the current USMLE Step 1.

Additionally, some students preparing for the Step 1 exam have started to incorporate case-based books intended primarily for clinical students on the wards or studying for the Step 2 CK exam. First Aid Cases for the USMLE Step 1 aims to directly address this need.

After taking a practice test, spend time on each question and each answer choice whether you were right or wrong. There are important teaching points in each explanation. Knowing why a wrong answer choice is incorrect is just as important as knowing why the right answer is correct. Do not panic if your practice scores are low as many questions try to trick or distract you to highlight a certain point. Use the questions you missed or were unsure about to develop focused plans during your scheduled catch-up time.

**Textbooks and Course Syllabi**

Limit your use of textbooks and course syllabi for Step 1 review. Many textbooks are too detailed for high-yield review and include material that is generally not tested on the USMLE Step 1 (eg, drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent across.

Charts and diagrams may be the best approach for physiology and biochemistry, whereas tables and outlines may be preferable for microbiology.

Most practice exams are shorter and less clinical than the real thing.

Use practice tests to identify concepts and areas of weakness, not just facts that you missed.
medical schools and frequently reflect the emphasis of individual faculty, which often does not correspond to that of the USMLE Step 1. Syllabi also tend to be less organized than top-rated books and generally contain fewer diagrams and study questions.

### TEST-TAKING STRATEGIES

Your test performance will be influenced by both your knowledge and your test-taking skills. You can strengthen your performance by considering each of these factors. Test-taking skills and strategies should be developed and perfected well in advance of the test date so that you can concentrate on the test itself. We suggest that you try the following strategies to see if they might work for you.

**Pacing**

You have seven hours to complete up to 280 questions. Note that each one-hour block contains up to 40 questions. This works out to approximately 90 seconds per question. We recommend following the “1 minute rule” to pace yourself. Spend no more than 1 minute on each question. If you are still unsure about the answer after this time, mark the question, make an educated guess, and move on. Following this rule, you should have approximately 20 minutes left after all questions are answered, which you can use to revisit all of your marked questions. Remember that some questions may be experimental and do not count for points (and reassure yourself that these experimental questions are the ones that are stumping you). In the past, pacing errors have been detrimental to the performance of even highly prepared examinees. The bottom line is to keep one eye on the clock at all times!

**Dealing with Each Question**

There are several established techniques for efficiently approaching multiple choice questions; find what works for you. One technique begins with identifying each question as easy, workable, or impossible. Your goal should be to answer all easy questions, resolve all workable questions in a reasonable amount of time, and make quick and intelligent guesses on all impossible questions. Most students read the stem, think of the answer, and turn immediately to the choices. A second technique is to first skim the answer choices to get a context, then read the last sentence of the question (the lead-in), and then read through the passage quickly, extracting only information relevant to answering the question. This can be particularly helpful for questions with long clinical vignettes. Try a variety of techniques on practice exams and see what works best for you. If you get overwhelmed, remember that a 30-second time out to refocus may get you back on track.
Guessing

There is no penalty for wrong answers. Thus, no test block should be left with unanswered questions. A hunch is probably better than a random guess. If you have to guess, we suggest selecting an answer you recognize over one with which you are totally unfamiliar.

Changing Your Answer

The conventional wisdom is not to change answers that you have already marked unless there is a convincing and logical reason to do so—in other words, go with your “first hunch.” Many question banks tell you how many questions you changed from right to wrong, wrong to wrong, and wrong to right. Use this feedback to judge how good a second-guesser you are. If you have extra time, reread the question stem and make sure you didn’t misinterpret the question.

CLINICAL VIGNETTE STRATEGIES

In recent years, the USMLE Step 1 has become increasingly clinically oriented. This change mirrors the trend in medical education toward introducing students to clinical problem solving during the basic science years. The increasing clinical emphasis on Step 1 may be challenging to those students who attend schools with a more traditional curriculum.

What Is a Clinical Vignette?

A clinical vignette is a short (usually paragraph-long) description of a patient, including demographics, presenting symptoms, signs, and other information concerning the patient. Sometimes this paragraph is followed by a brief listing of important physical findings and/or laboratory results. The task of assimilating all this information and answering the associated question in the span of one minute can be intimidating. So be prepared to read quickly and think on your feet. Remember that the question is often indirectly asking something you already know.

Strategy

Remember that Step 1 vignettes usually describe diseases or disorders in their most classic presentation. So look for cardinal signs (e.g., malar rash for SLE or nuchal rigidity for meningitis) in the narrative history. Be aware that the question will contain classic signs and symptoms instead of buzzwords. Sometimes the data from labs and the physical exam will help you confirm or reject possible diagnoses, thereby helping you rule answer choices in or out. In some cases, they will be a dead giveaway for the diagnosis.
Making a diagnosis from the history and data is often not the final answer. Not infrequently, the diagnosis is divulged at the end of the vignette, after you have just struggled through the narrative to come up with a diagnosis of your own. The question might then ask about a related aspect of the diagnosed disease. Consider skimming the answer choices and lead-in before diving into a long stem. However, be careful with skimming the answer choices; going too fast may warp your perception of what the vignette is asking.

IF YOU THINK YOU FAILED

After the test, many examinees feel that they have failed, and most are at the very least unsure of their pass/fail status. There are several sensible steps you can take to plan for the future in the event that you do not achieve a passing score. First, save and organize all your study materials, including review books, practice tests, and notes. Familiarize yourself with the reapplication procedures for Step 1, including application deadlines and upcoming test dates.

Make sure you know both your school’s and the NBME’s policies regarding retakes. The NBME allows a maximum of six attempts to pass each Step examination. You may take Step 1 no more than three times within a 12-month period. Your fourth and subsequent attempts must be at least 12 months after your first attempt at that exam and at least six months after your most recent attempt at that exam.

The performance profiles on the back of the USMLE Step 1 score report provide valuable feedback concerning your relative strengths and weaknesses. Study these profiles closely. Set up a study timeline to strengthen gaps in your knowledge as well as to maintain and improve what you already know. Do not neglect high-yield subjects. It is normal to feel somewhat anxious about retaking the test, but if anxiety becomes a problem, seek appropriate counseling.

TESTING AGENCIES

- National Board of Medical Examiners (NBME) / USMLE Secretariat
  Department of Licensing Examination Services
  3750 Market Street
  Philadelphia, PA 19104-3102
  (215) 590-9500 (operator) or (215) 590-9700 (automated information line)
  Fax: (215) 590-9457
  Email: webmail@nbme.org
  www.nbme.org
• Educational Commission for Foreign Medical Graduates (ECFMG)
  3624 Market Street
  Philadelphia, PA 19104-2685
  (215) 386-5900
  Fax: (215) 386-9196
  Email: info@ecfmg.org
  www.ecfmg.org

REFERENCES


Special Situations

Please visit www.firstaidteam.com/bonus/ to view this section.

- First Aid for the International Medical Graduate 2
- First Aid for the Osteopathic Medical Student 13
- First Aid for the Podiatric Medical Student 17
- First Aid for the Student Requiring Test Accommodations 20
SECTION II

High-Yield
General Principles

“There comes a time when for every addition of knowledge you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones.”
—Sir Arthur Conan Doyle, A Study in Scarlet

“Never regard study as a duty, but as the enviable opportunity to learn.”
—Albert Einstein

“Live as if you were to die tomorrow. Learn as if you were to live forever.”
—Gandhi
HOW TO USE THE DATABASE

The 2018 edition of First Aid for the USMLE Step I contains a revised and expanded database of basic science material that students, student authors, and faculty authors have identified as high yield for board review. The information is presented in a partially organ-based format. Hence, Section II is devoted to the foundational principles of biochemistry, microbiology, immunology, basic pathology, basic pharmacology, and public health sciences. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, clinical pathology, and clinical pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the Title of the fact in the first column, the Description of the fact in the second column, and the Mnemonic or Special Note in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

The database structure used in Sections II and III is useful for reviewing material already learned. These sections are not ideal for learning complex or highly conceptual material for the first time.

The database of high-yield facts is not comprehensive. Use it to complement your core study material and not as your primary study source. The facts and notes have been condensed and edited to emphasize the essential material, and as a result, each entry is “incomplete” and arguably “over-simplified.” Often, the more you research a topic, the more complex it becomes, with certain topics resisting simplification. Work with the material, add your own notes and mnemonics, and recognize that not all memory techniques work for all students.

We update the database of high-yield facts annually to keep current with new trends in boards emphasis, including clinical relevance. However, we must note that inevitably many other high-yield topics are not yet included in our database.

We actively encourage medical students and faculty to submit high-yield topics, well-written entries, diagrams, clinical images, and useful mnemonics so that we may enhance the database for future students. We also solicit recommendations of alternate tools for study that may be useful in preparing for the examination, such as charts, flash cards, apps, and online resources (see How to Contribute, p. xvii).
Image Acknowledgments

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Disclaimer

The entries in this section reflect student opinions of what is high yield. Because of the diverse sources of material, no attempt has been made to trace or reference the origins of entries individually. We have regarded mnemonics as essentially in the public domain. Errata will gladly be corrected if brought to the attention of the authors, either through our online errata submission form at www.firstaidteam.com or directly by email to firstaidteam@yahoo.com.
“Biochemistry is the study of carbon compounds that crawl.”
—Mike Adams

“We think we have found the basic mechanism by which life comes from life.”
—Francis H. C. Crick

“The biochemistry and biophysics are the notes required for life; they conspire, collectively, to generate the real unit of life, the organism.”
—Ursula Goodenough

This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease, as well as reactions targeted by pharmacologic interventions. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway. Do not spend time on hard-core organic chemistry, mechanisms, or physical chemistry. Detailed chemical structures are infrequently tested; however, many structures have been included here to help students learn reactions and the important enzymes involved. Familiarity with the biochemical techniques that have medical relevance—such as ELISA, immuno-electrophoresis, Southern blotting, and PCR—is useful. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.
Chromatin structure

DNA exists in the condensed, chromatin form to fit into the nucleus. DNA loops twice around a histone octamer to form a nucleosome ("beads on a string"). H1 binds to the nucleosome and to "linker DNA," thereby stabilizing the chromatin fiber. Phosphate groups give DNA a \( \ominus \) charge. Lysine and arginine give histones a \( \oplus \) charge.

In mitosis, DNA condenses to form chromosomes. DNA and histone synthesis occurs during S phase. Mitochondria have their own DNA, which is circular and does not utilize histones.

**Heterochromatin**

Condensed, appears darker on EM (labeled H in A; Nu, nucleolus). Transcriptionally inactive, sterically inaccessible. \( \uparrow \) methylation, \( \downarrow \) acetylation.

**Euchromatin**

Less condensed, appears lighter on EM (labeled E in A). Transcriptionally active, sterically accessible.

**DNA methylation**

Changes the expression of a DNA segment without changing the sequence. Involved with genomic imprinting, X-chromosome inactivation, repression of transposable elements, aging, and carcinogenesis.

**Histone methylation**

Usually causes reversible transcriptional suppression, but can also cause activation depending on location of methyl groups.

**Histone acetylation**

Relaxes DNA coiling, allowing for transcription.
Nucleotides

Nucleoside = base + (deoxy)ribose (Sugar).
Nucleotide = base + (deoxy)ribose + phosphate; linked by 3′-5′ phosphodiester bond.

5′ end of incoming nucleotide bears the triphosphate (energy source for the bond). Triphosphate bond is target of 3′ hydroxyl attack.

Purines (A,G)—2 rings.
Pyrimidines (C,U,T)—1 ring.

Deamination of cytosine forms uracil.
Deamination of adenine forms hypoxanthine.
Deamination of guanine forms xanthine.
Deamination of 5-methylcytosine forms thymine.
Uracil found in RNA; thymine in DNA.
Methylation of uracil makes thymine.

5′ end of incoming nucleotide bears the triphosphate (energy source for the bond). Triphosphate bond is target of 3′ hydroxyl attack.

Pur As Gold.
CUT the PY (pie).
Thymine has a methyl.
G-C bond (3 H bonds) stronger than A-T bond (2 H bonds). ↑ G-C content → ↑ melting temperature of DNA. "C-G bonds are like Crazy Glue."

Amino acids necessary for purine synthesis (Cats purr until they GAG):
Glycine
Aspartate
Glutamine
De novo pyrimidine and purine synthesis

Various immunosuppressive, antineoplastic, and antibiotic drugs function by interfering with nucleotide synthesis:

Pyrimidine synthesis:
- Leflunomide: inhibits dihydroorotate dehydrogenase
- Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine: inhibit dihydrofolate reductase (deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, respectively
- 5-fluorouracil (5-FU) and its prodrug capecitabine: form 5-F-dUMP, which inhibits thymidylate synthase (deoxythymidine monophosphate [dTMP])

Purine synthesis:
- 6-mercaptopurine (6-MP) and its prodrug azathioprine: inhibit de novo purine synthesis
- Mycophenolate and ribavirin: inhibit inosine monophosphate dehydrogenase

Purine and pyrimidine synthesis:
- Hydroxyurea: inhibits ribonucleotide reductase

CPS1 = mitochondria (urea cycle)
CPS2 = cytosol
Purine salvage deficiencies

![Diagram of purine metabolism](image)

**Adenosine deaminase deficiency**
- ADA is required for degradation of adenosine and deoxyadenosine. In ADA deficiency, dATP leads to lymphotoxicity.
- One of the major causes of autosomal recessive SCID.

**Lesch-Nyhan syndrome**
- Defective purine salvage due to absent HGPRT, which converts hypoxanthine to IMP and guanine to GMP. Results in excess uric acid production and de novo purine synthesis. X-linked recessive.
- Findings: intellectual disability, self-mutilation, aggression, hyperuricemia (orange "sand" [sodium urate crystals] in diaper), gout, dystonia.
- Treatment: allopurinol or febuxostat (2nd line).

**Genetic code features**

<table>
<thead>
<tr>
<th>Unambiguous</th>
<th>Each codon specifies only 1 amino acid.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerate/redundant</td>
<td>Most amino acids are coded by multiple codons. Exceptions: methionine (AUG) and tryptophan (UGG) encoded by only 1 codon.</td>
</tr>
<tr>
<td><strong>Wobble</strong></td>
<td>Codons that differ in 3rd, &quot;wobble&quot; position may code for the same tRNA/amine acid. Specific base pairing is usually required only in the first 2 nucleotide positions of mRNA codon.</td>
</tr>
<tr>
<td>Commaless, nonoverlapping</td>
<td>Read from a fixed starting point as a continuous sequence of bases. Exceptions: some viruses.</td>
</tr>
<tr>
<td>Universal</td>
<td>Genetic code is conserved throughout evolution. Exception in humans: mitochondria.</td>
</tr>
</tbody>
</table>
DNA replication

Eukaryotic DNA replication is more complex than the prokaryotic process but uses many enzymes analogous to those listed below. In both prokaryotes and eukaryotes, DNA replication is semiconservative, involves both continuous and discontinuous (Okazaki fragment) synthesis, and occurs in the 5′ → 3′ direction.

Origin of replication

Particular consensus sequence of base pairs in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes).

AT-rich sequences (such as TATA box regions) are found in promoters and origins of replication.

Replication fork

Y-shaped region along DNA template where leading and lagging strands are synthesized.

Helicase

Unwinds DNA template at replication fork.

Helicase Halves DNA.

Single-stranded binding proteins

Prevent strands from reannealing.

DNA topoisomerases

Create a single- or double-stranded break in the helix to add or remove supercoils.

In eukaryotes: irinotecan/topotecan inhibit topoisomerase (TOP) I, etoposide/teniposide inhibit TOP II.

In prokaryotes: fluoroquinolones inhibit TOP II (DNA gyrase) and TOP IV.

Primase

Makes an RNA primer on which DNA polymerase III can initiate replication.

DNA polymerase III

Prokaryotes only. Elongates leading strand by adding deoxynucleotides to the 3′ end. Elongates lagging strand until it reaches primer of preceding fragment. 3′ → 5′ exonuclease activity “proofreads” each added nucleotide.

DNA polymerase III has 5′ → 3′ synthesis and proofreads with 3′ → 5′ exonuclease.

Drugs blocking DNA replication often have a modified 3′OH, thereby preventing addition of the next nucleotide (“chain termination”).

DNA polymerase I

Prokaryotic only. Degrades RNA primer; replaces it with DNA.

Same functions as DNA polymerase III, also excises RNA primer with 5′ → 3′ exonuclease.

DNA ligase

Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA.

Joins Okazaki fragments.

Telomerase

Eukaryotes only. A reverse transcriptase (RNA-dependent DNA polymerase) that adds DNA (TTAGGG) to 3′ ends of chromosomes to avoid loss of genetic material with every duplication.

Often dysregulated in cancer cells, allowing unlimited replication.

Telomerase TAGs for Greatness and Glory.
Mutations in DNA

Severity of damage: silent << missense < nonsense < frameshift.

For point (silent, missense, and nonsense) mutations:

- **Transition**—purine to purine (e.g., A to G) or pyrimidine to pyrimidine (e.g., C to T).
- **Transversion**—purine to pyrimidine (e.g., A to T) or pyrimidine to purine (e.g., C to G).

### Silent

Nucleotide substitution but codes for same (synonymous) amino acid; often base change in 3rd position of codon (tRNA wobble).

### Missense

Nucleotide substitution resulting in changed amino acid (called conservative if new amino acid is similar in chemical structure).

- Sickle cell disease (substitution of glutamic acid with valine).

### Nonsense

Nucleotide substitution resulting in early **stop** codon (UAG, UAA, UGA). Usually results in nonfunctional protein.

- Duchenne muscular dystrophy, Tay-Sachs disease.

### Frameshift

Deletion or insertion of a number of nucleotides not divisible by 3, resulting in misreading of all nucleotides downstream. Protein may be shorter or longer, and its function may be disrupted or altered.

- Rare cause of cancers, dementia, epilepsy, some types of β-thalassemia.

### Splice site

Mutation at a splice site → retained intron in the mRNA → protein with impaired or altered function.

**Lac operon**

Classic example of a genetic response to an environmental change. Glucose is the preferred metabolic substrate in *E coli*, but when glucose is absent and lactose is available, the *lac* operon is activated to switch to lactose metabolism. Mechanism of shift:

- Low glucose → ↑ adenylate cyclase activity → ↑ generation of cAMP from ATP → activation of catabolite activator protein (CAP) → ↑ transcription.
- High lactose → unbinds repressor protein from repressor/operator site → ↑ transcription.
### DNA repair

#### Single strand

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Defects/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleotide excision repair</strong></td>
<td>Specific endonucleases release the oligonucleotides containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively. Repairs bulky helix-distorting lesions. Occurs in G1 phase of cell cycle.</td>
<td>Defective in xeroderma pigmentosum (inability to repair DNA pyrimidine dimers caused by UV exposure). Findings: dry skin, extreme light sensitivity, skin cancer.</td>
</tr>
<tr>
<td><strong>Base excision repair</strong></td>
<td>Base-specific Glycosylase removes altered base and creates AP site (apurinic/apyrimidinic). One or more nucleotides are removed by AP-Endonuclease, which cleaves the 5’ end. Lyase cleaves the 3’ end. DNA Polymerase-β fills the gap and DNA Ligase seals it. Occurs throughout cell cycle.</td>
<td>Important in repair of spontaneous/toxic deamination. “GEL PL ease”</td>
</tr>
<tr>
<td><strong>Mismatch repair</strong></td>
<td>Newly synthesized strand is recognized, mismatched nucleotides are removed, and the gap is filled and resealed. Occurs predominantly in S phase of cell cycle.</td>
<td>Defective in Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPPC]).</td>
</tr>
</tbody>
</table>

#### Double strand

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonhomologous end joining</strong></td>
<td>Brings together 2 ends of DNA fragments to repair double-stranded breaks. No requirement for homology. Some DNA may be lost.</td>
<td>Defective in ataxia telangiectasia and Fanconi anemia.</td>
</tr>
<tr>
<td><strong>Homologous recombination</strong></td>
<td>Requires two homologous DNA duplexes. A strand from the damaged dsDNA is repaired using a complementary strand from the intact homologous dsDNA as a template. Restores duplexes accurately without loss of nucleotides.</td>
<td>Defective in breast/ovarian cancers with BRCA1 mutation.</td>
</tr>
</tbody>
</table>

### Start and stop codons

<table>
<thead>
<tr>
<th>mRNA start codons</th>
<th>AUG (or rarely GUG). AUG in AUG urates protein synthesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eukaryotes</td>
<td>Codes for methionine, which may be removed before translation is completed.</td>
</tr>
<tr>
<td>Prokaryotes</td>
<td>Codes for N-formylmethionine (fMet). fMet stimulates neutrophil chemotaxis.</td>
</tr>
<tr>
<td>mRNA stop codons</td>
<td>UGA, UAA, UAG. UGA = U Go Away. UAA = U Are Away. UAG = U Are Gone.</td>
</tr>
</tbody>
</table>
Functional organization of a eukaryotic gene

Regulation of gene expression

Promoter
- Site where RNA polymerase II and multiple other transcription factors bind to DNA upstream from gene locus (AT-rich upstream sequence with TATA and CAAT boxes).
- Promoter mutation commonly results in dramatic ↓ in level of gene transcription.

Enhancer
- DNA locus where regulatory proteins ("activators") bind → increasing expression of a gene on the same chromosome.
- Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression it regulates.

Silencer
- DNA locus where regulatory proteins ("repressors") bind → decreasing expression of a gene on the same chromosome.

RNA polymerases

Eukaryotes
- RNA polymerase I makes rRNA, the most common (rampant) type; present only in nucleolus.
- RNA polymerase II makes mRNA (largest RNA, massive). mRNA is read 5’ to 3’.
- RNA polymerase III makes 5S rRNA, tRNA (smallest RNA, tiny).
- No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site.
- I, II, and III are numbered in the same order that their products are used in protein synthesis: rRNA, mRNA, then tRNA.
- α-amanitin, found in Amanita phalloides (death cap mushrooms), inhibits RNA polymerase II. Causes severe hepatotoxicity if ingested.
- Actinomycin D inhibits RNA polymerase in both prokaryotes and eukaryotes.

Prokaryotes
- 1 RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.
- Rifampin inhibits DNA-dependent RNA polymerase in prokaryotes.

RNA processing (eukaryotes)

Initial transcript is called heterogeneous nuclear RNA (hnRNA). hnRNA is then modified and becomes mRNA.
- Capping of 5’ end (addition of 7-methylguanosine cap)
- Polyadenylation of 3’ end (= 200 A’s)
- Splicing out of introns
- Capped, tailed, and spliced transcript is called mRNA.
- mRNA is transported out of the nucleus into the cytosol, where it is translated.
- mRNA quality control occurs at cytoplasmic processing bodies (P-bodies), which contain exonucleases, decapping enzymes, and microRNAs; mRNAs may be degraded or stored in P-bodies for future translation.
- Poly-A polymerase does not require a template.
- AAUAAA = polyadenylation signal.
Splicing of pre-mRNA

Primary transcript combines with small nuclear ribonucleoproteins (snRNPs) and other proteins to form spliceosome.

Cleavage at 5′ splice site; lariat-shaped (loop) intermediate is generated.

Cleavage at 3′ splice site; lariat is released to precisely remove intron and join 2 exons.
**Introns vs exons**

Exons contain the actual genetic information coding for protein.

Introns are intervening noncoding segments of DNA.

Different exons are frequently combined by alternative splicing to produce a larger number of unique proteins.

Alternative splicing can produce a variety of protein products from a single hnRNA sequence (eg, transmembrane vs secreted Ig, tropomyosin variants in muscle, dopamine receptors in the brain).

**Introns** are intervening sequences and stay in the nucleus, whereas **exons** exit and are expressed.

Variants in which splicing occurs abnormally are implicated in oncogenesis and many genetic disorders (eg, β-thalassemia, Gaucher disease, Tay-Sachs disease, Marfan syndrome).

---

**microRNAs**

MicroRNAs (miRNAs) are small, conserved, noncoding RNA molecules that posttranscriptionally regulate gene expression by targeting the 3′ untranslated region of specific mRNAs for degradation or translational repression. Abnormal expression of miRNAs contributes to certain malignancies (eg, by silencing an mRNA from a tumor suppressor gene).
tRNA

Structure
75–90 nucleotides, 2° structure, cloverleaf form, anticodon end is opposite 3’ aminoacyl end. All tRNAs, both eukaryotic and prokaryotic, have CCA at 3’ end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3’ end of the tRNA. CCA Can Carry Amino acids.
T-arm: contains the TΨC (ribothymidine, pseudouridine, cytidine) sequence necessary for tRNA-ribosome binding. T-arm $\text{T}$ethers tRNA molecule to ribosome.
D-arm: contains dihydrouridine residues necessary for tRNA recognition by the correct aminoacyl-tRNA synthetase. D-arm Dectects the tRNA by aminoacyl-tRNA synthetase.
Acceptor stem: the 5’-CCA-3’ is the amino acid acceptor site.

Charging
Aminoacyl-tRNA synthetase (1 per amino acid; “matchmaker”, uses ATP) scrutinizes amino acid before and after it binds to tRNA. If incorrect, bond is hydrolyzed. The amino acid-tRNA bond has energy for formation of peptide bond. A mischarged tRNA reads usual codon but inserts wrong amino acid.
Aminoacyl-tRNA synthetase and binding of charged tRNA to the codon are responsible for accuracy of amino acid selection.

Structure
Charging
Pairing
Protein synthesis

Initiation
Eukaryotic initiation factors (eIFs) identify either the 5' cap or an internal ribosome entry site (IRES). IRES can be located at many places in an mRNA (most often 5' UTR). The eIFs then help assemble the 40S ribosomal subunit with the initiator tRNA and are released when the mRNA and the ribosomal 60S subunit assemble with the complex. Requires GTP.

Eukaryotes: 40S + 60S → 80S (Even).
Prokaryotes: 30S + 50S → 70S (Odd).

Synthesis occurs from N-terminus to C-terminus.

Eukaryotes:
- ATP—tRNA Activation (charging).
- GTP—tRNA Gipping and Going places (translocation).

Think of “going APE”:
- A site = incoming Aminoacyl-tRNA.
- P site = accommodates growing Peptide.
- E site = holds Empty tRNA as it Exits.

Elongation
1. Aminoacyl-tRNA binds to A site (except for initiator methionine), requires an elongation factor and GTP
2. tRNA (“ribozyme”) catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site
3. Ribosome advances 3 nucleotides toward 3' end of mRNA, moving peptidyl tRNA to P site (translocation)

Termination
Release factor recognizes stop codon and halts translation → completed polypeptide is released from ribosome. Requires GTP.

Posttranslational modifications

Trimming
Removal of N- or C-terminal propeptides from zymogen to generate mature protein (eg, trypsinogen to trypsin).

Covalent alterations
Phosphorylation, glycosylation, hydroxylation, methylation, acetylation, and ubiquitination.

Chaperone protein
Intracellular protein involved in facilitating and/or maintaining protein folding. For example, in yeast, heat shock proteins (eg, HSP60) are expressed at high temperatures to prevent protein denaturing/misfolding.
Cell cycle phases

Checkpoints control transitions between phases of cell cycle. This process is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumor suppressors. M phase (shortest phase of cell cycle) includes mitosis (prophase, prometaphase, metaphase, anaphase, telophase) and cytokinesis (cytoplasm splits in two). G1 and G0 are of variable duration.

REGULATION OF CELL CYCLE

Cyclin-dependent kinases

Constitutive and inactive.

Cyclins

Regulatory proteins that control cell cycle events; phase specific; activate CDKs.

Cyclin-CDK complexes

Phosphorylate other proteins to coordinate cell cycle progression; must be activated and inactivated at appropriate times for cell cycle to progress.

Tumor suppressors

p53 induces p21, which inhibits CDKs

→ hypophosphorylation (activation) of Rb

→ inhibition of G1-S progression. Mutations in tumor suppressor genes can result in unrestrained cell division (eg, Li-Fraumeni syndrome).

Growth factors (eg, insulin, PDGF, EPO, EGF) bind tyrosine kinase receptors to transition the cell from G1 to S phase.

CELL TYPES

Permanent

Remain in G0, regenerate from stem cells. Neurons, skeletal and cardiac muscle, RBCs.

Stable (quiescent)

Enter G1 from G0 when stimulated. Hepatocytes, lymphocytes, PCT, periosteal cells.

Labile

Never go to G0, divide rapidly with a short G1. Most affected by chemotherapy. Bone marrow, gut epithelium, skin, hair follicles, germ cells.

Rough endoplasmic reticulum

Site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to many proteins. Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion. Free ribosomes—unattached to any membrane; site of synthesis of cytosolic and organelar proteins. Mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells are rich in RER.

Smooth endoplasmic reticulum

Site of steroid synthesis and detoxification of drugs and poisons. Lacks surface ribosomes. Liver hepatocytes and steroid hormone—producing cells of the adrenal cortex and gonads are rich in SER.
Cell trafficking

Golgi is the distribution center for proteins and lipids from the ER to the vesicles and plasma membrane. Modifies N-oligosaccharides on asparagine. Adds O-oligosaccharides on serine and threonine. Adds mannose-6-phosphate to proteins for trafficking to lysosomes. Endosomes are sorting centers for material from outside the cell or from the Golgi, sending it to lysosomes for destruction or back to the membrane/Golgi for further use.

I-cell disease (inclusion cell disease/mucolipidosis type II)—inherited lysosomal storage disorder; defect in N-acetylglucosaminyl-1-phosphotransferase → failure of the Golgi to phosphorylate mannose residues (mannose-6-phosphate) on glycoproteins → proteins are secreted extracellularly rather than delivered to lysosomes. Results in coarse facial features, gingival hyperplasia, clouded corneas, restricted joint movements, claw hand deformities, kyphoscoliosis, and high plasma levels of lysosomal enzymes. Often fatal in childhood.

Signal recognition particle (SRP)

Abundant, cytosolic ribonucleoprotein that traffics proteins from the ribosome to the RER. Absent or dysfunctional SRP → proteins accumulate in the cytosol.

Vesicular trafficking proteins

COPI: Golgi → Golgi (retrograde); cis-Golgi → ER.
COPII: ER → cis-Golgi (anterograde).
“Two (COPII) steps forward (anterograde); one (COPI) step back (retrograde).”
Clathrin: trans-Golgi → lysosomes; plasma membrane → endosomes (receptor-mediated endocytosis [e.g., LDL receptor activity]).

Peroxisome

Membrane-enclosed organelle involved in:
- β-oxidation of very-long-chain fatty acids (VLCFA)
- α-oxidation (strictly peroxisomal process)
- Catabolism of branched-chain fatty acids, amino acids, and ethanol
- Synthesis of cholesterol, bile acids, and plasmalogens (important membrane phospholipid, especially in white matter of brain)

Zellweger syndrome—autosomal recessive disorder of peroxisome biogenesis due to mutated PEX genes. Hypotonia, seizures, hepatomegaly, early death.

Refsum disease—autosomal recessive disorder of α-oxidation → phytanic acid not metabolized to pristanic acid. Scaly skin, ataxia, cataracts/night blindness, shortening of 4th toe, epiphyseal dysplasia. Treatment: diet, plasmapheresis.

Adrenoleukodystrophy—X-linked recessive disorder of β-oxidation → VLCFA buildup in adrenal glands, white (leuko) matter of brain, testes. Progressive disease that can lead to adrenal gland crisis, coma, and death.
Proteasome
A barrel-shaped protein complex that degrades damaged or ubiquitin-tagged proteins. Defects in the ubiquitin-proteasome system have been implicated in some cases of Parkinson disease.

Cytoskeletal elements
A network of protein fibers within the cytoplasm that supports cell structure, cell and organelle movement, and cell division.

<table>
<thead>
<tr>
<th>TYPE OF FILAMENT</th>
<th>PREDOMINANT FUNCTION</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microfilaments</td>
<td>Muscle contraction, cytokinesis</td>
<td>Actin, microvilli.</td>
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<tr>
<td>Intermediate filaments</td>
<td>Maintain cell structure</td>
<td>Vimentin, desmin, cytokeratin, lamins, glial fibrillary acidic protein (GFAP), neurofilaments.</td>
</tr>
<tr>
<td>Microtubules</td>
<td>Movement, cell division</td>
<td>Cilia, flagella, mitotic spindle, axonal trafficking, centrioles.</td>
</tr>
</tbody>
</table>

Microtubule
Cylindrical outer structure composed of a helical array of polymerized heterodimers of α- and β-tubulin. Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Grows slowly, collapses quickly. Also involved in slow axoplasmic transport in neurons.

Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule tracks.
- Dynein—retrograde to microtubule (+ → −).
- Kinesin—anterograde to microtubule (− → +).

Drugs that act on microtubules (Microtubules Get Constructed Very Poorly):
- Mebendazole (antihelminthic)
- Griseofulvin (antifungal)
- Colchicine (antigout)
- Vinca alkaloids (anticancer)
- Paclitaxel (anticancer)

Negative end Near Nucleus
Positive end Points to Periphery
Cilia structure

9 doublet + 2 singlet arrangement of microtubules.
Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets with no central microtubules.
Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.
Gap junctions enable coordinated ciliary movement.

Kartagener syndrome (1° ciliary dyskinesia)—immotile cilia due to a dynein arm defect.
Autosomal recessive. Results in male and female fertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; ↑ risk of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, chronic ear infections, conductive hearing loss, and situs inversus (eg, dextrocardia on CXR).
(Kartagener’s restaurant: take-out only, there’s no "dine-in").

Sodium-potassium pump

Na⁺-K⁺ ATPase is located in the plasma membrane with ATP site on cytosolic side.
For each ATP consumed, 3Na⁺ go out of the cell (pump phosphorylated) and 2K⁺ come into the cell (pump dephosphorylated).
Plasma membrane is an asymmetric lipid bilayer containing cholesterol, phospholipids, sphingolipids, glycolipids, and proteins.

Pumpkin = pump K⁺ in.
Ouabain (a cardiac glycoside) inhibits by binding to K⁺ site.
Cardiac glycosides (digoxin and digitoxin) directly inhibit the Na⁺-K⁺ ATPase, which leads to indirect inhibition of Na⁺/Ca²⁺ exchange → ↑ [Ca²⁺]i → ↑ cardiac contractility.
Collagen


Be (So Totally) Cool, Read Books.

Type I

Most common (90%)—Bone (made by osteoblasts), Skin, Tendon, dentin, fascia, cornea, late wound repair.

Type II

Cartilage (including hyaline), vitreous body, nucleus pulposus.

Type III

Reticulin—skin, blood vessels, uterus, fetal tissue, granulation tissue.

Type IV

Basement membrane, basal lamina, lens.

Type I: bone

Type II: cartilage.

Type III: deficient in the uncommon, vascular type of Ehlers-Danlos syndrome (ThreE D).

Type IV: under the floor (basement membrane). Defective in Alport syndrome; targeted by autoantibodies in Goodpasture syndrome.

Collagen synthesis and structure

1. Synthesis—translation of collagen α chains (preprocollagen)—usually Gly-X-Y (X and Y are proline or lysine). Glycine content best reflects collagen synthesis (collagen is \( \frac{1}{3} \) glycine).

2. Hydroxylation—hydroxylation of specific proline and lysine residues. Requires vitamin C; deficiency → scurvy.


4. Exocytosis—exocytosis of procollagen into extracellular space.


**Osteogenesis imperfecta**

Genetic bone disorder (brittle bone disease) caused by a variety of gene defects (most commonly *COL1A1* and *COL1A2*). Most common form is autosomal dominant with production of otherwise normal type I collagen. Manifestations can include:

- Multiple fractures with minimal trauma, may occur during the birth process
- Blue sclerae due to the translucent connective tissue over choroidal veins
- Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)
- Hearing loss (abnormal ossicles)

May be confused with child abuse. Treat with bisphosphonates to fracture risk.

Patients can’t BITE:

- **B**ones = multiple fractures
- **I** (eye) = blue sclerae
- **T**eeth = dental imperfections
- **E**ar = hearing loss

---

**Ehlers-Danlos syndrome**

Faulty collagen synthesis causing hyperextensible skin, hypermobile joints, and tendency to bleed (easy bruising).

Multiple types. Inheritance and severity vary. Can be autosomal dominant or recessive. May be associated with joint dislocation, berry and aortic aneurysms, organ rupture.

- Hypermobility type (joint instability): most common type.
- Classical type (joint and skin symptoms): caused by a mutation in type V collagen (eg, *COL5A1*, *COL5A2*).
- Vascular type (fragile tissues including vessels [eg, aorta], muscles, and organs that are prone to rupture): deficient type III procollagen.
Menkes disease

X-linked recessive connective tissue disease caused by impaired copper absorption and transport due to defective Menkes protein (ATP7A). Leads to ↓ activity of lysyl oxidase (copper is a necessary cofactor) → defective collagen. Results in brittle, “kinky” hair, growth retardation, and hypotonia.

Elastin

Stretchy protein within skin, lungs, large arteries, elastic ligaments, vocal cords, ligamenta flava (connect vertebrae → relaxed and stretched conformations).
Rich in nonhydroxylated proline, glycine, and lysine residues, vs the hydroxylated residues of collagen.
Tropoelastin with fibrillin scaffolding.
Cross-linking takes place extracellularly and gives elastin its elastic properties.
Broken down by elastase, which is normally inhibited by α₁-antitrypsin.
α₁-Antitrypsin deficiency results in unopposed elastase activity, which can cause emphysema.
Changes with aging: ↓ dermal collagen and elastin, ↓ synthesis of collagen fibrils; crosslinking remains normal.

Marfan syndrome—autosomal dominant connective tissue disorder affecting skeleton, heart, and eyes. FBN1 gene mutation on chromosome 15 results in defective fibrillin, a glycoprotein that forms a sheath around elastin. Findings: tall with long extremities; pectus carinatum (more specific) or pectus excavatum; hypermobile joints; long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta; aortic incompetence and dissecting aortic aneurysms; floppy mitral valve. Subluxation of lenses, typically upward and temporally. (Look up at a ceiling fan.)

Polymerase chain reaction

Molecular biology lab procedure used to amplify a desired fragment of DNA. Useful as a diagnostic tool (eg, neonatal HIV, herpes encephalitis).

1. **Denaturation**—DNA is heated to ~95°C to separate the strands.
2. **Annealing**—Sample is cooled to ~55°C. DNA primers, a heat-stable DNA polymerase (Taq), and deoxynucleotide triphosphates (dNTPs) are added. DNA primers anneal to the specific sequence to be amplified on each strand.
3. **Elongation**—Temperature is increased to ~72°C. DNA polymerase attaches dNTPs to the strand to replicate the sequence after each primer.

Heating and cooling cycles continue until the DNA sample size is sufficient.
CRISPR/Cas9

A genome editing tool, derived from bacteria. Composed of an endonuclease (Cas9, which cleaves dsDNA) and a guide RNA (gRNA) sequence that binds to a complementary target DNA sequence. Cell DNA repair machinery (nonhomologous end joining) fills in the gap introduced by the system (knock-out) or a donor DNA can be added to the system to fill the gap (knock-in). The gRNA can be designed to target any DNA sequence.

Blotting procedures

Southern blot
1. DNA sample is enzymatically cleaved into smaller pieces, which are separated on a gel by electrophoresis, and then transferred to a filter.
2. Filter is exposed to radiolabeled DNA probe that recognizes and anneals to its complementary strand.
3. Resulting double-stranded, labeled piece of DNA is visualized when filter is exposed to film.

Northern blot
Similar to Southern blot, except that an RNA sample is electrophoresed. Useful for studying mRNA levels, which are reflective of gene expression.

Western blot
Sample protein is separated via gel electrophoresis and transferred to a membrane. Labeled antibody is used to bind to relevant protein.

Southwestern blot
Identifies DNA-binding proteins (eg, transcription factors) using labeled oligonucleotide probes.

SNoW DRoP:
Southern = DNA
Northern = RNA
Western = Protein
Flow cytometry

Laboratory technique to assess size, granularity, and protein expression (immunophenotype) of individual cells in a sample.

Cells are tagged with antibodies specific to surface or intracellular proteins. Antibodies are then tagged with a unique fluorescent dye. Sample is analyzed one cell at a time by focusing a laser on the cell and measuring light scatter and intensity of fluorescence.

Data are plotted either as histogram (one measure) or scatter plot (any two measures, as shown). In illustration:
- Cells in left lower quadrant ⊗ for both CD8 and CD3.
- Cells in right lower quadrant ⊗ for CD8 and ⊘ for CD3. Right lower quadrant is empty because all CD8-expressing cells also express CD3.
- Cells in left upper quadrant ⊘ for CD3 and ⊗ for CD8.
- Cells in right upper quadrant ⊘ for CD8 and CD3 (red + blue → purple).

Commonly used in workup of hematologic abnormalities (eg, paroxysmal nocturnal hemoglobinuria, fetal RBCs in mother’s blood) and immunodeficiencies (eg, CD4 cell count in HIV).

Microarrays

Thousands of nucleic acid sequences are arranged in grids on glass or silicon. DNA or RNA probes are hybridized to the chip, and a scanner detects the relative amounts of complementary binding. Used to profile gene expression levels of thousands of genes simultaneously to study certain diseases and treatments. Able to detect single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) for a variety of applications including genotyping, clinical genetic testing, forensic analysis, cancer mutations, and genetic linkage analysis.

Enzyme-linked immunosorbent assay

Immunologic test used to detect the presence of either a specific antigen (eg, HBsAg) or antibody (eg, anti-HBs) in a patient’s blood sample. Detection involves the use of an antibody linked to an enzyme. Added substrate reacts with enzyme, producing a detectable signal. Can have high sensitivity and specificity, but is less specific than Western blot. Direct ELISA tests for the antigen directly, while indirect ELISA tests for the antibody (thus indirectly testing for the antigen).
Karyotyping

A process in which metaphase chromosomes are stained, ordered, and numbered according to morphology, size, arm-length ratio, and banding pattern (arrows in A point to extensive abnormalities in a cancer cell). Can be performed on a sample of blood, bone marrow, amniotic fluid, or placental tissue. Used to diagnose chromosomal imbalances (e.g., autosomal trisomies, sex chromosome disorders).

Fluorescence in situ hybridization

Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes (arrows in A point to abnormalities in a cancer cell, whose karyotype is seen above; each fluorescent color represents a chromosome-specific probe). Used for specific localization of genes and direct visualization of chromosomal anomalies at the molecular level.

- Microdeletion—no fluorescence on a chromosome compared to fluorescence at the same locus on the second copy of that chromosome
- Translocation—fluorescence signal that corresponds to one chromosome is found in a different chromosome (two white arrows in A show fragments of chromosome 17 that have translocated to chromosome 19)
- Duplication—a second copy of a chromosome, resulting in a trisomy or tetrasomy (two blue arrows show duplicated chromosomes 8, resulting in a tetrasomy)

Molecular cloning

Production of a recombinant DNA molecule in a bacterial host. Steps:
1. Isolate eukaryotic mRNA (post-RNA processing) of interest.
2. Add reverse transcriptase (an RNA-dependent DNA polymerase) to produce complementary DNA (cDNA, lacks introns).
3. Insert cDNA fragments into bacterial plasmids containing antibiotic resistance genes.
4. Transform (insert) recombinant plasmid into bacteria.
5. Surviving bacteria on antibiotic medium produce cloned DNA (copies of cDNA).
Gene expression modifications

Transgenic strategies in mice involve:
- Random insertion of gene into mouse genome
- Targeted insertion or deletion of gene through homologous recombination with mouse gene

Knock-out = removing a gene, taking it out.
Knock-in = inserting a gene.

Random insertion—constitutive.
Targeted insertion—conditional.

Cre-lox system
Can inducibly manipulate genes at specific developmental points (eg, to study a gene whose deletion causes embryonic death).

RNA interference
dsRNA is synthesized that is complementary to the mRNA sequence of interest. When transfected into human cells, dsRNA separates and promotes degradation of target mRNA, “knocking down” gene expression.

Gene expression modifications

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codominance</td>
<td>Both alleles contribute to the phenotype of the heterozygote.</td>
<td>Blood groups A, B, AB; α1-antitrypsin deficiency; HLA groups.</td>
</tr>
<tr>
<td>Variable expressivity</td>
<td>Patients with the same genotype have varying phenotypes.</td>
<td>2 patients with neurofibromatosis type 1 (NF1) may have varying disease severity.</td>
</tr>
<tr>
<td>Incomplete penetrance</td>
<td>Not all individuals with a mutant genotype show the mutant phenotype. % penetrance × probability of inheriting genotype = risk of expressing phenotype.</td>
<td>BRCA1 gene mutations do not always result in breast or ovarian cancer.</td>
</tr>
<tr>
<td>Pleiotropy</td>
<td>One gene contributes to multiple phenotypic effects.</td>
<td>Untreated phenylketonuria (PKU) manifests with light skin, intellectual disability, and musty body odor.</td>
</tr>
<tr>
<td>Anticipation</td>
<td>Increased severity or earlier onset of disease in succeeding generations.</td>
<td>Trinucleotide repeat diseases (eg, Huntington disease).</td>
</tr>
<tr>
<td>Loss of heterozygosity</td>
<td>If a patient inherits or develops a mutation in a tumor suppressor gene, the complementary allele must be deleted/mutated before cancer develops. This is not true of oncogenes.</td>
<td>Retinoblastoma and the “two-hit hypothesis,” Lynch syndrome (HNPCC), Li-Fraumeni syndrome.</td>
</tr>
<tr>
<td>Dominant negative mutation</td>
<td>Exerts a dominant effect. A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.</td>
<td>Mutation of a transcription factor in its allosteric site. Nonfunctioning mutant can still bind DNA, preventing wild-type transcription factor from binding.</td>
</tr>
<tr>
<td>Linkage disequilibrium</td>
<td>Tendency for certain alleles at 2 linked loci to occur together more or less often than expected by chance. Measured in a population, not in a family, and often varies in different populations.</td>
<td></td>
</tr>
</tbody>
</table>
### Genetic terms (continued)

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosaicism</td>
<td>Presence of genetically distinct cell lines in the same individual. Somatic mosaicism—mutation arises from mitotic errors after fertilization and propagates through multiple tissues or organs. Gonadal mosaicism—mutation only in egg or sperm cells. If parents and relatives do not have the disease, suspect gonadal (or germline) mosaicism.</td>
<td>McCune-Albright syndrome—due to mutation affecting G-protein signaling. Presents with unilateral café-au-lait spots with ragged edges, polyostotic fibrous dysplasia (bone is replaced by collagen and fibroblasts), and at least one endocrinopathy (eg, precocious puberty). Lethal if mutation occurs before fertilization (affecting all cells), but survivable in patients with mosaicism.</td>
</tr>
<tr>
<td>Locus heterogeneity</td>
<td>Mutations at different loci can produce a similar phenotype.</td>
<td>Albinism.</td>
</tr>
<tr>
<td>Allelic heterogeneity</td>
<td>Different mutations in the same locus produce the same phenotype.</td>
<td>β-thalassemia.</td>
</tr>
<tr>
<td>Heteroplasmy</td>
<td>Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrially inherited disease.</td>
<td>mtDNA passed from mother to all children.</td>
</tr>
<tr>
<td>Uniparental disomy</td>
<td>Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent. Heterodisomy (heterozygous) indicates a meiosis I error. Homodisomy (homozygous) indicates a meiosis II error or postzygotic chromosomal duplication of one of a pair of chromosomes, and loss of the other of the original pair.</td>
<td>Uniparental is euploid (correct number of chromosomes). Most occurrences of uniparental disomy (UPD) → normal phenotype. Consider UPD in an individual manifesting a recessive disorder when only one parent is a carrier. Examples: Prader-Willi and Angelman syndromes.</td>
</tr>
</tbody>
</table>

#### Hardy-Weinberg population genetics

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<thead>
<tr>
<th></th>
<th>pA</th>
<th>qa</th>
</tr>
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<tbody>
<tr>
<td>pA</td>
<td>AA</td>
<td>Aa</td>
</tr>
<tr>
<td></td>
<td>p×p = p²</td>
<td>p×q</td>
</tr>
<tr>
<td>qa</td>
<td>Aa</td>
<td>aa</td>
</tr>
<tr>
<td></td>
<td>p×q</td>
<td>q×q = q²</td>
</tr>
</tbody>
</table>

If a population is in Hardy-Weinberg equilibrium and if p and q are the frequencies of separate alleles, then: p² + 2pq + q² = 1 and p + q = 1, which implies that:

- p² = frequency of homozygosity for allele A
- q² = frequency of homozygosity for allele a
- 2pq = frequency of heterozygosity (carrier frequency, if an autosomal recessive disease).

The frequency of an X-linked recessive disease in males = q and in females = q².

Hardy-Weinberg law assumptions include:
- No mutation occurring at the locus
- Natural selection is not occurring
- Completely random mating
- No net migration
**Disorders of imprinting**  
Imprinting—one gene copy is silenced by methylation, and only the other copy is expressed → parent-of-origin effects.

<table>
<thead>
<tr>
<th>Disorders of imprinting</th>
<th>Prader-Willi syndrome</th>
<th>AngelMan syndrome</th>
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<tbody>
<tr>
<td><strong>Maternally derived genes are silenced (imprinted).</strong> Disease occurs when the <strong>Paternal allele is deleted or mutated.</strong> Results in hyperphagia, obesity, intellectual disability, hypogonadism, and hypotonia.</td>
<td>Associated with a mutation or deletion of chromosome 15 of paternal origin. 25% of cases due to maternal uniparental disomy.</td>
<td><strong>Paternally derived UBE3A gene is silenced (imprinted).</strong> Disease occurs when the <strong>Maternal allele is deleted or mutated.</strong> Results in inappropriate laughter (“happy puppet”), seizures, ataxia, and severe intellectual disability. Associated with mutation or deletion of the UBE3A gene on the maternal copy of chromosome 15. 5% of cases due to paternal uniparental disomy.</td>
</tr>
</tbody>
</table>
Modes of inheritance

**Autosomal dominant**
- Often due to defects in structural genes. Many generations, both males and females are affected. Often pleiotropic (multiple apparently unrelated effects) and variably expressive (different between individuals). Family history crucial to diagnosis. With one affected (heterozygous) parent, on average, ½ of children affected.

**Autosomal recessive**
- Often due to enzyme deficiencies. Usually seen in only 1 generation. Commonly more severe than dominant disorders; patients often present in childhood. ↑ risk in consanguineous families. With 2 carrier (heterozygous) parents, on average: ¼ of children will be affected (homozygous), ½ of children will be carriers, and ¼ of children will be neither affected nor carriers.

**X-linked recessive**
- Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission. Skips generations. Commonly more severe in males. Females usually must be homozygous to be affected.

**X-linked dominant**
- Transmitted through both parents. Mothers transmit to 50% of daughters and sons; fathers transmit to all daughters but no sons. Hypophosphatemic rickets—formerly known as vitamin D–resistant rickets. Inherited disorder resulting in ↑ phosphate wasting at proximal tubule. Results in rickets-like presentation. Other examples: fragile X syndrome, Alport syndrome.

**Mitochondrial inheritance**
- Transmitted only through the mother. All offspring of affected females may show signs of disease. Variable expression in a population or even within a family due to heteroplasmy. Mitochondrial myopathies—rare disorders; often present with myopathy, lactic acidosis, and CNS disease, eg, MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). 2° to failure in oxidative phosphorylation. Muscle biopsy often shows “ragged red fibers” (due to accumulation of diseased mitochondria). Leber hereditary optic neuropathy—cell death in optic nerve neurons → subacute bilateral vision loss in teens/young adults, 90% males. Usually permanent.

□ = unaffected male; ■ = affected male; ○ = unaffected female; ● = affected female.
Autosomal dominant diseases

Achondroplasia, autosomal dominant polycystic kidney disease, familial adenomatous polyposis, familial hypercholesterolemia, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), hereditary spherocytosis, Huntington disease, Li-Fraumeni syndrome, Marfan syndrome, multiple endocrine neoplasias, myotonic muscular dystrophy, neurofibromatosis type 1 (von Recklinghausen disease), neurofibromatosis type 2, tuberous sclerosis, von Hippel-Lindau disease.

Autosomal recessive diseases

Albinism, autosomal recessive polycystic kidney disease (ARPKD), cystic fibrosis, Friedreich ataxia, glycogen storage diseases, hemochromatosis, Kartagener syndrome, mucopolysaccharidoses (except Hunter syndrome), phenylketonuria, sickle cell anemia, sphingolipidoses (except Fabry disease), thalassemias, Wilson disease.

Cystic fibrosis

**GENETICS**

Autosomal recessive; defect in CFTR gene on chromosome 7; commonly a deletion of Phe508. Most common lethal genetic disease in Caucasian population.

**PATHOPHYSIOLOGY**

CFTR encodes an ATP-gated Cl\(^-\) channel that secretes Cl\(^-\) in lungs and GI tract, and reabsorbs Cl\(^-\) in sweat glands. Most common mutation → misfolded protein → protein retained in RER and not transported to cell membrane, causing ↓ Cl\(^-\) (and H\(_2\)O) secretion; ↑ intracellular Cl\(^-\) results in compensatory ↓ Na\(^+\) reabsorption via epithelial Na\(^+\) channels → ↑ H\(_2\)O reabsorption → abnormally thick mucus secreted into lungs and GI tract. ↑ Na\(^+\) reabsorption also causes more negative transepithelial potential difference.

**DIAGNOSIS**

↑ Cl\(^-\) concentration in pilocarpine-induced sweat test is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF H\(_2\)O/Na\(^+\) losses and concomitant renal K\(^+\)/H\(^+\) wasting. ↑ immunoreactive trypsinogen (newborn screening).

**COMPLICATIONS**

Recurrent pulmonary infections (eg, *S aureus* [early infancy], *P aeruginosa* [adolescence]), chronic bronchitis and bronchiectasis → reticulonodular pattern on CXR, opacification of sinuses. Pancreatic insufficiency, malabsorption with steatorrhea, fat-soluble vitamin deficiencies (A, D, E, K), biliary cirrhosis, liver disease. Meconium ileus in newborns. Infertility in men (absence of vas deferens, spermatogenesis may be unaffected) and subfertility in women (amenorrhea, abnormally thick cervical mucus). Nasal polyps, clubbing of nails.

**TREATMENT**

Multifactorial: chest physiotherapy, albuterol, aerosolized dornase alfa (DNase), and hypertonic saline facilitate mucus clearance. Azithromycin used as anti-inflammatory agent. Ibuprofen slows disease progression. In patients with Phe508 deletion: combination of lumacaftor (corrects misfolded proteins and improves their transport to cell surface) and ivacaftor (opens Cl\(^-\) channels → improved chloride transport).

X-linked recessive disorders


**X-inactivation (lyonization)**—female carriers variably affected depending on the pattern of inactivation of the X chromosome carrying the mutant vs normal gene.

Oblivious Female Will Often Give Her Boys Her x-Linked Disorders

Females with Turner syndrome (45,XO) are more likely to have an X-linked recessive disorder.
Muscular dystrophies

**Duchenne**

X-linked disorder typically due to **frameshift** or nonsense mutations → truncated or absent dystrophin protein → progressive myofiber damage. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle fibers. Waddling gait.

Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.

**Gower sign**—patient uses upper extremities to help stand up. Classically seen in Duchenne muscular dystrophy, but also seen in other muscular dystrophies and inflammatory myopathies (eg, polymyositis).

**Duchenne = deleted dystrophin.**

Dystrophin gene (*DMD*) is the largest protein-coding human gene → 1 chance of spontaneous mutation. Dystrophin helps anchor muscle fibers, primarily in skeletal and cardiac muscle. It connects the intracellular cytoskeleton (actin) to the transmembrane proteins α- and β-dystroglycan, which are connected to the extracellular matrix (ECM). Loss of dystrophin → myonecrosis. ↑ CK and aldolase; genetic testing confirms diagnosis.

**Becker**

X-linked disorder typically due to **non-frameshift** deletions in dystrophin gene (partially functional instead of truncated). Less severe than Duchenne. Onset in adolescence or early adulthood.

Deletions can cause both Duchenne and Becker muscular dystrophies. 2⁄3 of cases have large deletions spanning one or more exons.

**Myotonic type 1**

Autosomal dominant. **CTG** trinucleotide repeat expansion in the **DMPK** gene → abnormal expression of myotonin protein kinase → myotonia, muscle wasting, cataracts, testicular atrophy, frontal balding, arrhythmia.

**Rett syndrome**

Sporadic disorder seen almost exclusively in girls (affected males die in utero or shortly after birth). Most cases are caused by de novo mutation of **MECP2** on X chromosome. Symptoms of **Rett syndrome** usually appear between ages 1–4 and are characterized by regression (**Rett**urn) in motor, verbal, and cognitive abilities; ataxia; seizures; growth failure; and stereotyped hand-wringing.
Fragile X syndrome

X-linked dominant inheritance. Trinucleotide repeat in FMR1 gene → hypermethylation → ↓ expression. Most common cause of inherited intellectual disability and 2nd most common cause of genetically associated mental deficiency (after Down syndrome). Findings: post-pubertal macroorchidism (enlarged testes), long face with a large jaw, large everted ears, autism, mitral valve prolapse.

Trinucleotide repeat expansion [CGG]n occurs during oogenesis.

Trinucleotide repeat expansion diseases

Huntington disease, myotonic dystrophy, fragile X syndrome, and Friedreich ataxia. May show genetic anticipation (disease severity ↑ and age of onset ↓ in successive generations).

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TRINUCLEOTIDE REPEAT</th>
<th>MODE OF INHERITANCE</th>
<th>MNEMONIC</th>
</tr>
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<tbody>
<tr>
<td>Huntington disease</td>
<td>(CAG)n</td>
<td>AD</td>
<td>Caudate has ↓ ACh and GABA</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>(CTG)n</td>
<td>AD</td>
<td>Cataracts, Toupee (early balding in men), Gonadal atrophy</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>(CGG)n</td>
<td>XD</td>
<td>Chin (protruding), Giant Gonads</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>(GAA)n</td>
<td>AR</td>
<td>Ataxic GAAit</td>
</tr>
</tbody>
</table>
Autosomal trisomies

**Down syndrome (trisomy 21)**

Findings: intellectual disability, flat facies, prominent epicanthal folds, single palmar crease, gap between 1st 2 toes, duodenal atresia, Hirschsprung disease, congenital heart disease (eg, atrioventricular septal defect), Brushfield spots. Associated with early-onset Alzheimer disease (chromosome 21 codes for amyloid precursor protein) and ↑ risk of ALL and AML.

95% of cases due to meiotic nondisjunction (↑ with advanced maternal age; from 1:1500 in women < 20 to 1:25 in women > 45 years old). 4% of cases due to unbalanced Robertsonian translocation, most typically between chromosomes 14 and 21. Only 1% of cases are due to postfertilization mitotic error.

Incidence 1:700. Drinking age (21).

Most common viable chromosomal disorder and most common cause of genetic intellectual disability.

First-trimester ultrasound commonly shows ↑ nuchal translucency and hypoplastic nasal bone.

The 5 As of Down syndrome:
- Advanced maternal age
- Atresia (duodenal)
- Atrioventricular septal defect
- Alzheimer disease (early onset)
- AML/ALL

**Edwards syndrome (trisomy 18)**


Incidence 1:8000. Election age (18).

2nd most common autosomal trisomy resulting in live birth (most common is Down syndrome).

**Patau syndrome (trisomy 13)**


Incidence 1:15,000. Puberty (13).

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<table>
<thead>
<tr>
<th>Serum markers</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-hCG</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>2nd trimester</td>
<td></td>
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<tr>
<td>AFP</td>
<td>↓</td>
<td>↓</td>
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</tr>
<tr>
<td>β-hCG</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
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<tr>
<td>Estriol</td>
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<td>↑</td>
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<tr>
<td>Inhibin A</td>
<td>↑</td>
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<td>↓</td>
</tr>
</tbody>
</table>

N = normal.
Genetic disorders by chromosome

<table>
<thead>
<tr>
<th>CHROMOSOME</th>
<th>SELECTED EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>von Hippel-Lindau disease, renal cell carcinoma</td>
</tr>
<tr>
<td>4</td>
<td>ADPKD (PKD2), achondroplasia, Huntington disease</td>
</tr>
<tr>
<td>5</td>
<td>Cri-du-chat syndrome, familial adenomatous polyposis</td>
</tr>
<tr>
<td>6</td>
<td>Hemochromatosis (HFE)</td>
</tr>
<tr>
<td>7</td>
<td>Williams syndrome, cystic fibrosis</td>
</tr>
<tr>
<td>9</td>
<td>Friedreich ataxia, tuberous sclerosis (TSCI)</td>
</tr>
<tr>
<td>11</td>
<td>Wilms tumor, β-globin gene defects (eg, sickle cell disease, β-thalassemia), MEN1</td>
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<tr>
<td>13</td>
<td>Patau syndrome, Wilson disease, retinoblastoma (RB1), BRCA2</td>
</tr>
<tr>
<td>15</td>
<td>Prader-Willi syndrome, Angelman syndrome, Marfan syndrome</td>
</tr>
<tr>
<td>16</td>
<td>ADPKD (PKD1), α-globin gene defects (eg, α-thalassemia), tuberous sclerosis (TSC2)</td>
</tr>
<tr>
<td>17</td>
<td>Neurofibromatosis type 1, BRCA1, p53</td>
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<tr>
<td>18</td>
<td>Edwards syndrome</td>
</tr>
<tr>
<td>21</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>22</td>
<td>Neurofibromatosis type 2, DiGeorge syndrome (22q11)</td>
</tr>
<tr>
<td>X</td>
<td>Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY)</td>
</tr>
</tbody>
</table>

Robertsonian translocation

Chromosomal translocation that commonly involves chromosome pairs 13, 14, 15, 21, and 22. One of the most common types of translocation. Occurs when the long arms of 2 acrocentric chromosomes (chromosomes with centromeres near their ends) fuse at the centromere and the 2 short arms are lost. Balanced translocations normally do not cause any abnormal phenotype. Unbalanced translocations can result in miscarriage, stillbirth, and chromosomal imbalance (eg, Down syndrome, Patau syndrome).

Cri-du-chat syndrome

Congenital deletion on short arm of chromosome 5 (46,XX or XY, 5p−). Findings: microcephaly, moderate to severe intellectual disability, high-pitched crying/meowing, epicanthal folds, cardiac abnormalities (VSD). *Cri du chat* = cry of the cat.

Williams syndrome

Congenital microdeletion of long arm of chromosome 7 (deleted region includes elastin gene). Findings: distinctive "elfin" facies, intellectual disability, hypercalcemia († sensitivity to vitamin D), well-developed verbal skills, extreme friendliness with strangers, cardiovascular problems (eg, supravalvular aortic stenosis, renal artery stenosis). Think Will Ferrell in Elf.
22q11 deletion syndromes

Microdeletion at chromosome 22q11 → variable presentations including Cleft palate, Abnormal facies, Thymic aplasia → T-cell deficiency, Cardiac defects, and Hypocalcemia 2° to parathyroid aplasia.

DiGeorge syndrome—thymic, parathyroid, and cardiac defects.

Velocardiofacial syndrome—palate, facial, and cardiac defects.

CATCH-22.

Due to aberrant development of 3rd and 4th branchial (pharyngeal) pouches.

Vitamins: fat soluble

A, D, E, K. Absorption dependent on gut and pancreas. Toxicity more common than for water-soluble vitamins because fat-soluble vitamins accumulate in fat.

Malabsorption syndromes with steatorrhea (eg, cystic fibrosis and celiac disease) or mineral oil intake can cause fat-soluble vitamin deficiencies.

Vitamins: water soluble

B₁ (thiamine: TPP)
B₂ (riboflavin: FAD, FMN)
B₃ (niacin: NAD⁺)
B₅ (pantothenic acid: CoA)
B₆ (pyridoxine: PLP)
B₇ (biotin)
B₉ (folate)
B₁₂ (cobalamin)
C (ascorbic acid)

All wash out easily from body except B₁₂ and B₉ (folate). B₁₂ stored in liver for ~ 3–4 years. B₉ stored in liver for ~ 3–4 months.

B-complex deficiencies often result in dermatitis, glossitis, and diarrhea. Can be coenzymes (eg, ascorbic acid) or precursors to organic cofactors (eg, FAD, NAD⁺).
### Vitamin A

**Also called retinol.**

**FUNCTION**

Antioxidant; constituent of visual pigments (retinal); essential for normal differentiation of epithelial cells into specialized tissue (pancreatic cells, mucus-secreting cells); prevents squamous metaplasia. Used to treat measles and acute promyelocytic leukemia (APL).

**DEFICIENCY**

Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); corneal degeneration (keratomalacia); Bitot spots (foamy appearance) on conjunctiva; immunosuppression.

**EXCESS**

Acute toxicity—nausea, vomiting, vertigo, and blurred vision.

Chronic toxicity—alopecia, dry skin (eg, scaliness), hepatic toxicity and enlargement, arthralgias, and pseudotumor cerebri.

Teratogenic (cleft palate, cardiac abnormalities), therefore a pregnancy test and two forms of contraception are required before isotretinoin (vitamin A derivative) is prescribed.

**Retinol** is vitamin A, so think *retin-A* (used topically for wrinkles and Acne). Found in liver and leafy vegetables. Use oral isotretinoin to treat severe cystic acne. Use all-trans retinoic acid to treat acute promyelocytic leukemia.

### Vitamin B₁

**Also called thiamine.**

**FUNCTION**

In thiamine pyrophosphate (TPP), a cofactor for several dehydrogenase enzyme reactions:

- Pyruvate dehydrogenase (links glycolysis to TCA cycle)
- α-ketoglutarate dehydrogenase (TCA cycle)
- Transketolase (HMP shunt)
- Branched-chain ketoacid dehydrogenase

Think **ATP**: α-ketoglutarate dehydrogenase, Transketolase, and Pyruvate dehydrogenase. Spell beriberi as *Ber1Ber1* to remember vitamin B₁.

**Wernicke-Korsakoff syndrome**—confusion, ophthalmoplegia, ataxia (classic triad) + confabulation, personality change, memory loss (permanent). Damage to medial dorsal nucleus of thalamus, mammillary bodies.

Dry beriberi—polyneuropathy, symmetrical muscle wasting.

Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema.

**DEFICIENCY**

Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first.

In alcoholic or malnourished patients, give thiamine before dextrose to risk of precipitating Wernicke encephalopathy. Diagnosis made by ↑ in RBC transketolase activity following vitamin B₁ administration.

Isotretinoin is teratogenic.
Vitamin B₂  Also called riboflavin.

**FUNCTION**  Component of flavins FAD and FMN, used as cofactors in redox reactions, eg, the succinate dehydrogenase reaction in the TCA cycle. FAD and FMN are derived from riboflavin \( (B₂ \approx 2 \text{ ATP}) \).

**DEFICIENCY**  Cheilosis (inflammation of lips, scaling and fissures at the corners of the mouth), Corneal vascularization. The 2 C's of B₂.

---

Vitamin B₃  Also called niacin.

**FUNCTION**  Constituent of NAD⁺, NADP⁺ (used in redox reactions). Derived from tryptophan. Synthesis requires vitamins B₂ and B₆. Used to treat dyslipidemia; lowers levels of VLDL and raises levels of HDL. NAD derived from Niacin \( (B₃ \approx 3 \text{ ATP}) \).

**DEFICIENCY**  Glossitis. Severe deficiency leads to pellagra, which can also be caused by Hartnup disease, malignant carcinoid syndrome (1 tryptophan metabolism), and isoniazid (4 vitamin B₆). Symptoms of pellagra: Diarrhea, Dementia (also hallucinations), Dermatitis (C3/C4 dermatome circumferential “broad collar” rash [Casal necklace]), hyperpigmentation of sun-exposed limbs \( \bar{A} \). The 3 D's of B₃.

Hartnup disease—autosomal recessive. Deficiency of neutral amino acid (eg, tryptophan) transporters in proximal renal tubular cells and on enterocytes → neutral aminoaciduria and \( \bar{A} \) absorption from the gut → \( \bar{A} \) tryptophan for conversion to niacin → pellagra-like symptoms. Treat with high-protein diet and nicotinic acid. Deficiency of vitamin B₃ → pellagra.

**EXCESS**  Facial flushing (induced by prostaglandin, not histamine; can avoid by taking aspirin with niacin), hyperglycemia, hyperuricemia. Excess of vitamin B₃ → podagra.

---

Vitamin B₅  Also called pantothenic acid.

**FUNCTION**  Essential component of coenzyme A (CoA, a cofactor for acyl transfers) and fatty acid synthase. \( B₅ \) is “pento”thenic acid.

**DEFICIENCY**  Dermatitis, enteritis, alopecia, adrenal insufficiency.

---

Vitamin B₆  Also called pyridoxine.

**FUNCTION**  Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (eg, ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of cystathionine, heme, niacin, histamine, and neurotransmitters including serotonin, epinephrine, norepinephrine (NE), dopamine, and GABA.

**DEFICIENCY**  Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by isoniazid and oral contraceptives), sideroblastic anemias (due to impaired hemoglobin synthesis and iron excess).
### Vitamin B₇

**FUNCTION**
Cofactor for carboxylation enzymes (which add a 1-carbon group):
- Pyruvate carboxylase: pyruvate (3C) → oxaloacetate (4C)
- Acetyl-CoA carboxylase: acetyl-CoA (2C) → malonyl-CoA (3C)
- Propionyl-CoA carboxylase: propionyl-CoA (3C) → methylmalonyl-CoA (4C)

**DEFICIENCY**
Relatively rare. Dermatitis, enteritis, alopecia. Caused by antibiotic use or excessive ingestion of raw egg whites. “Avidin in egg whites avidly binds biotin.”

### Vitamin B₉

**FUNCTION**
Converted to tetrahydrofolic acid (THF), a coenzyme for 1-carbon transfer/methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.

**DEFICIENCY**
Macrocytic, megaloblastic anemia; hypersegmented polymorphonuclear cells (PMNs); glossitis; no neurologic symptoms (as opposed to vitamin B₁₂ deficiency). Labs: ↑ homocysteine, normal methylmalonic acid levels. Seen in alcoholism and pregnancy. Deficiency can be caused by several drugs (eg, phenytoin, sulfonamides, methotrexate). Supplemental maternal folic acid at least 1 month prior to conception and during early pregnancy to reduce risk of neural tube defects. Give vitamin B₉ for the 9 months of pregnancy.
**Vitamin B₁₂**  
**FUNCTION**  
Cofactor for methionine synthase (transfers CH₃ groups as methylcobalamin) and methylmalonyl-CoA mutase. Important for DNA synthesis.  
Found in animal products. Synthesized only by microorganisms. Very large reserve pool (several years) stored primarily in the liver. Deficiency caused by malabsorption (eg, sprue, enteritis, *Diphyllobothrium latum*, achlorhydria, bacterial overgrowth, alcohol excess), lack of intrinsic factor (eg, pernicious anemia, gastric bypass surgery), absence of terminal ileum (surgical resection, eg, for Crohn disease), or insufficient intake (eg, veganism). Anti-intrinsic factor antibodies diagnostic for pernicious anemia. Folate supplementation can mask the hematologic symptoms of B₁₂ deficiency, but not the neurologic symptoms.  

**DEFICIENCY**  
Macrocystic, megaloblastic anemia; hypersegmented PMN's, paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels, along with ↑² folate deficiency. Prolonged deficiency → irreversible nerve damage.  

Vitamin C  
**FUNCTION**  
Antioxidant; also facilitates iron absorption by reducing it to Fe²⁺ state. Necessary for hydroxylation of proline and lysine in collagen synthesis. Necessary for dopamine β-hydroxylase, which converts dopamine to NE.  
Found in fruits and vegetables. Pronounce “absorb”ic acid. Ancillary treatment for methemoglobinemia by reducing Fe³⁺ to Fe²⁺.  

**DEFICIENCY**  
Scurvy—swollen gums, bruising, petechiae, hemarthrosis, anemia, poor wound healing, perifollicular and subperiosteal hemorrhages, “corkscrew” hair. Weakened immune response.  
Vitamin C deficiency causes Scurvy due to a Collagen synthesis defect.  

**EXCESS**  
Nausea, vomiting, diarrhea, fatigue, calcium oxalate nephrolithiasis. Can ↑ iron toxicity in predisposed individuals by increasing dietary iron absorption (ic, can worsen hereditary hemochromatosis or transfusion-related iron overload).
**Vitamin D**

- **D₃** (cholecalciferol) from exposure of skin (stratum basale) to sun, ingestion of fish, milk, plants.
- **D₂** (ergocalciferol) from ingestion of plants, fungi, yeasts.
- Both converted to 25-OH D₃ (storage form) in liver and to the active form 1,25-(OH)₂ D₃ (calcitriol) in kidney.

**FUNCTION**
- ↑ intestinal absorption of Ca²⁺ and PO₄³⁻.
- ↑ bone mineralization at low levels.
- ↑ bone resorption at higher levels.

**REGULATION**
- ↑ PTH, ↓ Ca²⁺, ↑ PO₄³⁻ → ↑ 1,25-(OH)₂ D₃ production.
- 1,25-(OH)₂ D₃ feedback inhibits its own production.
- ↑ PTH → ↑ Ca²⁺ reabsorption and ↓ PO₄³⁻ reabsorption in the kidney.

**DEFICIENCY**
- Rickets in children (deformity, such as genu varum “bow legs”), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany.
- Caused by malabsorption, ↓ sun exposure, poor diet, chronic kidney disease.
- Give oral vitamin D to breastfed infants.
- Deficiency is exacerbated by pigmented skin, premature birth.

**EXCESS**
- Hypercalcemia, hypercalciuria, loss of appetite, stupor. Seen in granulomatous disease (↑ activation of vitamin D by epithelioid macrophages).

**Vitamin E**

- Includes tocopherol, tocotrienol.

**FUNCTION**
- Antioxidant (protects RBCs and membranes from free radical damage).
- High-dose supplementation may alter metabolism of vitamin K → enhanced anticoagulant effects of warfarin.

**DEFICIENCY**
- Hemolytic anemia, acanthocytosis, muscle weakness, posterior column and spinocerebellar tract demyelination.
- Neurologic presentation may appear similar to vitamin B₁₂ deficiency, but without megaloblastic anemia, hypersegmented neutrophils, or ↑ serum methylmalonic acid levels.

**EXCESS**
- Risk of enterocolitis in infants.
**Vitamin K**

**Includes phytomenadione, phylloquinone, phytonadione, menaquinone.**

**FUNCTION**
Activated by epoxide reductase to the reduced form, which is a cofactor for the γ-carboxylation of glutamic acid residues on various proteins required for blood clotting. Synthesized by intestinal flora.

K is for Koagulation. Necessary for the maturation of clotting factors II, VII, IX, X, and proteins C and S. Warfarin inhibits vitamin K–dependent synthesis of these factors and proteins.

**DEFICIENCY**
Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time (neonates have sterile intestines and are unable to synthesize vitamin K). Can also occur after prolonged use of broad-spectrum antibiotics.

Not in breast milk; neonates are given vitamin K injection at birth to prevent hemorrhagic disease of the newborn.

---

**Zinc**

**FUNCTION**
Mineral essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).

**DEFICIENCY**
Delayed wound healing, suppressed immunity, hypogonadism, ↓ adult hair (axillary, facial, pubic), dysgeusia, anosmia, acrodermatitis enteropathica [A]. May predispose to alcoholic cirrhosis.

---

**Protein-energy malnutrition**

**Kwashiorkor**
Protein malnutrition resulting in skin lesions, edema due to ↓ plasma oncotic pressure, liver malfunction (fatty change due to ↓ apolipoprotein synthesis). Clinical picture is small child with swollen abdomen [A].

Kwashiorkor results from protein-deficient MEALS:

- Malnutrition
- Edema
- Anemia
- Liver (fatty)
- Skin lesions (eg, hyperkeratosis, dyspigmentation)

**Marasmus**
Malnutrition not causing edema. Diet is deficient in calories but no nutrients are entirely absent.

Marasmus results in Muscle wasting [B].
Ethanol metabolism

**FOME**—Epizole inhibits alcohol dehydrogenase and is an antidote for overdoses of methanol or ethylene glycol.

**Disulfiram**—inhibits acetaldehyde dehydrogenase (acetaldehyde accumulates, contributing to hangover symptoms), discouraging drinking.

NAD⁺ is the limiting reagent.

Alcohol dehydrogenase operates via zero-order kinetics.

Ethanol metabolism ↑ NADH/NAD⁺ ratio in liver, causing:
- Pyruvate → lactate (lactic acidosis)
- Oxaloacetate → malate (prevents gluconeogenesis → fasting hypoglycemia)
- Dihydroxyacetone phosphate → glycerol-3-phosphate (combines with fatty acids to make triglycerides → hepatosteatosis)

Additionally, ↑ NADH/NAD⁺ ratio disfavors
- TCA production of NADH → ↑ utilization of acetyl-CoA for ketogenesis (→ ketoacidosis) and lipogenesis (→ hepatosteatosis).

**Metabolism sites**

| Mitochondria | Fatty acid oxidation (β-oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation, ketogenesis. |
| Cytoplasm | Glycolysis, HMP shunt, and synthesis of steroids (SER), proteins (ribosomes, RER), fatty acids, cholesterol, and nucleotides. |
| Both | Heme synthesis, Urea cycle, Gluconeogenesis. | HUGs take two (ie, both). |
**Enzyme terminology**

An enzyme’s name often describes its function. For example, glucokinase is an enzyme that catalyzes the phosphorylation of glucose using a molecule of ATP. The following are commonly used enzyme descriptors.

- **Kinase**
  - Catalyzes transfer of a phosphate group from a high-energy molecule (usually ATP) to a substrate (e.g., phosphofructokinase).

- **Phosphorylase**
  - Adds inorganic phosphate onto substrate without using ATP (e.g., glycogen phosphorylase).

- **Phosphatase**
  - Removes phosphate group from substrate (e.g., fructose-1,6-bisphosphatase).

- **Dehydrogenase**
  - Catalyzes oxidation-reduction reactions (e.g., pyruvate dehydrogenase).

- **Hydroxylase**
  - Adds hydroxyl group (−OH) onto substrate (e.g., tyrosine hydroxylase).

- **Carboxylase**
  - Transfers CO₂ groups with the help of biotin (e.g., pyruvate carboxylase).

- **Mutase**
  - Relocates a functional group within a molecule (e.g., vitamin B₁₂-dependent methylmalonyl-CoA mutase).

- **Synthase/synthetase**
  - Joins two molecules together using a source of energy (e.g., ATP, acetyl CoA, nucleotide sugar).

**Rate-determining enzymes of metabolic processes**

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>ENZYME</th>
<th>REGULATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolysis</td>
<td>Phosphofructokinase-1 (PFK-1)</td>
<td>AMP ☺, fructose-2,6-bisphosphate ☻, ATP ☻, citrate ☻</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>Fructose-1,6-bisphosphatase</td>
<td>Citrate ☻, AMP ☻, fructose-2,6-bisphosphate ☻</td>
</tr>
<tr>
<td>TCA cycle</td>
<td>Isocitrate dehydrogenase</td>
<td>ADP ☻, ATP ☻, NADH ☻</td>
</tr>
<tr>
<td>Glycogenesis</td>
<td>Glycogen synthase</td>
<td>Glucose-6-phosphate ☻, insulin ☻, cortisol ☻, Epinephrine ☻, glucagon ☻</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>Glycogen phosphorylase</td>
<td>Epinephrine ☻, glucagon ☻, AMP ☻, Glucose-6-phosphate ☻, insulin ☻, ATP ☻</td>
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<tr>
<td>HMP shunt</td>
<td>Glucose-6-phosphate dehydrogenase (G6PD)</td>
<td>NAD⁺ ☻, NADPH ☻</td>
</tr>
<tr>
<td>De novo pyrimidine synthesis</td>
<td>Carbamoyl phosphate synthetase II</td>
<td>ATP ☻, PRPP ☻</td>
</tr>
<tr>
<td>De novo purine synthesis</td>
<td>Glutamine-phosphoribosylpyrophosphate (PRPP) amidotransferase</td>
<td>AMP ☻, inosine monophosphate (IMP) ☻, GMP ☻</td>
</tr>
<tr>
<td>Urea cycle</td>
<td>Carbamoyl phosphate synthetase I</td>
<td>N-acetylglutamate ☻</td>
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<tr>
<td>Fatty acid synthesis</td>
<td>Acetyl-CoA carboxylase (ACC)</td>
<td>Insulin ☻, citrate ☻, Glucagon ☻, palmitoyl-CoA ☻</td>
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<tr>
<td>Fatty acid oxidation</td>
<td>Carnitine acyltransferase I</td>
<td>Malonyl-CoA ☻</td>
</tr>
<tr>
<td>Ketogenesis</td>
<td>HMG-CoA synthase</td>
<td>Insulin ☻, thyroxine ☻, Glucagon ☻, cholesterol ☻</td>
</tr>
<tr>
<td>Cholesterol synthesis</td>
<td>HMG-CoA reductase</td>
<td>Insulin ☻, thyroxine ☻, Glucagon ☻, cholesterol ☻</td>
</tr>
</tbody>
</table>
Summary of pathways

1. Galactokinase (mild galactosemia)
2. Galactose-1-phosphate uridylyltransferase (severe galactosemia)
3. Hexokinase/glucokinase
4. Glucose-6-phosphatase (von Gierke disease)
5. Glucose-6-phosphate dehydrogenase
6. Transketolase
7. Phosphofructokinase-1
8. Fructose-1,6-biphosphatase
9. Fructokinase (essential fructosuria)
10. Aldolase B (fructose intolerance)
11. Aldolase B (liver, A (muscle))
12. Triose phosphate isomerase
13. Pyruvate kinase
14. Pyruvate dehydrogenase
15. Pyruvate carboxylase
16. PEP carboxykinase
17. Citrate synthase
18. Isocitrate dehydrogenase
19. α-Ketoglutarate dehydrogenase
20. Carboxamidophosphoribosyltransferase (HGPRT)
21. Ornithine transcarbamylase
22. Propionyl-CoA carboxylase
23. HMG-CoA reductase

Galactose metabolism

- Galactose
- UDP-glucose
- Glucose-1-phosphate
- Fructose-6-phosphate
- Ribulose-5-phosphate
- 6-phosphogluconolactone

Glycogen

- Glucose-1-phosphate
- Glucose
- Glucose-6-phosphate
- 6-phosphogluconolactone
- Ribulose-5-phosphate

Glycerol metabolism

- Glucose-6-phosphate
- Fructose-6-phosphate
- 6-phosphogluconolactone
- Ribulose-5-phosphate

Glycolysis

- Glucose
- Glucose-6-phosphate
- Fructose-6-phosphate
- 6-phosphogluconolactone
- Ribulose-5-phosphate

Glucose-6-phosphate

- Fructose-6-phosphate
- 6-phosphogluconolactone
- Ribulose-5-phosphate

TCA cycle

- Citrate
- α-Ketoglutarate
- Isocitrate
- Oxaloacetate
- α-Ketoglutarate

Ketogenesis

- Methylmalonyl-CoA
- Propionyl-CoA
- Bu2
- A

Protein metabolism

- Ornithine
- Argininosuccinate
- Arginine
- Citrulline

Urea cycle

- NH₃ + CO₂
- Citrulline
- Argininosuccinate
- Ornithine
- Arginine
- H₂O

ATP production

Aerobic metabolism of one glucose molecule produces 32 net ATP via malate-aspartate shuttle (heart and liver), 30 net ATP via glycerol-3-phosphate shuttle (muscle). Anaerobic glycolysis produces only 2 net ATP per glucose molecule. ATP hydrolysis can be coupled to energetically unfavorable reactions.

Arsenic causes glycolysis to produce zero net ATP.
Activated carriers

<table>
<thead>
<tr>
<th>CARRIER MOLECULE</th>
<th>CARRIED IN ACTIVATED FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>Phosphoryl groups</td>
</tr>
<tr>
<td>NADH, NADPH, FADH₂</td>
<td>Electrons</td>
</tr>
<tr>
<td>CoA, lipoamide</td>
<td>Acyl groups</td>
</tr>
<tr>
<td>Biotin</td>
<td>CO₂</td>
</tr>
<tr>
<td>Tetrahydrofolates</td>
<td>1-carbon units</td>
</tr>
<tr>
<td>S-adenosylmethionine (SAM)</td>
<td>CH₃ groups</td>
</tr>
<tr>
<td>TPP</td>
<td>Aldehydes</td>
</tr>
</tbody>
</table>

Universal electron acceptors

Nicotinamides (NAD⁺, NADP⁺ from vitamin B₃) and flavin nucleotides (FAD⁺ from vitamin B₂).

NAD⁺ is generally used in catabolic processes to carry reducing equivalents away as NADH.

NADPH is used in:
- Anabolic processes
- Respiratory burst
- Cytochrome P-450 system
- Glutathione reductase

NADPH is a product of the HMP shunt.

Hexokinase vs glucokinase

Phosphorylation of glucose to yield glucose-6-phosphate is catalyzed by glucokinase in the liver and hexokinase in other tissues. Hexokinase sequesters glucose in tissues, where it is used even when glucose concentrations are low. At high glucose concentrations, glucokinase helps to store glucose in liver.

<table>
<thead>
<tr>
<th></th>
<th>Hexokinase</th>
<th>Glucokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Most tissues, except liver and pancreatic β cells</td>
<td>Liver, β cells of pancreas</td>
</tr>
<tr>
<td>Kₘ</td>
<td>Lower († affinity)</td>
<td>Higher (‡ affinity)</td>
</tr>
<tr>
<td>Vₘₐₓ</td>
<td>Lower (‡ capacity)</td>
<td>Higher (‡ capacity)</td>
</tr>
<tr>
<td>Induced by insulin</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Feedback-inhibited by glucose-6-phosphate</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
**Glycolysis regulation, key enzymes**

Net glycolysis (cytoplasm):

\[
\text{Glucose} + 2\text{P}_i + 2\text{ADP} + 2\text{NAD}^+ \rightarrow 2\text{pyruvate} + 2\text{ATP} + 2\text{NADH} + 2\text{H}^+ + 2\text{H}_2\text{O}.
\]

Equation not balanced chemically, and exact balanced equation depends on ionization state of reactants and products.

---

**REQUIRE ATP**

- **Glucose** → Glucose-6-P (Hexokinase/glucokinase*)
- **Fructose-6-P** → Fructose-1,6-BP (Phosphofructokinase-1)

*Glucokinase in liver and β cells of pancreas; hexokinase in all other tissues.

**PRODUCE ATP**

- **1,3-BPG** → **3-PG** (Phosphoglycerate kinase)
- **Fructose-1,6-bisphosphate** → **ATP**, **citrate**

---

**Regulation by fructose-2,6-bisphosphate**

FBPase-2 (fructose bisphosphatase-2) and PFK-2 (phosphofructokinase-2) are the same bifunctional enzyme whose function is reversed by phosphorylation by protein kinase A.

**Fasting state:**

- Glucagon → cAMP → protein kinase A → FBPase-2, less glycolysis, more gluconeogenesis.

**Fed state:**

- Insulin → cAMP → protein kinase A → FBPase-2, more glycolysis, less gluconeogenesis.

---

**Pyruvate dehydrogenase complex**

Mitochondrial enzyme complex linking glycolysis and TCA cycle. Differentially regulated in fed/fasting states (active in fed state).

- Reactions: pyruvate + NAD$^+$ + CoA → acetyl-CoA + CO$_2$ + NADH.
- The complex contains 5 enzymes that require 5 cofactors:
  1. Thiamine pyrophosphate (B$_1$)
  2. Lipoic acid
  3. CoA (B$_2$, pantothenic acid)
  4. FAD (B$_3$, riboflavin)
  5. NAD$^+$ (B$_5$, niacin)
- Activated by:
  * NAD$^+$/NADH ratio
  * ADP
  * Ca$^{2+}$

The complex is similar to the α-ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action), which converts α-ketoglutarate → succinyl-CoA (TCA cycle).

---

The Lovely Co-enzymes For Nerds.

Arsenic inhibits lipoic acid. Arsenic poisoning clinical findings: imagine a vampire (pigmentary skin changes, skin cancer), vomiting and having diarrhea, running away from a cutie (QT prolongation) with garlic breath.
Pyruvate dehydrogenase complex deficiency

Causes a buildup of pyruvate that gets shunted to lactate (via LDH) and alanine (via ALT). X-linked.

**FINDINGS**
Neurologic defects, lactic acidosis, ↑ serum alanine starting in infancy.

**TREATMENT**
↑ intake of ketogenic nutrients (eg, high fat content or ↑ lysine and leucine).

---

### Pyruvate metabolism

**Pyruvate dehydrogenase complex**

- Converts pyruvate to acetyl-CoA
- Requires cofactors: B1, B2, B3, B5, lipoic acid

**Alcohol dehydrogenase (B3)**

- Converts pyruvate to lactate
- Requires cofactors: NAD+ and NADH

**Alanine aminotransferase (B6)**

- Transfers amino groups from alanine to the liver
- Requires cofactors: pyruvate carboxylase (biotin)

**Pyruvate carboxylase (biotin)**

- Converts oxaloacetate to malate
- Requires cofactors: biotin

**Pyruvate metabolism**

- **Pyruvate** enters the mitochondria and is converted to acetyl-CoA
- Acetyl-CoA enters the TCA cycle
- TCA cycle produces 3 NADH, 1 FADH2, 2 CO2, 1 GTP per acetyl-CoA

**TCA cycle (Krebs cycle)**

- Pyruvate → acetyl-CoA produces 1 NADH, 1 CO2
- The TCA cycle produces 3 NADH, 1 FADH2, 2 CO2, 1 GTP per acetyl-CoA = 10 ATP/acetyl-CoA

**α-ketoglutarate dehydrogenase complex**

- Requires the same cofactors as the pyruvate dehydrogenase complex (B1, B2, B3, B5, lipoic acid)

**Citrate is Krebs’ starting substrate for making oxaloacetate.**

---

---

---
Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. FADH$_2$ electrons are transferred to complex II (at a lower energy level than NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.

![Diagram of electron transport chain and oxidative phosphorylation]

ATP PRODUCED VIA ATP SYNTHASE

1 NADH $\rightarrow$ 2.5 ATP, 1 FADH$_2$ $\rightarrow$ 1.5 ATP.

OXIDATIVE PHOSPHORylation POISONS

<table>
<thead>
<tr>
<th>Electron transport inhibitors</th>
<th>Directly inhibit electron transport, causing a ↓ proton gradient and block of ATP synthesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotenone</td>
<td>Complex one inhibitor.</td>
</tr>
<tr>
<td>Cyanide, carbon monoxide, azide (the -ides, 4 letters)</td>
<td>Inhibit complex IV.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATP synthase inhibitors</th>
<th>Directly inhibit mitochondrial ATP synthase, causing an ↑ proton gradient. No ATP is produced because electron transport stops.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligomycin</td>
<td>Inhibitor.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncoupling agents</th>
<th>permeability of membrane, causing a ↓ proton gradient and ↑ O$_2$ consumption. ATP synthesis stops, but electron transport continues. Produces heat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-Dinitrophenol</td>
<td>Used illicitly for weight loss, aspirin overdose, thermogenin in brown fat (has more mitochondria than white fat).</td>
</tr>
</tbody>
</table>

Gluconeogenesis, irreversible enzymes

<table>
<thead>
<tr>
<th>Pyruvate carboxylase</th>
<th>In mitochondria. Pyruvate $\rightarrow$ oxaloacetate. Requires biotin, ATP. Activated by acetyl-CoA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoenolpyruvate carboxykinase</td>
<td>In cytosol. Oxaloacetate $\rightarrow$ phosphoenolpyruvate. Requires GTP.</td>
</tr>
<tr>
<td>Fructose-1,6-bisphosphatase</td>
<td>In cytosol. Fructose-1,6-bisphosphate $\rightarrow$ fructose-6-phosphate. Citrate ⊕, AMP ⊕, fructose 2,6-bisphosphate ⊕.</td>
</tr>
<tr>
<td>Glucose-6-phosphatase</td>
<td>In ER. Glucose-6-phosphate $\rightarrow$ glucose.</td>
</tr>
</tbody>
</table>

Pathway Produces Fresh Glucose. Occurs primarily in liver; serves to maintain euglycemia during fasting. Enzymes also found in kidney, intestinal epithelium. Deficiency of the key gluconeogenic enzymes causes hypoglycemia. (Muscle cannot participate in gluconeogenesis because it lacks glucose-6-phosphatase.) Odd-chain fatty acids yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle (as succinyl-CoA), undergo gluconeogenesis, and serve as a glucose source. Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.
**HMP shunt (pentose phosphate pathway)**

Provides a source of NADPH from abundantly available glucose-6-P (NADPH is required for reductive reactions, eg, glutathione reduction inside RBCs, fatty acid and cholesterol biosynthesis). Additionally, this pathway yields ribose for nucleotide synthesis. Two distinct phases (oxidative and nonoxidative), both of which occur in the cytoplasm. No ATP is used or produced. Sites: lactating mammary glands, liver, adrenal cortex (sites of fatty acid or steroid synthesis), RBCs.

<table>
<thead>
<tr>
<th>REACTIONS</th>
<th>KEY ENZYMES</th>
<th>PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxidative</strong> (irreversible)</td>
<td>Glucose-6-P dehydrogenase</td>
<td>NADP+ \rightarrow NADPH, CO2, 2 NADPH, Ribulose-5-Pi</td>
</tr>
<tr>
<td><strong>Nonoxidative</strong> (reversible)</td>
<td>Phosphopentose isomerase, transketolases</td>
<td>Requires B1, Ribose-5-P, Glycerol-3-phosphate, Fructose-6-P</td>
</tr>
</tbody>
</table>

**Glucose-6-phosphate dehydrogenase deficiency**

NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to hemolytic anemia due to poor RBC defense against oxidizing agents (eg, fava beans, sulfonamides, nitrofurantoin, primaquine/chloroquine, antituberculosis drugs). Infection (most common cause) can also precipitate hemolysis; inflammatory response produces free radicals that diffuse into RBCs, causing oxidative damage.

X-linked recessive disorder; most common human enzyme deficiency; more prevalent among African Americans. ↑ malarial resistance.

Heinz bodies—denatured globin chains precipitate within RBCs due to oxidative stress. Bite cells—result from the phagocytic removal of Heinz bodies by splenic macrophages. Think, “Bite into some Heinz ketchup.”
Disorders of fructose metabolism

**Essential fructosuria**
Involves a defect in fructokinase. Autosomal recessive. A benign, asymptomatic condition (fructokinase deficiency is kinder), since fructose is not trapped in cells. Hexokinase becomes 1° pathway for converting fructose to fructose-6-phosphate.

Symptoms: fructose appears in blood and urine.

Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.

**Hereditary fructose intolerance**
Hereditary deficiency of aldolase B. Autosomal recessive. Fructose-1-phosphate accumulates, causing a depletion of available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be positive (tests for glucose only); reducing sugar can be detected in the urine (nonspecific test for inborn errors of carbohydrate metabolism).

Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting.

Treatment: 4 intake of both fructose and sucrose (glucose + fructose).

---

Disorders of galactose metabolism

**Galactokinase deficiency**
Hereditary deficiency of galactokinase. Galactitol accumulates if galactose is present in diet. Relatively mild condition. Autosomal recessive.

Symptoms: galactose appears in blood (galactosemia) and urine (galactosuria); infantile cataracts. May present as failure to track objects or to develop a social smile. Galactokinase deficiency is kinder (benign condition).

**Classic galactosemia**
Absence of galactose-1-phosphate uridylytransferase. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye). Symptoms develop when infant begins feeding (lactose present in breast milk and routine formula) and include failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can predispose to E. coli sepsis in neonates.

Treatment: exclude galactose and lactose (galactose + glucose) from diet.

---

Fructose is to Aldolase B as Galactose is to Uridylytransferase (FAB GUT). The more serious defects lead to PO$_4^{3-}$ depletion.
Sorbitol

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, sorbitol, via aldose reductase. Some tissues then convert sorbitol to fructose using sorbitol dehydrogenase; tissues with an insufficient amount/activity of this enzyme are at risk of intracellular sorbitol accumulation, causing osmotic damage (e.g., cataracts, retinopathy, and peripheral neuropathy seen with chronic hyperglycemia in diabetes).

High blood levels of galactose also result in conversion to the osmotically active galactitol via aldose reductase.

Liver, Ovaries, and Seminal vesicles have both enzymes (they LOSe sorbitol).

Lens has primarily aldose reductase. Retina, Kidneys, and Schwann cells have only aldose reductase (LaRKs).

Lactase deficiency

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the intestinal brush border to digest lactose (in milk and milk products) into glucose and galactose.

Primary: age-dependent decline after childhood (absence of lactase-persistent allele), common in people of Asian, African, or Native American descent.

Secondary: loss of intestinal brush border due to gastroenteritis (e.g., rotavirus), autoimmune disease, etc.

Congenital lactase deficiency: rare, due to defective gene.


FINDINGS

Bloating, cramps, flatulence, osmotic diarrhea.

TREATMENT

Avoid dairy products or add lactase pills to diet; lactose-free milk.

Amino acids

Only l-amino acids are found in proteins.

Essential

PVT TIM HaLL: Phenylalanine, Valine, Tyrosine, Threonine, Isoleucine, Methionine, Histidine, Leucine, Lysine.

Glucogenic: Methionine, histidine, valine. I met his valentine, she is so sweet (glucogenic).

Glucogenic/ketogenic: Isoleucine, phenylalanine, threonine, tyrosine.

Ketogenic: Leucine, Lysine. The onLy pureLy ketogenic amino acids.

Acidic

Aspartic acid, glutamic acid.

Negatively charged at body pH.

Basic

Arginine, histidine, lysine.

Arginine is most basic. Histidine has no charge at body pH.

Arginine and histidine are required during periods of growth.

Arginine and lysine are ↑ in histones which bind negatively charged DNA.

His lys (lies) are basic.
**Urea cycle**

Amino acid catabolism results in the formation of common metabolites (e.g., pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen generated by this process is converted to urea and excreted by the kidneys.

Ordinarily, Careless Crappers Are Also Frivolous About Urination.

**Transport of ammonia by alanine**

Can be acquired (e.g., liver disease) or hereditary (e.g., urea cycle enzyme deficiencies). Excess NH$_3$ depletes glutamate (GABA) in the CNS and $\alpha$-ketoglutarate → inhibition of TCA cycle.

Treatment: limit protein in diet. May be given to ↓ ammonia levels:

- Lactulose to acidify the GI tract and trap NH$_3$$^+$ for excretion.
- Antibiotics (e.g., rifaximin, neomycin) to ↓ colonic ammoniagenic bacteria.
- Benzoate, phenylacetate, or phenylbutyrate react with glycine or glutamine, forming products that are renally excreted.

**Hyperammonemia**

Ammonia accumulation—flapping tremor (asterisk), slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

Can be acquired (e.g., liver disease) or hereditary (e.g., urea cycle enzyme deficiencies).

Hyperammonemia can be acquired (e.g., liver disease) or hereditary (e.g., urea cycle enzyme deficiencies). Excess NH$_3$ depletes glutamate (GABA) in the CNS and $\alpha$-ketoglutarate → inhibition of TCA cycle.

Treatment: limit protein in diet. May be given to ↓ ammonia levels:

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- Benzoate, phenylacetate, or phenylbutyrate react with glycine or glutamine, forming products that are renally excreted.
Ornithine transcarbamylase deficiency

Most common urea cycle disorder. X-linked recessive (vs other urea cycle enzyme deficiencies, which are autosomal recessive). Interferes with the body’s ability to eliminate ammonia. Often evident in the first few days of life, but may present later. Excess carbamoyl phosphate is converted to orotic acid (part of the pyrimidine synthesis pathway).

Findings: ↑ orotic acid in blood and urine, ↓ BUN, symptoms of hyperammonemia. No megaloblastic anemia (vs orotic aciduria).

Amino acid derivatives

Catecholamine synthesis/tyrosine catabolism
**Phenylketonuria**

Due to deficiencies of phenylalanine hydroxylase or tetrahydrobiopterin (BH4) cofactor (malignant PKU). Tyrosine becomes essential. Phenylalanine → excess phenyl ketones in urine.

Findings: intellectual disability, growth retardation, seizures, fair complexion, eczema, musty body odor.

Treatment: phenylalanine and tyrosine in diet, tetrahydrobiopterin supplementation.

**Maternal PKU** — lack of proper dietary therapy during pregnancy. Findings in infant: microcephaly, intellectual disability, growth retardation, congenital heart defects.

**Maple syrup urine disease**

Blocked degradation of branched amino acids (Isoleucine, Leucine, Valine) due to deficiencies of branched-chain α-ketoacid dehydrogenase (B1). Causes α-ketoacids in the blood, especially those of leucine.

Causes severe CNS defects, intellectual disability, and death.

Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

Autosomal recessive. Incidence ≈ 1:10,000.

Screening occurs 2–3 days after birth (normal at birth because of maternal enzyme during fetal life).

Phenyl ketones—phenylacetate, phenyllactate, and phenylpyruvate. Disorder of aromatic amino acid metabolism → musty body odor.

PKU patients must avoid the artificial sweetener aspartame, which contains phenylalanine.

**Alkaptonuria**

Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate → pigment-forming homogentisic acid accumulates in tissue A. Autosomal recessive. Usually benign.

Findings: bluish-black connective tissue, ear cartilage, and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

**Homocystinuria**

Types (all autosomal recessive):

- Cystathionine synthase deficiency (treatment: methionine, cysteine, B6, B12, and folate in diet)
- Affinity of cystathionine synthase for pyridoxal phosphate (treatment: B6 and cysteine in diet)
- Methionine synthase (homocysteine methyltransferase) deficiency (treatment: methionine in diet)

All forms result in excess homocysteine.

HOMOCystinuria: ↑ Homocysteine in urine, Osteoporosis, Marfanoid habitus, Ocular changes (downward and inward lens subluxation), Cardiovascular effects (thrombosis and atherosclerosis → stroke and MI), Kyphosis, intellectual disability. In homocystinuria, lens subluxes “down and in” (vs Marfan, “up and fans out”).

**Homocysteine**

Methionine → Cystathionine synthase → Cystathionine → Cysteine
Cystinuria

Hereditary defect of renal PCT and intestinal amino acid transporter that prevents reabsorption of Cystine, Ornithine, Lysine, and Arginine (COLA).

Excess cystine in the urine can lead to recurrent precipitation of hexagonal cystine stones. Treatment: urinary alkalinization (e.g., potassium citrate, acetazolamide) and chelating agents (e.g., penicillamine) to solubility of cystine stones; good hydration.


Cystine is made of 2 cysteines connected by a disulfide bond.

Glycogen regulation by insulin and glucagon/epinephrine

Glycogen regulation by insulin and glucagon/epinephrine involves a complex interplay of enzymes and signaling molecules. The diagram illustrates the role of these factors in regulating glycogen levels in tissues such as liver and muscle. The regulatory mechanisms include the activation of glycogen phosphorylase by insulin and the inhibition by glucagon and epinephrine. The role of calcium-calmodulin and protein kinase A is also depicted in the regulation of glycogen metabolism during muscle contraction.

The diagram outlines the pathways for glycogen phosphorylase activation and glycogen synthase inactivation. These processes are crucial for maintaining blood glucose levels and energy homeostasis in the body.
<table>
<thead>
<tr>
<th>Glycogen</th>
<th>Branches have $\alpha$-(1,6) bonds; linkages have $\alpha$-(1,4) bonds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle</td>
<td>Glycogen undergoes glycogenolysis $\rightarrow$ glucose-1-phosphate $\rightarrow$ glucose-6-phosphate, which is rapidly metabolized during exercise.</td>
</tr>
<tr>
<td>Hepatocytes</td>
<td>Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels. Glycogen phosphorylase ❶ liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then 4-$\alpha$-d-glucanotransferase (debranching enzyme ❷) moves 3 of the 4 glucose units from the branch to the linkage. Then $\alpha$-1,6-glucosidase (debranching enzyme ❸) cleaves off the last residue, liberating glucose. “Limit dextrin” refers to the one to four residues remaining on a branch after glycogen phosphorylase has already shortened it.</td>
</tr>
</tbody>
</table>

**Note:** A small amount of glycogen is degraded in lysosomes by ❹ $\alpha$-1,4-glucosidase (acid maltase).

---

**Diagram:**

- Glucose $\rightarrow$ Glucose-6-P $\rightarrow$ Glucose-1-P $\rightarrow$ UDP-glucose $\rightarrow$ Glycogen $\rightarrow$ Lysosome only $\rightarrow$ α-1,4-glucosidase
- Glycogen storage disease type
- UDP-glucose pyrophosphorylase
- Glycogen synthase
- Branching enzyme
- Glycogen phosphorylase
- Debranching enzyme ($4$-$\alpha$-d-glucanotransferase)
- Debranching enzyme ($\alpha$-1,6-glucosidase)
- Note: A small amount of glycogen is degraded in lysosomes by $\alpha$-1,4-glucosidase (acid maltase).
### Glycogen storage diseases

At least 15 types have been identified, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells. Periodic acid–Schiff stain identifies glycogen and is useful in identifying these diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Findings</th>
<th>Deficient Enzyme</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Gierke disease (type I)</td>
<td>Severe fasting hypoglycemia, ↑↑ Glycogen in liver and kidneys, ↑ blood lactate, ↑ triglycerides, ↑ uric acid (Gout), and hepatomegaly, renomegaly. Liver does not regulate blood glucose.</td>
<td>Glucose-6-phosphatase</td>
<td>Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose. Impaired gluconeogenesis and glycogenolysis.</td>
</tr>
<tr>
<td>Pompe disease (type II)</td>
<td>Cardiomegaly, hypertrophic cardiomyopathy, hypotonia, exercise intolerance, and systemic findings lead to early death.</td>
<td>Lysosomal acid α-1,4-glucosidase with α-1,6-glucosidase activity (acid maltase)</td>
<td>PomPe trashes the PumP (1,4) (heart, liver, and muscle)</td>
</tr>
<tr>
<td>Cori disease (type III)</td>
<td>Milder form of von Gierke (type I) with normal blood lactate levels. Accumulation of limit dextrin–like structures in cytosol.</td>
<td>Debranching enzyme (α-1,6-glucosidase)</td>
<td>Gluconeogenesis is intact</td>
</tr>
<tr>
<td>McArdle disease (type V)</td>
<td>↑ glycogen in muscle, but muscle cannot break it down → painful Muscle cramps, Myoglobinuria (red urine) with strenuous exercise, and arrhythmia from electrolyte abnormalities. Second-wind phenomenon noted during exercise due to ↑ muscular blood flow.</td>
<td>Skeletal muscle glycogen phosphorylase (Myophosphorylase)</td>
<td>Hallmark is a flat venous lactate curve with normal rise in ammonia levels during exercise. Blood glucose levels typically unaffected. McArdle = Muscle</td>
</tr>
</tbody>
</table>

*Very Poor Carbohydrate Metabolism. Types I, II, III, and V are autosomal recessive.*
Lysosomal storage diseases

Each is caused by a deficiency in one of the many lysosomal enzymes. Results in an accumulation of abnormal metabolic products.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Findings</th>
<th>Deficient Enzyme</th>
<th>Accumulated Substrate</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphingolipidoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Progressive neurodegeneration, developmental delay, “cherry-red” spot on macula, lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick).</td>
<td>1. Hexosaminidase A (“TAy-SaX”)</td>
<td>GM2 ganglioside</td>
<td>AR</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Early: Triad of episodic peripheral neuropathy, angiokeratoma, hypohidrosis. Late: progressive renal failure, cardiovascular disease.</td>
<td>2. α-galactosidase A</td>
<td>Ceramide trihexoside</td>
<td>XR</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Central and peripheral demyelination with ataxia, dementia.</td>
<td>3. Arylsulfatase A</td>
<td>Cerebroside sulfate</td>
<td>AR</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>Peripheral neuropathy, destruction of oligodendrocytes, developmental delay, optic atrophy, globoid cells.</td>
<td>4. Galactocerebrosidase</td>
<td>Galactocerebroside, psychosine</td>
<td>AR</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femur, bone crises, Gaucher cells (lipid-laden macrophages resembling crumpled tissue paper).</td>
<td>5. Glucocerebrosidase (β-glucosidase); treat with recombinant glucocerebrosidase</td>
<td>Glucocerebroside</td>
<td>AR</td>
</tr>
<tr>
<td>Niemann-Pick disease</td>
<td>Progressive neurodegeneration, hepatosplenomegaly, foam cells (lipid-laden macrophages), “cherry-red” spot on macula.</td>
<td>6. Sphingomyelinase</td>
<td>Sphingomyelin</td>
<td>AR</td>
</tr>
</tbody>
</table>

Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Findings</th>
<th>Deficient Enzyme</th>
<th>Accumulated Substrate</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler syndrome</td>
<td>Developmental delay, gargoylism, airway obstruction, corneal clouding, hepatosplenomegaly.</td>
<td>α-l-iduronidase</td>
<td>Heparan sulfate, dermatan sulfate</td>
<td>AR</td>
</tr>
<tr>
<td>Hunter syndrome</td>
<td>Mild Hurler + aggressive behavior, no corneal clouding</td>
<td>Iduronate-2-sulfatase</td>
<td>Heparan sulfate, dermatan sulfate</td>
<td>XR</td>
</tr>
</tbody>
</table>

No man picks (Niemann-Pick) his nose with his sphinger (sphingomyelinase). Tay-SaX lacks hexosaminidase. Hunters see clearly (no corneal clouding) and aggressively aim for the X (X-linked recessive).† incidence of Tay-Sachs, Niemann-Pick, and some forms of Gaucher disease in Ashkenazi Jews.
Fatty acid metabolism

Fatty acid synthesis requires transport of citrate from mitochondria to cytosol. Predominantly occurs in liver, lactating mammary glands, and adipose tissue. Long-chain fatty acid (LCFA) degradation requires carnitine-dependent transport into the mitochondrial matrix.

“SYntate” = SYNthesis.
CARnitine = CARnage of fatty acids.

Systemic 1° carnitine deficiency—inherted defect in transport of LCFA’s into the mitochondria → toxic accumulation. Causes weakness, hypotonia, and hypoketotic hypoglycemia.

Medium-chain acyl-CoA dehydrogenase deficiency → inability to break down fatty acids into acetyl-CoA → accumulation of fatty acyl carnitines in the blood with hypoketotic hypoglycemia. Causes vomiting, lethargy, seizures, coma, liver dysfunction, hyperammonemia. Can lead to sudden death in infants or children. Treat by avoiding fasting.
Ketone bodies

In the liver, fatty acids and amino acids are metabolized to acetoacetate and β-hydroxybutyrate (to be used in muscle and brain). In prolonged starvation and diabetic ketoacidosis, oxaloacetate is depleted for gluconeogenesis. In alcoholism, excess NADH shunts oxaloacetate to malate. Both processes cause a buildup of acetyl-CoA, which shunts glucose, amino acids, and FFAs toward the production of ketone bodies.

Ketone bodies: acetone, acetoacetate, β-hydroxybutyrate.
Breath smells like acetone (fruity odor).
Urine test for ketones can detect acetoacetate, but not β-hydroxybutyrate.
RBCs cannot utilize ketones; they strictly use glucose.
HMG-CoA lyase for ketone production.
HMG-CoA reductase for cholesterol synthesis.
Metabolic fuel use

![Graph showing the use of stored energy sources during exercise]

- Stored ATP
- Creatine phosphate
- Anaerobic metabolism
- Aerobic metabolism
- Overall performance

Duration of exercise

<table>
<thead>
<tr>
<th>Time</th>
<th>% Maximal energy by source</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 sec</td>
<td>100%</td>
</tr>
<tr>
<td>10 sec</td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td></td>
</tr>
<tr>
<td>2 hr</td>
<td></td>
</tr>
</tbody>
</table>

Fasting and starvation

<table>
<thead>
<tr>
<th>State</th>
<th>Priorities</th>
<th>Metabolic Processes</th>
<th>Hormonal Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fed (after a meal)</td>
<td></td>
<td>Glycolysis and aerobic respiration.</td>
<td>Insulin stimulates storage of lipids, proteins, and glycogen.</td>
</tr>
<tr>
<td>Fasting (between meals)</td>
<td></td>
<td>Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor).</td>
<td>Glucagon and epinephrine stimulate use of fuel reserves.</td>
</tr>
</tbody>
</table>
| Starvation days 1–3            |            | Blood glucose levels maintained by:  
* Hepatic glycogenolysis  
* Adipose release of FFA  
* Muscle and liver, which shift fuel use from glucose to FFA  
* Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA (from odd-chain FFA—the only triacylglycerol components that contribute to gluconeogenesis) | Glycogen reserves depleted after day 1.  
RBCs lack mitochondria and therefore cannot use ketones. |
| Starvation after day 3         |            | Adipose stores (ketone bodies become the main source of energy for the brain). After these are depleted, vital protein degradation accelerates, leading to organ failure and death.  
Amount of excess stores determines survival time. | |

- 1g carb/protein (eg, whey) = 4 kcal
- 1g alcohol = 7 kcal
- 1g fatty acid = 9 kcal

(# letters = # kcal)
Lipid transport

Dietary fat + cholesterol

Micelles

Lumen

Intestinal cell

Thoracic duct

Subclavian vein

Adipocyte

Systemic circulation

Lipoprotein lipase

Liver releases VLDL

VLDL Apo CII activates LPL

IDL delivers to liver via Apo E

Endocytosis of LDL

Hepatocyte

Bile Canaliculus

Cholesterol + TGs

HDL transfers Apo CII and Apo E

Chylomicron Apo CII activates LPL

Chylomicron enters lymphatics

IDL delivers to liver via Apo E

Endocytosis of LDL
Key enzymes in lipid transport

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol ester transfer protein</td>
<td>Mediates transfer of cholesterol esters to other lipoprotein particles.</td>
</tr>
<tr>
<td>Hepatic lipase</td>
<td>Degrades TGs remaining in IDL.</td>
</tr>
<tr>
<td>Hormone-sensitive lipase</td>
<td>Degrades TGs stored in adipocytes.</td>
</tr>
<tr>
<td>Lecithin-cholesterol acyltransferase</td>
<td>Catalyzes esterification of ( \frac{2}{3} ) of plasma cholesterol.</td>
</tr>
<tr>
<td>Lipoprotein lipase</td>
<td>Degrades TGs circulating chylomicrons and VLDLs. Found on vascular endothelial surface.</td>
</tr>
<tr>
<td>Pancreatic lipase</td>
<td>Degrades dietary TGs in small intestine.</td>
</tr>
</tbody>
</table>

Major apolipoproteins

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Function</th>
<th>Chylomicron</th>
<th>Chylomicron remnant</th>
<th>VLDL</th>
<th>IDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Mediates remnant uptake (Everything Except LDL)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>A-I</td>
<td>Activates LCAT</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-II</td>
<td>Lipoprotein lipase Cofactor that Catalyzes Cleavage</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-48</td>
<td>Mediates chylomicron secretion into lymphatics Only on particles originating from the intestines</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-100</td>
<td>Binds LDL receptor Only on particles originating from the liver</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Lipoprotein functions
Lipoproteins are composed of varying proportions of cholesterol, TGs, and phospholipids. LDL and HDL carry the most cholesterol.

LDL transports cholesterol from liver to tissues. LDL is Lousy.
HDL transports cholesterol from periphery to liver. HDL is Healthy.

Cholesterol
Needed to maintain cell membrane integrity and synthesize bile acid, steroids, and vitamin D.

Chylomicron
Delivers dietary TGs to peripheral tissues. Delivers cholesterol to liver in the form of chylomicron remnants, which are mostly depleted of their TGs. Secreted by intestinal epithelial cells.

VLDL
Delivers hepatic TGs to peripheral tissue. Secreted by liver.

IDL
Formed in the degradation of VLDL. Delivers TGs and cholesterol to liver.

LDL
Delivers hepatic cholesterol to peripheral tissues. Formed by hepatic lipase modification of IDL in the liver and peripheral tissue. Taken up by target cells via receptor-mediated endocytosis.

HDL
Mediates reverse cholesterol transport from periphery to liver. Acts as a repository for apolipoproteins C and E (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine. Alcohol ↑ synthesis.

Abetalipoproteinemia
Autosomal recessive. Chylomicrons, VLDL, LDL absent. Deficiency in ApoB-48, ApoB-100. Affected infants present with severe fat malabsorption, steatorrhea, failure to thrive. Later manifestations include retinitis pigmentosa, spinocerebellar degeneration due to vitamin E deficiency, progressive ataxia, acanthocytosis.
Treatment: restriction of long-chain fatty acids, large doses of oral vitamin E.

<table>
<thead>
<tr>
<th>Familial dyslipidemias</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE</td>
</tr>
<tr>
<td>I—Hyperchylomicronemia</td>
</tr>
<tr>
<td>II—Familial hypercholesterolemia</td>
</tr>
<tr>
<td>III—Dysbeta-lipoproteinemia</td>
</tr>
<tr>
<td>IV—Hypertriglyceridemia</td>
</tr>
</tbody>
</table>
HIGH-YIELD PRINCIPLES IN

Immunology

“I hate to disappoint you, but my rubber lips are immune to your charms.”
—Batman & Robin

“An apple a day keeps the doctor away.”
—English proverb

Understand how the many components of the immune system operate and interact in the normal immune response to infection at both the clinical and cellular levels. Know the immune mechanisms of responses to vaccines. Both congenital and acquired immunodeficiencies are very testable. Cell surface markers are high yield for understanding immune cell interactions and for laboratory diagnosis. Know the roles and functions of major cytokines and chemokines.
**Immunology—Lymphoid Structures**

### Immune system organs

1° organs:
- Bone marrow—immune cell production, B cell maturation
- Thymus—T cell maturation

2° organs:
- Spleen, lymph nodes, tonsils, Peyer patches
- Allow immune cells to interact with antigen

### Lymph node

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae. Functions are nonspecific filtration by macrophages, storage of B and T cells, and immune response activation.

### Follicle

Site of B-cell localization and proliferation. In outer cortex, 1° follicles are dense and dormant. 2° follicles have pale central germinal centers and are active.

### Medulla

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses. Medullary sinuses communicate with efferent lymphatics and contain reticular cells and macrophages.

### Paracortex

Houses T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. Not well developed in patients with DiGeorge syndrome. Paracortex enlarges in an extreme cellular immune response (eg, viral infection).
Lymphatic drainage associations

<table>
<thead>
<tr>
<th>Lymph node cluster</th>
<th>Area of body drained</th>
<th>Associated pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Head and neck</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious mononucleosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>Trachea and esophagus</td>
<td>Primary lung cancer</td>
</tr>
<tr>
<td>Hilar</td>
<td>Lungs</td>
<td>Granulomatous disease</td>
</tr>
<tr>
<td>Axillary</td>
<td>Upper limb, breast, skin above umbilicus</td>
<td>Mastitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastasis (especially breast cancer)</td>
</tr>
<tr>
<td>Celiac</td>
<td>Liver, stomach, spleen, pancreas, upper duodenum</td>
<td>Mesenteric lymphadenitis</td>
</tr>
<tr>
<td>Superior mesenteric</td>
<td>Lower duodenum, jejunum, ileum, colon to splenic flexure</td>
<td>Typhoid fever</td>
</tr>
<tr>
<td>Inferior mesenteric</td>
<td>Colon from splenic flexure to upper rectum</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Para-aortic</td>
<td>Testes, ovaries, kidneys, uterus</td>
<td>Metastasis</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate</td>
<td>Sexually transmitted infections</td>
</tr>
<tr>
<td>Superficial inguinal</td>
<td>Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva</td>
<td></td>
</tr>
<tr>
<td>Popliteal</td>
<td>Dorsolateral foot, posterior calf</td>
<td>Foot/leg cellulitis</td>
</tr>
</tbody>
</table>

- **Palpable lymph node**
- **Non-palpable lymph node**

- Right lymphatic duct drains right side of body above diaphragm into junction of the right subclavian and internal jugular vein.
- Thoracic duct drains everything into junction of left subclavian and internal jugular veins. (Rupture of thoracic duct can cause chylothorax.)
Spleen

Located in LUQ of abdomen, anterior to left kidney, protected by 9th-11th ribs. Sinusoids are long, vascular channels in red pulp (red arrows in A) with fenestrated “barrel hoop” basement membrane.

- T cells are found in the periarteriolar lymphatic sheath (PALS) within the white pulp (white arrows in A).
- B cells are found in follicles within the white pulp.
- The marginal zone, in between the red pulp and white pulp, contains macrophages and specialized B cells, and is where antigen-presenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes. Splenic macrophages remove encapsulated bacteria.

Splenic dysfunction (eg, postsplenectomy state in sickle cell disease): ↓ IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms.

Postsplenectomy blood findings:
- Howell-Jolly bodies (nuclear remnants)
- Target cells
- Thrombocytosis (loss of sequestration and removal)
- Lymphocytosis (loss of sequestration)

Vaccinate patients undergoing splenectomy against encapsulated organisms (pneumococcal, Hib, meningococcal).

Thymus

Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. Thymus is derived from the Third pharyngeal pouch. Lymphocytes of mesenchymal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and Hassall corpuscles containing epithelial reticular cells. Normal neonatal thymus “sail-shaped” on CXR B, involutes with age.

T cells = Thymus
B cells = Bone marrow

Hypoplastic in DiGeorge syndrome and severe combined immunodeficiency (SCID).

Thymoma—neoplasm of thymus. Associated with myasthenia gravis and superior vena cava syndrome.
### Innate vs Adaptive Immunity

<table>
<thead>
<tr>
<th>Component</th>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Components</strong></td>
<td>Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement, physical epithelial barriers, secreted enzymes.</td>
<td>T cells, B cells, circulating antibodies</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Germline encoded</td>
<td>Variation through V(D)J recombination during lymphocyte development</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td>Resistance persists through generations; does not change within an organism’s lifetime</td>
<td>Microbial resistance not heritable</td>
</tr>
<tr>
<td><strong>Response to Pathogens</strong></td>
<td>Nonspecific Occurs rapidly (minutes to hours) No memory response</td>
<td>Highly specific, refined over time Develops over long periods; memory response is faster and more robust</td>
</tr>
<tr>
<td><strong>Secreted Proteins</strong></td>
<td>Lysozyme, complement, C-reactive protein (CRP), defensins</td>
<td>Immunoglobulins</td>
</tr>
<tr>
<td><strong>Key Features in Pathogen Recognition</strong></td>
<td>Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs) and lead to activation of NF-κB. Examples of PAMPs include LPS (gram — bacteria), flagellin (bacteria), nucleic acids (viruses).</td>
<td>Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response</td>
</tr>
</tbody>
</table>
Major histocompatibility complex I and II

MHC encoded by HLA genes. Present antigen fragments to T cells and bind T-cell receptors (TCRs).

<table>
<thead>
<tr>
<th>LOC</th>
<th>MHC I</th>
<th>MHC II</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCI</td>
<td>HLA-A, HLA-B, HLA-C</td>
<td>HLA-DP, HLA-DQ, HLA-DR</td>
</tr>
<tr>
<td>MHC I loci have 1 letter</td>
<td>MHC II loci have 2 letters</td>
<td></td>
</tr>
<tr>
<td>BINDING</td>
<td>TCR and CD8</td>
<td>TCR and CD4</td>
</tr>
<tr>
<td>STRUCTURE</td>
<td>1 long chain, 1 short chain</td>
<td>2 equal-length chains (2 α, 2 β)</td>
</tr>
<tr>
<td>EXPRESSION</td>
<td>All nucleated cells, APCs, platelets</td>
<td>APCs</td>
</tr>
<tr>
<td>Not on RBCs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUNCTION</td>
<td>Present endogenously synthesized antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells</td>
<td>Present exogenously synthesized antigens (eg, bacterial proteins) to CD4+ helper T cells</td>
</tr>
</tbody>
</table>

ANTIGEN LOADING

Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing)

Antigen loaded following release of invariant chain in an acidified endosome

ASSOCIATED PROTEINS

MHC I: β2-microglobulin
MHC II: Invariant chain

STRUCTURE

Hemochromatosis
Addison disease, myasthenia gravis, Graves disease
Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis
Celiac disease
Multiple sclerosis, hay fever, SLE, Goodpasture syndrome
Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease
Rheumatoid arthritis, diabetes mellitus type 1, Addison disease
Hashimoto thyroiditis

Don’t Be late(8), Dr. Addison, or else you’ll send my patient to the grave.
PAIR. Also known as seronegative arthropathies.
I ate (8) too (2) much gluten at Dairy Queen.
Multiple hay pastures have dirt.
2-3, S-L-E
There are 4 walls in a “rheum” (room).
Hashimoto is an odd doctor (DR3, DR5).
**Natural killer cells**

Lymphocyte member of innate immune system.
Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells.
Activity enhanced by IL-2, IL-12, IFN-α, and IFN-β.
Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of MHC I on target cell surface.
Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound Ig, activating the NK cell).

**Major functions of B and T cells**

**B cells**
- Humoral immunity.
- Recognize antigen—undergo somatic hypermutation to optimize antigen specificity.
- Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins.
- Maintain immunologic memory—memory B cells persist and accelerate future response to antigen.

**T cells**
- Cell-mediated immunity.
- CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes.
- CD8+ T cells directly kill virus-infected cells.
- Delayed cell-mediated hypersensitivity (type IV).
- Acute and chronic cellular organ rejection.

**Rule of 8**: MHC II × CD4 = 8; MHC I × CD8 = 8.

**Differentiation of T cells**

Thymic cortex. T cells expressing TCRs capable of binding self-MHC on cortical epithelial cells survive.

Thymic medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis or become regulatory T cells. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (AIRE); deficiency leads to autoimmune polyendocrine syndrome-1.
**T cell subsets**

<table>
<thead>
<tr>
<th></th>
<th>Th1 cell</th>
<th>Th2 cell</th>
<th>Th17 cell</th>
<th>Treg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SECRETS</strong></td>
<td>IFN-γ</td>
<td>IL-4, IL-5, IL-6, IL-10, IL-13</td>
<td>IL-17, IL-21, IL-22</td>
<td>TGF-β, IL-10, IL-35</td>
</tr>
<tr>
<td><strong>FUNCTION</strong></td>
<td>Activates macrophages and cytotoxic T cells to kill phagocytosed microbes</td>
<td>Activate eosinophils and promote production of IgE for parasite defense</td>
<td>Immunity against extracellular microbes, through induction of neutrophilic inflammation</td>
<td>Prevent autoimmunity by maintaining tolerance to self-antigens</td>
</tr>
<tr>
<td><strong>INDUCED BY</strong></td>
<td>IFN-γ, IL-12</td>
<td>IL-2, IL-4</td>
<td>TGF-β, IL-1, IL-6</td>
<td>TGF-β, IL-2</td>
</tr>
<tr>
<td><strong>INHIBITED BY</strong></td>
<td>IL-4, IL-10 (from Th2 cell)</td>
<td>IFN-γ (from Th1 cell)</td>
<td>IFN-γ, IL-4</td>
<td>IL-6</td>
</tr>
<tr>
<td><strong>IMMUNODEFICIENCY</strong></td>
<td>Mendelian susceptibility to mycobacterial disease</td>
<td>Hyper-IgE syndrome</td>
<td>IPEX</td>
<td></td>
</tr>
</tbody>
</table>

**Macrophage-lymphocyte interaction**

Th1 cells secrete IFN-γ, which enhances the ability of monocytes and macrophages to kill microbes they ingest. This function is also enhanced by interaction of T cell CD40L with CD40 on macrophages.

**Cytotoxic T cells**

Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis. Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B). Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

**Regulatory T cells**

Help maintain specific immune tolerance by suppressing CD4 and CD8 T-cell effector functions. Identified by expression of CD3, CD4, CD25, and FOXP3. Activated regulatory T cells (Tregs) produce anti-inflammatory cytokines (eg, IL-10, TGF-β).

**IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome** — genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants.
**T- and B-cell activation**  
APCs: B cells, dendritic cells, Langerhans cells, macrophages.  
Two signals are required for T-cell activation, B-cell activation, and class switching.

**T-cell activation**
1. Dendritic cell (specialized APC) samples antigen, processes antigen, and migrates to the draining lymph node.
2. T-cell activation (signal 1): antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell.
3. Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein (CD80/86) on dendritic cell and CD28 on naïve T cell.
4. Th cell activates and produces cytokines. Tc cell activates and is able to recognize and kill virus-infected cell.

**B-cell activation and class switching**
1. Th-cell activation as above.
2. B-cell receptor–mediated endocytosis; foreign antigen is presented on MHC II and recognized by TCR on Th cell.
3. CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
4. Th cell secretes cytokines that determine Ig class switching of B cell. B cell activates and undergoes class switching, affinity maturation, and antibody production.
Antibody structure and function

Fab (containing the variable/hypervariable regions) consisting of light (L) and heavy (H) chains recognizes antigens. Fc region of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab regions. Light chain contributes only to Fab region.

**Fab:**
- **Fragment, antigen binding**
- Determines idioype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

**Fc:**
- **Constant**
- **Carboxy terminal**
- **Complement binding**
- **Carbohydrate side chains**
- Determines isotype (IgM, IgD, etc)

**Generation of antibody diversity** (antigen independent)
1. Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
2. Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
3. Random combination of heavy chains with light chains

**Generation of antibody specificity** (antigen dependent)
4. Somatic hypermutation and affinity maturation (variable region)
5. Isotype switching (constant region)
**Immunoglobulin isotypes**  
All isotypes can exist as monomers. Mature, naive B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.

<table>
<thead>
<tr>
<th>Isotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgG</strong></td>
<td>Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity).</td>
</tr>
<tr>
<td><strong>IgA</strong></td>
<td>Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, <em>Giardia</em>). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.</td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td>Produced in the 1° (immediate) response to an antigen. Fixes complement. Cannot cross the placenta. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves.</td>
</tr>
<tr>
<td><strong>IgD</strong></td>
<td>Unclear function. Found on surface of many B cells and in serum.</td>
</tr>
<tr>
<td><strong>IgE</strong></td>
<td>Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating eosinophils. Lowest concentration in serum.</td>
</tr>
</tbody>
</table>

**Antigen type and memory**  
Thymus-independent antigens: Antigens lacking a peptide component (eg, lipopolysaccharides from gram ⊗ bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, pneumococcal polysaccharide vaccine).

Thymus-dependent antigens: Antigens containing a protein component (eg, diphtheria vaccine). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells.
Complement System of hepatically synthesized plasma proteins that play a role in innate immunity and inflammation. Membrane attack complex (MAC) defends against gram-negative bacteria.

**Activation Pathways**
- **Classic**—IgG or IgM mediated.
- **Alternative**—microbe surface molecules.
- **Lectin**—mannose or other sugars on microbe surface.

**Functions**
- C3b—opsonization.
- C3a, C4a, C5a—anaphylaxis.
- C5a—neutrophil chemotaxis.
- C5b-9—cytolysis by MAC.

**Opsonins**—C3b and IgG are the two first opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes.

**Inhibitors**—decay-accelerating factor (DAF, aka CD55) and C1 esterase inhibitor help prevent complement activation on self cells (eg, RBCs).

![Complement Activation Pathways Diagram]

*Historically, the larger fragment of C2 was called C2a but is now referred to as C2b.*
## Complement disorders

<table>
<thead>
<tr>
<th>Complement protein deficiencies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Early complement deficiencies (C1-C4)</td>
<td>Increased risk of severe, recurrent pyogenic sinus and respiratory tract infections. Increased risk of SLE.</td>
</tr>
<tr>
<td>Terminal complement deficiencies (C5–C9)</td>
<td>Increased susceptibility to recurrent <em>Neisseria</em> bacteremia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complement regulatory protein deficiencies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C1 esterase inhibitor deficiency</strong></td>
<td>Causes hereditary angioedema due to unregulated activation of kallikrein $\rightarrow$ bradykinin.</td>
</tr>
<tr>
<td></td>
<td>Characterized by ↓ C4 levels. ACE inhibitors are contraindicated.</td>
</tr>
<tr>
<td><strong>Paroxysmal nocturnal hemoglobinuria</strong></td>
<td>A defect in the <em>PIGA</em> gene preventing the formation of anchors for complement inhibitors, such as decay-acclerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59). Causes complement-mediated lysis of RBCs.</td>
</tr>
</tbody>
</table>
**Important cytokines**

<table>
<thead>
<tr>
<th>Secreted by Macrophages</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interleukin-1</strong></td>
<td>Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs. Also known as osteoclast-activating factor.</td>
</tr>
<tr>
<td><strong>Interleukin-6</strong></td>
<td>Causes fever and stimulates production of acute-phase proteins.</td>
</tr>
<tr>
<td><strong>Interleukin-8</strong></td>
<td>Major chemotactic factor for neutrophils.</td>
</tr>
<tr>
<td><strong>Interleukin-10</strong></td>
<td>Attenuates inflammatory response. Decreases expression of MHC class II and Th1 cytokines. Inhibits activated macrophages and dendritic cells. Also secreted by regulatory T cells.</td>
</tr>
<tr>
<td><strong>Interleukin-12</strong></td>
<td>Induces differentiation of T cells into Th1 cells. Activates NK cells.</td>
</tr>
<tr>
<td><strong>Tumor necrosis factor-α</strong></td>
<td>Activates endothelium. Causes WBC recruitment, vascular leak. Causes cachexia in malignancy. Maintains granulomas in TB. IL-1, IL-6, TNF-α can mediate fever and sepsis.</td>
</tr>
<tr>
<td><strong>Interleukin-2</strong></td>
<td>Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.</td>
</tr>
<tr>
<td><strong>Interleukin-3</strong></td>
<td>Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF.</td>
</tr>
<tr>
<td><strong>Interferon-γ</strong></td>
<td>Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells. Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells.</td>
</tr>
<tr>
<td><strong>Interleukin-4</strong></td>
<td>Induces differentiation of T cells into Th (helper) 2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG.</td>
</tr>
<tr>
<td><strong>Interleukin-5</strong></td>
<td>Promotes growth and differentiation of B cells. Enhances class switching to IgA. Stimulates growth and differentiation of eosinophils.</td>
</tr>
</tbody>
</table>

**From Th1 cells**

| **Interferon-γ**        | Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells. Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells. |

**From Th2 cells**

| **Interleukin-4**       | Induces differentiation of T cells into Th (helper) 2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG. |
| **Interleukin-5**       | Promotes growth and differentiation of B cells. Enhances class switching to IgA. Stimulates growth and differentiation of eosinophils. |

---

"Hot T-bone stEAK":
- IL-1: fever (hot).
- IL-2: stimulates T cells.
- IL-3: stimulates bone marrow.
- IL-4: stimulates IgE production.
- IL-5: stimulates IgA production.
- IL-6: stimulates acute-phase protein production.

"Clean up on aisle 8." Neutrophils are recruited by IL-8 to clear infections.
Respiratory burst (oxidative burst)

Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes $O_2$ as a substrate. Plays an important role in the immune response → rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase contains a blue-green heme-containing pigment that gives sputum its color.

Phagocytes of patients with CGD can utilize $H_2O_2$ generated by invading organisms and convert it to ROS. Patients are at risk for infection by catalase species (eg, S aureus, Aspergillus) capable of neutralizing their own $H_2O_2$, leaving phagocytes without ROS for fighting infections.

Pyocyanin of P aeruginosa generates ROS to kill competing pathogens. Oxidative burst also leads to $K^+$ influx, which releases lysosomal enzymes from proteoglycans. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

Interferon-α and -β

A part of innate host defense against both RNA and DNA viruses. Interferons are glycoproteins synthesized by virus-infected cells that act on local cells, “priming them” for viral defense by downregulating protein synthesis to resist potential viral replication and upregulating MHC expression to facilitate recognition of infected cells.

Interfer with viruses.
Cell surface proteins

**T cells**
- TCR (binds antigen-MHC complex)
- CD3 (associated with TCR for signal transduction)
- CD28 (binds B7 on APC)

**Helper T cells**
- CD4, CD40L, CXCR4/CCR5 (co-receptor for HIV)

**Cytotoxic T cells**
- CD8

**Regulatory T cells**
- CD4, CD25

**B cells**
- Ig (binds antigen)
- CD19, CD20, CD21 (receptor for EBV), CD40, MHC II, B7

**Macrophages**
- CD14 (receptor for PAMPs, eg, LPS), CD40, CCR5, MHC II, B7 (CD80/86)
- Fc and C3b receptors (enhanced phagocytosis)

**NK cells**
- CD16, CD56 (suggestive marker for NK)

**Hematopoietic stem cells**
- CD34

**Anergy**
State during which a cell cannot become activated by exposure to its antigen. T and B cells become anergic when exposed to their antigen without costimulatory signal (signal 2). Another mechanism of self-tolerance.

### Passive vs active immunity

<table>
<thead>
<tr>
<th>Passive</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEANS OF ACQUISITION</strong></td>
<td>Receiving preformed antibodies</td>
</tr>
<tr>
<td><strong>ONSET</strong></td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>DURATION</strong></td>
<td>Short span of antibodies (half-life = 3 weeks)</td>
</tr>
<tr>
<td><strong>EXAMPLES</strong></td>
<td>IgA in breast milk, maternal IgG crossing placenta, antitoxin, humanized monoclonal antibody</td>
</tr>
</tbody>
</table>

**NOTES**: After exposure to *Tetanus toxin, Botulinum toxin, HBV, Varicella, Rabies virus, or diphtheria toxin*, unvaccinated patients are given preformed antibodies (passive)—“To Be Healed Very Rapidly”

You can drink *Beer at the Bar* when you’re 21: B cells, Epstein-Barr virus, CD21.
Vaccination

<table>
<thead>
<tr>
<th>VACCINE TYPE</th>
<th>DESCRIPTION</th>
<th>PROS/CONS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live attenuated vaccine</td>
<td>Microorganism loses its pathogenicity but retains capacity for transient growth within inoculated host. Induces <strong>cellular and humoral responses</strong>. MMR and varicella vaccines can be given to HIV ⊕ patients without evidence of immunity if CD4 cell count ≥ 200 cells/mm³.</td>
<td>Pros: induces strong, often lifelong immunity. Cons: may revert to virulent form. Often contraindicated in pregnancy and immunodeficiency.</td>
<td>Adenovirus (nonattenuated, given to military recruits), Varicella (chickenpox), Smallpox, BCG, Yellow fever, Influenza (intranasal), MMR, Rotavirus &quot;Attention! Please Vaccinate Small, Beautiful Young Infants with MMR Regularly!&quot;</td>
</tr>
<tr>
<td>Killed or inactivated vaccine</td>
<td>Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a <strong>humoral response</strong>.</td>
<td>Pros: safer than live vaccines. Cons: weaker immune response; booster shots usually required.</td>
<td>Rabies, Influenza (injection), Polio (Salk), hepatitis A SalK = Killed RIP Always</td>
</tr>
<tr>
<td>Subunit</td>
<td>Includes only the antigens that best stimulate the immune system.</td>
<td>Pros: lower chance of adverse reactions. Cons: expensive, weaker immune response.</td>
<td>HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18), acellular pertussis (aP), Neisseria meningitidis (various strains), Streptococcus pneumoniae, Haemophilus influenzae type b.</td>
</tr>
<tr>
<td>Toxoid</td>
<td>Denatured bacterial toxin with an intact receptor binding site. Stimulates the immune system to make antibodies without potential for causing disease.</td>
<td>Pros: protects against the bacterial toxins. Cons: antitoxin levels decrease with time, may require a booster.</td>
<td>Clostridium tetani, Corynebacterium diphtheriae</td>
</tr>
</tbody>
</table>
### Hypersensitivity types

Four types (ABCD): Anaphylactic and Atopic (type I), Antibody-mediated (type II), Immune Complex (type III), Delayed (cell-mediated, type IV). Types I, II, and III are all antibody-mediated.

#### Type I hypersensitivity

Anaphylactic and atopic—two phases:
- **Immediate** (minutes): antigen crosslinks preformed IgE on presensitized mast cells → immediate degranulation → release of histamine (a vasoactive amine) and tryptase (a marker of mast cell activation).
- **Late** (hours): chemokines (attract inflammatory cells, eg, eosinophils) and cytokines (eg, leukotrienes) from mast cells → inflammation and tissue damage.

#### Type II hypersensitivity

Antibodies bind to cell-surface antigens → cellular destruction, inflammation, and cellular dysfunction.

Cellular destruction—cell is opsonized (coated) by antibodies, leading to either:
- Phagocytosis and/or activation of complement system.
- NK cell killing (antibody-dependent cellular cytotoxicity).

Inflammation—binding of antibodies to cell surfaces → activation of complement system and Fc receptor-mediated inflammation.

Cellular dysfunction—antibodies bind to cell surface receptors → abnormal blockade or activation of downstream process.

#### Type III hypersensitivity

Antibodies attach to antigens on the surface of cells, leading to cellular destruction and inflammation.

- **Direct Coombs test**—detects antibodies attached directly to the RBC surface.
- **Indirect Coombs test**—detects presence of unbound antibodies in the serum.

Examples:
- Autoimmune-hemolytic anemia
- Immune thrombocytopenia
- Transfusion reactions
- Hemolytic disease of the newborn

#### Type IV hypersensitivity

Delayed (cell-mediated, type IV)

Examples:
- Goodpasture syndrome
- Rheumatic fever
- Hyperacute transplant rejection

Examples:
- Myasthenia gravis
- Graves disease
- Pemphigus vulgaris
### Hypersensitivity types (continued)

**Type III hypersensitivity**

Immune complex—antigen-antibody (mostly IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes. Can be associated with vasculitis and systemic manifestations.

**Serum sickness**—the prototype immune complex disease. Antibodies to foreign proteins are produced and 1–2 weeks later, antibody-antigen complexes form and deposit in tissues → complement activation → inflammation and tissue damage.

**Arthus reaction**—a local subacute immune complex-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin. Characterized by edema, necrosis, and activation of complement.

In type III reaction, imagine an immune complex as 3 things stuck together: antigen-antibody-complement.

Examples:
- SLE
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis

Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure. Serum sickness-like reactions are associated with some drugs (may act as haptens, eg, penicillin) and infections (eg, hepatitis B).

**Type IV hypersensitivity**

Two mechanisms, each involving T cells:

1. Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.
2. Inflammatory reaction: effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines (shown in illustration).

Response does not involve antibodies (vs types I, II, and III).

Examples: contact dermatitis (eg, poison ivy, nickel allergy) and graft-versus-host disease.

Tests (purpose): PPD (tuberculosis infection); patch test (cause of contact dermatitis); Candida extract (T cell immune function).

4T’s: T cells, Transplant rejections, TB skin tests, Touching (contact dermatitis).

**Fourth (type) and last (delayed).**
### Blood transfusion reactions

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PATHOGENESIS</th>
<th>CLINICAL PRESENTATION</th>
<th>TIMING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic/anaphylactic reaction</strong></td>
<td>Type I hypersensitivity reaction against plasma proteins in transfused blood. IgA-deficient individuals must receive blood products without IgA.</td>
<td>Urticaria, pruritus, fever, wheezing, hypotension, respiratory arrest, shock.</td>
<td>Within minutes to 2–3 hours</td>
</tr>
<tr>
<td><strong>Febrile nonhemolytic transfusion reaction</strong></td>
<td>Two known mechanisms: type II hypersensitivity reaction with host antibodies against donor HLA and WBCs; and induced by cytokines that are created and accumulate during the storage of blood products.</td>
<td>Fever, headaches, chills, flushing.</td>
<td>Within 1–6 hours</td>
</tr>
<tr>
<td><strong>Acute hemolytic transfusion reaction</strong></td>
<td>Type II hypersensitivity reaction. Intravascular hemolysis (ABO blood group incompatibility) or extravascular hemolysis (host antibody reaction against foreign antigen on donor RBCs).</td>
<td>Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular hemolysis), jaundice (extravascular).</td>
<td>Within 1 hour</td>
</tr>
<tr>
<td><strong>Transfusion-related acute lung injury</strong></td>
<td>Donor anti-leukocyte antibodies against recipient neutrophils and pulmonary endothelial cells.</td>
<td>Respiratory distress and noncardiogenic pulmonary edema.</td>
<td>Within 6 hours</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>AUTOANTIBODY</td>
<td>ASSOCIATED DISORDER</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
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<td></td>
</tr>
<tr>
<td>Anti-ACh receptor</td>
<td>Myasthenia gravis</td>
<td></td>
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<tr>
<td>Anti-presynaptic voltage-gated calcium channel</td>
<td>Lambert-Eaton myasthenic syndrome</td>
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<tr>
<td>Anti-β2 glycoprotein</td>
<td>Antiphospholipid syndrome</td>
<td></td>
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<tr>
<td>Antinuclear (ANA)</td>
<td>Nonspecific screening antibody, often associated with SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin, lupus anticoagulant</td>
<td>SLE, antiphospholipid syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Anti-dsDNA, anti-Smith</td>
<td>SLE</td>
<td></td>
<td></td>
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<tr>
<td>Anti-histone</td>
<td>Drug-induced lupus</td>
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<td></td>
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<tr>
<td>Anti-U1 RNP (ribonucleoprotein)</td>
<td>Mixed connective tissue disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor (IgM antibody against IgG Fc region), anti-CCP (more specific)</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Anti-Ro/SSA, anti-La/SSB</td>
<td>Sjogren syndrome</td>
<td></td>
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</tr>
<tr>
<td>Anti-Scl-70 (anti-DNA topoisomerase I)</td>
<td>Scleroderma (diffuse)</td>
<td></td>
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</tr>
<tr>
<td>Anticentromere</td>
<td>Limited scleroderma (CREST syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisynthetase (eg, anti-Jo-1), anti-SRP, anti-helicase (anti-Mi-2)</td>
<td>Polymyositis, dermatomyositis</td>
<td></td>
<td></td>
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<tr>
<td>Antimitochondrial 1° biliary cirrhosis</td>
<td>1° biliary cholangitis</td>
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<td></td>
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<tr>
<td>Anti-smooth muscle</td>
<td>Autoimmune hepatitis type 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPO-ANCA/p-ANCA</td>
<td>Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), ulcerative colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR3-ANCA/c-ANCA</td>
<td>Granulomatosis with polyangiitis (Wegener)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-phospholipase A2 receptor</td>
<td>1° membranous nephropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-hemidesmosome</td>
<td>Bullous pemphigoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-desmoglein (anti-desmosome)</td>
<td>Pemphigus vulgaris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimicrosomal, antithyroglobulin, antithyroid peroxidase</td>
<td>Hashimoto thyroiditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TSH receptor</td>
<td>Graves disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA anti-endomyosial, IgA anti-tissue transglutaminase, IgA and IgG deamidated gliadin peptide</td>
<td>Celiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies</td>
<td>Type 1 diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiparietal cell, anti-intrinsic factor</td>
<td>Pernicious anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-glomerular basement membrane</td>
<td>Goodpasture syndrome</td>
<td></td>
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</tr>
</tbody>
</table>
## Immunodeficiencies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect</th>
<th>Presentation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked (Bruton) agammaglobulinemia</td>
<td>Defect in BTK, a tyrosine kinase gene → no B-cell maturation. X-linked recessive († in boys)</td>
<td>Recurrent bacterial and enteroviral infections after 6 months († maternal IgG).</td>
<td>Absent B cells in peripheral blood, † Ig of all classes. Absent/scanty lymph nodes and tonsils. Live vaccines contraindicated.</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
<td>Unknown. Most common 1° immunodeficiency.</td>
<td>Majority Asymptomatic. Can see Airway and GI infections, Autoimmune disease, Atopy, Anaphylaxis to IgA-containing products.</td>
<td>† IgA with normal IgG, IgM levels. † susceptibility to giardiasis.</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Defect in B-cell differentiation. Cause is unknown in most cases.</td>
<td>Usually presents after age 2 and may be considerably delayed; † risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections.</td>
<td>† plasma cells, † immunoglobulins.</td>
</tr>
<tr>
<td><strong>T-cell disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymic aplasia (DiGeorge syndrome)</td>
<td>22q11 deletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids.</td>
<td>Tetany (hypocalcemia), recurrent viral/fungal infections (T-cell deficiency), conotruncal abnormalities (eg, tetralogy of Fallot, truncus arteriosus).</td>
<td>† T cells, † PTH, † Ca²⁺. Thymic shadow absent on CXR.</td>
</tr>
<tr>
<td>IL-12 receptor deficiency</td>
<td>† Th1 response. Autosomal recessive.</td>
<td>Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine.</td>
<td>† IFN-γ</td>
</tr>
<tr>
<td>Autosomal dominant hyper-IgE syndrome</td>
<td>Deficiency of Th17 cells due to STAT3 mutation → impaired recruitment of neutrophils to sites of infection.</td>
<td><strong>FATED:</strong> coarse Facies, cold (noninflamed) staphylococcal Abscesses, retained primary Teeth, † IgE, <strong>Dermatologic problems</strong> (eczema). Bone fractures from minor trauma.</td>
<td>† IgE. † eosinophils.</td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td>T-cell dysfunction. Can result from congenital genetic defects in IL-17 or IL-17 receptors.</td>
<td>Noninvasive <em>Candida albicans</em> infections of skin and mucous membranes.</td>
<td>Absent in vitro T-cell proliferation in response to <em>Candida</em> antigens. Absent cutaneous reaction to <em>Candida</em> antigens.</td>
</tr>
</tbody>
</table>
### Immunodeficiencies (continued)

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DEFECT</th>
<th>PRESENTATION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B- and T-cell disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>Several types including defective IL-2R gamma chain (most common, X-linked recessive), adenosine deaminase deficiency (autosomal recessive).</td>
<td>Failure to thrive, chronic diarrhea, thrush. Recurrent viral, bacterial, fungal, and protozoal infections. Treatment: avoid live vaccines, give antimicrobial prophylaxis and IVIG; bone marrow transplant curative (no concern for rejection).</td>
<td>↑ T-cell receptor excision circles (TRECs). Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry).</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Defects in ATM gene → failure to detect DNA damage → failure to halt progression of cell cycle → mutations accumulate; autosomal recessive.</td>
<td>Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia), IgA deficiency.</td>
<td>↑ AFP. ↓ IgA, IgG, and IgE. Lymphopenia, cerebellar atrophy. ↑ risk of lymphoma and leukemia.</td>
</tr>
<tr>
<td>Hyper-IgM syndrome</td>
<td>Most commonly due to defective CD40L on Th cells → class switching defect; X-linked recessive.</td>
<td>Severe pyogenic infections early in life; opportunistic infection with Pneumocystis, Cryptosporidium, CMV.</td>
<td>Normal or ↑ IgM. ↓ IgG, IgA, IgE. Failure to make germinal centers.</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Mutation in WASp gene; leukocytes and platelets unable to reorganize actin cytoskeleton → defective antigen presentation; X-linked recessive.</td>
<td>WATER: Wiskott-Aldrich: Thrombocytopenia, Eczema, Recurrent (pyogenic) infections. ↑ risk of autoimmune disease and malignancy.</td>
<td>↓ to normal IgG, IgM. ↑ IgE, IgA. Fewer and smaller platelets.</td>
</tr>
<tr>
<td>Phagocyte dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency (type 1)</td>
<td>Defect in LFA-1 integrin (CD18) protein on phagocytes; impaired migration and chemotaxis; autosomal recessive.</td>
<td>Recurrent skin and mucosal bacterial infections, absent pus, impaired wound healing, delayed (&gt; 30 days) separation of umbilical cord.</td>
<td>↑ neutrophils in blood. Absence of neutrophils at infection sites.</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Defect of NADPH oxidase → ↓ reactive oxygen species (eg, superoxide) and ↓ respiratory burst in neutrophils; X-linked form most common.</td>
<td>↑ susceptibility to catalase organisms.</td>
<td>Abnormal dihydrorhodamine (flow cytometry) test (↑ green fluorescence). Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue.</td>
</tr>
</tbody>
</table>
### Infections in immunodeficiency

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>↓ T CELLS</th>
<th>↓ B CELLS</th>
<th>↓ GRANULOCYTES</th>
<th>↓ COMPLEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>Sepsis</td>
<td>Encapsulated (Please SHINE my SKiS): Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus Influenzae type b, Neisseria meningitidis, Escherichia coli, Salmonella, Klebsiella pneumoniae, Group B Streptococcus</td>
<td>Staphylococcus, Burkholderia cepacia, Pseudomonas aeruginosa, Serratia, Nocardia</td>
<td>Encapsulated species with early complement deficiencies Neisseria with late complement (C5–C9) deficiencies</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>CMV, EBV, JC virus, VZV, chronic infection with respiratory/GI viruses</td>
<td>Enteroviral encephalitis, poliovirus (live vaccine contraindicated)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Fungi/parasites</strong></td>
<td>Candida (local), PCP, Cryptococcus</td>
<td>GI giardiasis (no IgA)</td>
<td>Candida (systemic), Aspergillus, Mucor</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: B-cell deficiencies tend to produce recurrent bacterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

### Grafts

- **Autograft**: From self.
- **Syngeneic graft (isograft)**: From identical twin or clone.
- **Allograft**: From nonidentical individual of same species.
- **Xenograft**: From different species.
## Transplant rejection

<table>
<thead>
<tr>
<th>Type of Rejection</th>
<th>Onset</th>
<th>Pathogenesis</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperacute</strong></td>
<td>Within minutes</td>
<td>Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement.</td>
<td>Widespread thrombosis of graft vessels → ischemia/necrosis. Graft must be removed.</td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td>Weeks to months</td>
<td>Cellular: CD8+ T cells and/or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction). Humoral: similar to hyperacute, except antibodies develop after transplant.</td>
<td>Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate. Prevent/reverse with immunosuppressants.</td>
</tr>
</tbody>
</table>
| **Chronic**       | Months to years | CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC. Both cellular and humoral components (type II and IV hypersensitivity reactions). | Recipient T cells react and secrete cytokines → proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis. Dominated by arteriosclerosis. Organ-specific examples:  
  - Bronchiolitis obliterans (lung)  
  - Accelerated atherosclerosis (heart)  
  - Chronic graft nephropathy (kidney)  
  - Vanishing bile duct syndrome (liver) |
| **Graft-versus-host disease** | Varies | Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with “foreign” proteins → severe organ dysfunction. Type IV hypersensitivity reaction. | Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly. Usually in bone marrow and liver transplants (rich in lymphocytes). Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect). |
### Immunosuppressants

Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity (used as prophylaxis). Frequently combined to achieve greater efficacy with ↓ toxicity. Chronic suppression ↑ risk of infection and malignancy.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>OTHER USE</th>
<th>TOXICITY</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>Calcineurin inhibitor; binds cyclophilin. Blocks T-cell activation by preventing IL-2 transcription.</td>
<td>Psoriasis, rheumatoid arthritis.</td>
<td>Nephrotoxicity, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism.</td>
<td>Both calcineurin inhibitors are highly nephrotoxic.</td>
</tr>
<tr>
<td>Tacrolimus (FK506)</td>
<td>Calcineurin inhibitor; binds FK506 binding protein (FKBP). Blocks T-cell activation by preventing IL-2 transcription.</td>
<td></td>
<td>Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism.</td>
<td>Kidney “sir-vives.” Synergistic with cyclosporine. Also used in drug-eluting stents.</td>
</tr>
<tr>
<td>Sirolimus (Rapamycin)</td>
<td>mTOR inhibitor; binds FKBP. Blocks T-cell activation and B-cell differentiation by preventing response to IL-2.</td>
<td>Kidney transplant rejection prophylaxis specifically.</td>
<td>“PanSirtopenia” (pancytopenia), insulin resistance, hyperlipidemia; not nephrotoxic.</td>
<td></td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Monoclonal antibody; blocks IL-2R.</td>
<td></td>
<td>Edema, hypertension, tremor.</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Antimetabolite precursor of 6-mercaptopurine. Inhibits lymphocyte proliferation by blocking nucleotide synthesis.</td>
<td>Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions.</td>
<td>Pancytopenia.</td>
<td></td>
</tr>
<tr>
<td>Mofetil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Inhibit NF-κB. Suppress both B- and T-cell function by ↓ transcription of many cytokines. Induce T cell apoptosis.</td>
<td>Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma.</td>
<td>Cushing syndrome, osteoporosis, hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head).</td>
<td>Demargination of WBCs causes artificial leukocytosis. Adrenal insufficiency may develop if drug is stopped abruptly after chronic use.</td>
</tr>
</tbody>
</table>
**Immunosuppression targets**

- **DNA replication**
  - Calcineurin
  - Proliferation genes
  - Inflammatory cytokine genes

- **NF-κB**
  - 6-MP
  - Purine nucleotides
  - De novo purine synthesis

- **mTOR/NFAT–P**
  - IMP dehydrogenase
  - PRPP amidotransferase

- **Azathioprine**
  - Cyclosporine
  - Tacrolimus
  - Sirolimus (rapamycin)

- **FKBP +**
  - Cyclophilin

- **Cytosine arabinoside (Ara-C)**
  - Mycophenolate

- **12-Me-Ara-C**
  - Azathoprine

- **12-Me-Ara-A**
  - Azathoprine

- **CD4**
  - TCR

- **CD3**

- **Janus kinase (JAK) inhibitors**
  - sirolimus (rapamycin)

- **Arginase inhibitor**
  - 12-Me-Ara-A

- **Bone marrow stimulation**
  - **Erythropoietin** (Epoetin alfa [EPO analog]): Anemias (especially in renal failure)
  - **Colony stimulating factors**
    - Filgrastim (G-CSF), Sargramostim (GM-CSF): Leukopenia; recovery of granulocyte and monocyte counts
  - **Thrombopoietin**
    - Romiplostim (TPO analog), eltrombopag (TPO receptor agonist): Autoimmune thrombocytopenia

- **Immunotherapy**
  - **Interleukin-2** (Aldesleukin): Renal cell carcinoma, metastatic melanoma
  - **Interferon**
    - IFN-α: Chronic hepatitis C (not preferred) and B, renal cell carcinoma
    - IFN-β: Multiple sclerosis
    - IFN-γ: Chronic granulomatous disease

---

**Recombinant cytokines and clinical uses**

<table>
<thead>
<tr>
<th>CYTOKINE</th>
<th>AGENT</th>
<th>CLINICAL USES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone marrow stimulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Epoetin alfa (EPO analog)</td>
<td>Anemias (especially in renal failure)</td>
</tr>
<tr>
<td>Colony stimulating factors</td>
<td>Filgrastim (G-CSF), Sargramostim (GM-CSF)</td>
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</tr>
<tr>
<td>Thrombopoietin</td>
<td>Romiplostim (TPO analog), eltrombopag (TPO receptor agonist)</td>
<td>Autoimmune thrombocytopenia</td>
</tr>
<tr>
<td><strong>Immunotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>Aldesleukin</td>
<td>Renal cell carcinoma, metastatic melanoma</td>
</tr>
<tr>
<td>Interferon</td>
<td>IFN-α</td>
<td>Chronic hepatitis C (not preferred) and B, renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>IFN-β</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>IFN-γ</td>
<td>Chronic granulomatous disease</td>
</tr>
</tbody>
</table>
## Therapeutic Antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Clinical Use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
<td>CLL, MS</td>
<td>“Alymtuzumab”—chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Colorectal cancer, renal cell carcinoma, non-small cell lung cancer</td>
<td>Also used for neovascular age-related macular degeneration, proliferative diabetic retinopathy, and macular edema</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Stage IV colorectal cancer, head and neck cancer</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>B-cell non-Hodgkin lymphoma, CLL, rheumatoid arthritis, ITP, multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>Breast cancer, gastric cancer</td>
<td>HER2—“tras2zumab”</td>
</tr>
<tr>
<td><strong>Autoimmune Disease Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab, certolizumab, golimumab, infliximab</td>
<td>Soluble TNF-α</td>
<td>IBD, rheumatoid arthritis, ankylosing spondylitis, psoriasis</td>
<td>Etanercept is a decoy TNF-α receptor and not a monoclonal antibody</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>CD25 (part of IL-2 receptor)</td>
<td>Relapsing multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Complement protein C5</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>Natalizumab</td>
<td>α4-integrin</td>
<td>Multiple sclerosis, Crohn disease</td>
<td>α4-integrin: WBC adhesion Risk of PML in patients with JC virus</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-12/IL-23</td>
<td>Psoriasis, psoriatic arthritis</td>
<td></td>
</tr>
<tr>
<td><strong>Other Applications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td>Platelet glycoproteins IIb/IIIa</td>
<td>Antiplaetelet agent for prevention of ischemic complications in patients undergoing percutaneous coronary intervention</td>
<td>IIb times IIIa equals “absiximab”</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL.</td>
<td>Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin)</td>
<td>Denosumab affects osteoclasts</td>
</tr>
<tr>
<td>Digoxin immune Fab</td>
<td>Digoxin</td>
<td>Antidote for digoxin toxicity</td>
<td></td>
</tr>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>Refractory allergic asthma; prevents IgE binding to FcεRI</td>
<td></td>
</tr>
<tr>
<td>Palivizumab</td>
<td>RSV F protein</td>
<td>RSV prophylaxis for high-risk infants</td>
<td>PaliVIzumab—VIrus</td>
</tr>
</tbody>
</table>
“Support bacteria. They’re the only culture some people have.”
—Steven Wright

“What lies behind us and what lies ahead of us are tiny matters compared to what lies within us.”
—Henry S. Haskins

“Infectious disease is merely a disagreeable instance of a widely prevalent tendency of all living creatures to save themselves the bother of building, by their own efforts, the things they require.”
—Hans Zinsser

Microbiology questions on the Step 1 exam often require two (or more) steps: Given a certain clinical presentation, you will first need to identify the most likely causative organism, and you will then need to provide an answer regarding some feature of that organism. For example, a description of a child with fever and a petechial rash will be followed by a question that reads, “From what site does the responsible organism usually enter the blood?”

This section therefore presents organisms in two major ways: in individual microbial “profiles” and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features of each microbe by returning to the individual profiles. Also be sure to memorize the laboratory characteristics that allow you to identify microbes.
### Bacterial structures

<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>CHEMICAL COMPOSITION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flagellum</td>
<td>Proteins.</td>
<td>Motility.</td>
</tr>
<tr>
<td>Pili/fimbria</td>
<td>Glycoprotein.</td>
<td>Mediate adherence of bacteria to cell surface; sex pilus forms during conjugation.</td>
</tr>
</tbody>
</table>

### Specialized structures

<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>CHEMICAL COMPOSITION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spore</td>
<td>Keratin-like coat; dipicolinic acid; peptidoglycan, DNA.</td>
<td>Gram ⊕ only. Survival: resist dehydration, heat, chemicals.</td>
</tr>
</tbody>
</table>

### Cell envelope

<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>CHEMICAL COMPOSITION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule</td>
<td>Organized, discrete polysaccharide layer (except poly-o-glutamate on <em>B. anthracis</em>).</td>
<td>Protects against phagocytosis.</td>
</tr>
<tr>
<td>Glycocalyx</td>
<td>Loose network of polysaccharides.</td>
<td>Mediates adherence to surfaces, especially foreign surfaces (eg, indwelling catheters).</td>
</tr>
<tr>
<td>Periplasm</td>
<td>Space between cytoplasmic membrane and outer membrane in gram ⊕ bacteria. (Peptidoglycan in middle.)</td>
<td>Accumulates components exiting gram ⊕ cells, including hydrolytic enzymes (eg, β-lactamases).</td>
</tr>
<tr>
<td>Cell wall</td>
<td>Peptidoglycan is a sugar backbone with peptide side chains cross-linked by transpeptidase.</td>
<td>Net-like structure gives rigid support, protects against osmotic pressure damage.</td>
</tr>
<tr>
<td>Cytoplasmic membrane</td>
<td>Phospholipid bilayer sac with embedded proteins (eg, penicillin-binding proteins [PBPs]) and other enzymes. Lipoteichoic acids (gram ⊕ only) extend from membrane to exterior.</td>
<td>Site of oxidative and transport enzymes; PBPs involved in cell wall synthesis. Lipoteichoic acids induce TNF-α and IL-1.</td>
</tr>
</tbody>
</table>

### Cell envelope

![Cell envelope diagram]

**Unique to gram ⊕**
- Lipoteichoic acid

**Common to both**
- Flagellum
- Pili
- Capsule

**Unique to gram ⊕**
- Endotoxin/LPS
- Periplasmic space ([β-lactamase location])
- Outer membrane

**Unique to gram ⊕**
- Porin

---

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10/10/17 10:48 AM
## Bacterial taxonomy

<table>
<thead>
<tr>
<th>MORPHOLOGY</th>
<th>Gram examples</th>
<th>Gram examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spherical (coccus)</strong></td>
<td><em>Staphylococcus</em> (clusters)</td>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus</em> (chains or pairs)</td>
<td><em>Neisseria</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em> (pairs or short chains)</td>
<td></td>
</tr>
<tr>
<td><strong>Rod (bacillus)</strong></td>
<td><em>Bacillus</em></td>
<td><em>Enterics:</em></td>
</tr>
<tr>
<td></td>
<td><em>Clostridium</em></td>
<td>- <em>Bacteroides</em></td>
</tr>
<tr>
<td></td>
<td><em>Corynebacterium</em></td>
<td>- <em>Campylobacter</em></td>
</tr>
<tr>
<td></td>
<td><em>Gardnerella</em> (gram variable)</td>
<td>- <em>E. coli</em></td>
</tr>
<tr>
<td></td>
<td><em>Lactobacillus</em></td>
<td>- <em>Enterobacter</em></td>
</tr>
<tr>
<td></td>
<td><em>Listeria</em></td>
<td>- <em>Fusobacterium</em></td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium</em> (acid fast)</td>
<td>- <em>Helicobacter</em></td>
</tr>
<tr>
<td></td>
<td><em>Cutibacterium</em> (formerly <em>Propionibacterium</em>)</td>
<td>- <em>Klebsiella</em></td>
</tr>
<tr>
<td><strong>Branching filamentous</strong></td>
<td><em>Actinomyces</em></td>
<td>- <em>Proteus</em></td>
</tr>
<tr>
<td></td>
<td><em>Nocardia</em> (weakly acid fast)</td>
<td>- <em>Pseudomonas</em></td>
</tr>
<tr>
<td><strong>Pleomorphic (no cell wall)</strong></td>
<td><em>Anaplasma, Ehrlichia</em></td>
<td>- <em>Salmonella</em></td>
</tr>
<tr>
<td></td>
<td><em>Chlamydiae</em> (Giemsa)</td>
<td>- <em>Serratia</em></td>
</tr>
<tr>
<td></td>
<td><em>Rickettsiae</em> (Giemsa)</td>
<td>- <em>Shigella</em></td>
</tr>
<tr>
<td></td>
<td><em>Mycoplasma</em> (contains sterols, which do not Gram stain), <em>Ureaplasma</em></td>
<td>- <em>Vibrio</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <em>Yersinia</em></td>
</tr>
<tr>
<td><strong>Spiral</strong></td>
<td><em>Spirochetes:</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <em>Borrelia</em> (Giemsa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <em>Leptospira</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <em>Treponema</em></td>
<td></td>
</tr>
</tbody>
</table>
Stains

Gram stain
First-line lab test in bacterial identification. Bacteria with thick peptidoglycan layer retain crystal violet dye (gram +); bacteria with thin peptidoglycan layer turn red or pink (gram −) with counterstain. These bugs do not Gram stain well (These Little Microbes May Unfortunately Lack Real Color But Are Everywhere).
- Treponema, Leptospira
  - Too thin to be visualized.
- Mycobacteria
  - Cell wall has high lipid content.
- Mycoplasma, Ureaplasma
  - No cell wall.
- Legionella, Rickettsia, Chlamydia, Bartonella, Anaplasma, Ehrlichia
  - Primarily intracellular; also, Chlamydia lack classic peptidoglycan because of muramic acid.

Giemsa stain
- Rickettsia, Chlamydia, Trypanosomes
  - Ricky got Chlamydia as he Tried to Please the Bored "Geisha."

Periodic acid–Schiff stain
Stains glycogen, mucopolysaccharides; used to diagnose Whipple disease (Tropheryma whippelii)
- PaSs the sugar.

Ziehl-Neelsen stain (carbol fuchsin)
Acid-fast bacteria (eg, Mycobacteria, Nocardia; stains mycolic acid in cell wall); protozoa (eg, Cryptosporidium oocysts)
- Auramine-rhodamine stain is more often used for screening (inexpensive, more sensitive).

India ink stain
Cryptococcus neoformans; mucicarmine can also be used to stain thick polysaccharide capsule red

Silver stain
Fungi (eg, Coccidioides, Pneumocystis jirovecii), Legionella, Helicobacter pylori

Fluorescent antibody stain
Used to identify many bacteria and viruses. Example is FTA-ABS for syphilis.

Properties of growth media
The same type of media can possess both (or neither) of these properties.

Selective media
Favors the growth of particular organism while preventing growth of other organisms, eg, Thayer-Martin agar contains antibiotics that allow the selective growth of Neisseria by inhibiting the growth of other sensitive organisms.

Indicator (differential) media
Yields a color change in response to the metabolism of certain organisms, eg, MacConkey agar contains a pH indicator; a lactose fermenter like E. coli will convert lactose to acidic metabolites → color change.
### Special culture requirements

<table>
<thead>
<tr>
<th>Bug</th>
<th>Media used for isolation</th>
<th>Media contents/other</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em></td>
<td>Chocolate agar</td>
<td>Factors V (NAD⁺) and X (hematin)</td>
</tr>
<tr>
<td><em>N. gonorrhoeae, N. meningitidis</em></td>
<td>Thayer-Martin agar</td>
<td>Selectively favors growth of <em>Neisseria</em> by inhibiting growth of gram ⊕ organisms with <em>Vancomycin</em>, gram ⊋ organisms except <em>Neisseria</em> with <em>Trimethoprim</em> and <em>Colistin</em>, and fungi with <em>Nystatin</em> Very Typically Cultures <em>Neisseria</em></td>
</tr>
<tr>
<td><em>B. pertussis</em></td>
<td>Bordet-Gengou agar (<em>Bordet for Bordetella</em>) Regan-Lowe medium</td>
<td>Potato extract</td>
</tr>
<tr>
<td><em>C. diphtheriae</em></td>
<td>Tellurite agar, Loeffler medium</td>
<td>Charcoal, blood, and antibiotic</td>
</tr>
<tr>
<td><em>M. tuberculosis</em></td>
<td>Löwenstein-Jensen agar</td>
<td></td>
</tr>
<tr>
<td><em>M. pneumoniae</em></td>
<td>Eaton agar</td>
<td>Requires cholesterol</td>
</tr>
<tr>
<td>Lactose-fermenting enterics</td>
<td>MacConkey agar</td>
<td>Fermentation produces acid, causing colonies to turn pink</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Eosin–methylene blue (EMB) agar</td>
<td>Colonies with green metallic sheen</td>
</tr>
<tr>
<td><em>Legionella</em></td>
<td>Charcoal yeast extract agar buffered with cysteine and iron</td>
<td></td>
</tr>
<tr>
<td><em>Fungi</em></td>
<td>Sabouraud agar</td>
<td>“Sab’s a fun guy!”</td>
</tr>
</tbody>
</table>

#### Aerobes

Use an O₂-dependent system to generate ATP. Examples include *Nocardia, Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis*. Reactivation of *M. tuberculosis* (eg, after immunocompromise or TNF-α inhibitor use) has a predilection for the apices of the lung. Nagging Pests Must Breathe.

#### Anaerobes

Examples include *Clostridium, Bacteroides, Fusobacterium*, and *Actinomyces israelii*. They lack catalase and/or superoxide dismutase and are thus susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO₂ and H₂). Anaerobes Can’t Breathe Fresh Air. Anaerobes are normal flora in GI tract, typically pathogenic elsewhere. AminO₂glycosides are ineffective against anaerobes because these antibiotics require O₂ to enter into bacterial cell.

#### Facultative anaerobes

May use O₂ as a terminal electron acceptor to generate ATP, but can also use fermentation and other O₂-independent pathways. Streptococci, staphylococci, and enteric gram ⊋ bacteria.
Intracellular bugs

**Obligate intracellular**
- *Rickettsia, CHlamydia, COxiella*. Rely on host ATP. Stay inside (cells) when it is Really CHilly and COld.

**Facultative intracellular**
- *Salmonella, Neisseria, Brucella, Mycobacterium, Listeria, Francisella, Legionella, Yersinia pestis.* Some Nasty Bugs May Live FacultativeLY.

Encapsulated bacteria

Examples are *Pseudomonas aeruginosa, Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis, Escherichia coli, Salmonella, Klebsiella pneumoniae*, and group B *Strep*. Their capsules serve as an antiphagocytic virulence factor. Capsular polysaccharide + protein conjugate serves as an antigen in vaccines.

Encapsulated bacteria vaccines

Some vaccines containing polysaccharide capsule antigens are conjugated to a carrier protein, enhancing immunogenicity by promoting T-cell activation and subsequent class switching. A polysaccharide antigen alone cannot be presented to T cells.

Urease-positive organisms

- *Proteus, Cryptococcus, H pylori, Ureaplasma, Nocardia, Klebsiella, S epidermidis, S saprophyticus*. Urease hydrolyzes urea to release ammonia and CO₂ → ↑ pH. Predisposes to struvite (ammonium magnesium phosphate) stones, particularly *Proteus*.

Catalase-positive organisms

Catalase degrades H₂O₂ into H₂O and bubbles of O₂ before it can be converted to microbialidal products by the enzyme myeloperoxidase. People with chronic granulomatous disease (NADPH oxidase deficiency) have recurrent infections with certain catalase organisms.

Examples: *Nocardia, Pseudomonas, Listeria, Aspergillus, Candida, E coli, Staphylococci, Serratia, B cepacia, H pylori.*

Please SHiNE my SKiS. Are opsonized, and then cleared by spleen. Asplenics (No Spleen Here) have ↓ opsonizing ability and thus ↑ risk for severe infections; need vaccines to protect against:
- *N meningitidis*
- *S pneumoniae*
- *H influenzae*

Pneumococcal vaccines: PCV13 (pneumococcal conjugate vaccine), PPSV23 (pneumococcal polysaccharide vaccine with no conjugated protein)
- *H influenzae* type b (conjugate vaccine)
- Meningococcal vaccine (conjugate vaccine)

Pee CHUNKSS.

Cats Need PLACESS to Belch their Hairballs.
## Pigment-producing bacteria

<table>
<thead>
<tr>
<th>Species</th>
<th>Description</th>
<th>Example/Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Actinomyces israelii</em></td>
<td>Yellow “sulfur” granules, which are composed of filaments of bacteria.</td>
<td>Israel has yellow sand.</td>
</tr>
<tr>
<td><em>S aureus</em></td>
<td>Yellow pigment.</td>
<td><em>Aureus</em> (Latin) = gold.</td>
</tr>
<tr>
<td><em>P aeruginosa</em></td>
<td>Blue-green pigment (pyocyanin and pyoverdin).</td>
<td><em>Aerugula is green.</em></td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>Red pigment.</td>
<td>Think red Sriracha hot sauce.</td>
</tr>
</tbody>
</table>

## In vivo biofilm-producing bacteria

<table>
<thead>
<tr>
<th>Species</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S epidermidis</em></td>
<td>Catheter and prosthetic device infections</td>
</tr>
<tr>
<td><em>Viridans streptococci</em> (<em>S mutans, S sanguinis</em>)</td>
<td>Dental plaques, infective endocarditis</td>
</tr>
<tr>
<td><em>P aeruginosa</em></td>
<td>Respiratory tree colonization in patients with cystic fibrosis, ventilator-associated pneumonia, contact lens–associated keratitis</td>
</tr>
<tr>
<td>Nontypeable (unencapsulated) <em>H influenzae</em></td>
<td>Otitis media</td>
</tr>
</tbody>
</table>

## Bacterial virulence factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein A</td>
<td>Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by <em>S aureus</em>.</td>
</tr>
<tr>
<td>IgA protease</td>
<td>Enzyme that cleaves IgA, allowing bacteria to adhere to and colonize mucous membranes. Secreted by <em>S pneumoniae, H influenzae</em> type b, and <em>Neisseria</em> (<em>SHiN</em>).</td>
</tr>
<tr>
<td>M protein</td>
<td>Helps prevent phagocytosis. Expressed by group A streptococci. Shares similar epitopes to human cellular proteins (molecular mimicry); possibly underlies the autoimmune response seen in acute rheumatic fever.</td>
</tr>
</tbody>
</table>

## Type III secretion system

Also known as “injectisome.” Needle-like protein appendage facilitating direct delivery of toxins from certain gram − bacteria (e.g., *Pseudomonas, Salmonella, Shigella, E coli*) to eukaryotic host cell.
Bacterial genetics

Transformation

Competent bacteria can bind and import short pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially *S. pneumoniae*, *H. influenzae* type b, and *Neisseria* (SHiN). Adding deoxyribonuclease degrades naked DNA, preventing transformation.

Conjugation

\( F^+ \times F^- \)

\( F^+ \) plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed \( F^- \). Sex pilus on \( F^+ \) bacterium contacts \( F^- \) bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge (“mating bridge”). No transfer of chromosomal DNA.

\( Hfr \times F^- \)

\( F^+ \) plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. Recipient cell remains \( F^- \) but now may have new bacterial genes.

Transduction

Generalized

A packaging “error.” Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.

Specialized

An “excision” event. Lysogenic phage infects bacterium; viral DNA incorporates into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium. Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (ABCD’S): Group A strep erythrogenic toxin, Botulinum toxin, Cholera toxin, Diphtheria toxin, Shiga toxin.
Bacterial genetics (continued)

Transposition
Segment of DNA (e.g., transposon) that can “jump” (copy/excite and reinsert) from one location to another, can transfer genes from plasmid to chromosome and vice versa. This is a critical process in creating plasmids with multiple antibiotic resistance which can be transferred across species lines (e.g., Tn1546 carrying vanA gene from vancomycin-resistant Enterococcus to S aureus).

Spore-forming bacteria
Some bacteria can form spores A when nutrients are limited.
Spores lack metabolic activity.
Spores are highly resistant to heat and chemicals. Core contains dipicolinic acid. Must autoclave to kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes.

Main features of exotoxins and endotoxins

<table>
<thead>
<tr>
<th>Source</th>
<th>Exotoxins</th>
<th>Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secreted from cell</td>
<td>Certain species of gram ⊗ and gram ⊝ bacteria</td>
<td>Outer cell membrane of most gram ⊗ bacteria</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Polypeptide</td>
<td>No</td>
</tr>
<tr>
<td>Location of genes</td>
<td>Plasmid or bacteriophage</td>
<td>Lipid A component of LPS (structural part of bacteria; released when lysed)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>High (fatal dose on the order of 1 µg)</td>
<td>Low (fatal dose on the order of hundreds of micrograms)</td>
</tr>
<tr>
<td>Clinical effects</td>
<td>Various effects (see following pages)</td>
<td>Fever, shock (hypotension), DIC</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Various modes (see following pages)</td>
<td>Induces TNF, IL-1, and IL-6</td>
</tr>
<tr>
<td>Antigenicity</td>
<td>Induces high-titer antibodies called antitoxins</td>
<td>Poorly antigenic</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Toxoids used as vaccines</td>
<td>No toxoids formed and no vaccine available</td>
</tr>
<tr>
<td>Heat stability</td>
<td>Destroyed rapidly at 60°C (except staphylococcal enterotoxin and E coli heat-stable toxin)</td>
<td>Stable at 100°C for 1 hr</td>
</tr>
<tr>
<td>Typical diseases</td>
<td>Tetanus, botulism, diphtheria</td>
<td>Meningococcemia; sepsis by gram ⊝ rods</td>
</tr>
</tbody>
</table>
# Bugs with Exotoxins

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>TOXIN</th>
<th>MECHANISM</th>
<th>MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibit protein synthesis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Diphtheria toxin(^a)</td>
<td>Inactivate elongation factor (EF-2)</td>
<td>Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Exotoxin A(^a)</td>
<td></td>
<td>Host cell death</td>
</tr>
<tr>
<td><em>Shigella spp.</em></td>
<td>Shiga toxin (ST)(^a)</td>
<td>Inactivate 60S ribosome by removing adenine from tRNA</td>
<td>GI mucosal damage → dysentery; ST also enhances cytokine release, causing hemolytic-uremic syndrome (HUS)</td>
</tr>
<tr>
<td>Enterohemorrhagic <em>E. coli</em></td>
<td>Shiga-like toxin (SLT)(^a)</td>
<td></td>
<td>SLT enhances cytokine release, causing HUS (prototypically in EHEC serotype O157:H7). Unlike <em>Shigella</em>, EHEC does not invade host cells</td>
</tr>
<tr>
<td><strong>Increase fluid secretion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em></td>
<td>Heat-labile toxin (LT)(^a)</td>
<td>Overactivates adenylate cyclase ((\dagger) cAMP) → (\dagger) Cl(^{−}) secretion in gut and H(_2)O efflux</td>
<td>Watery diarrhea: “labile in the Air (Adenylate cyclase), stable on the Ground (Guanylate cyclase)”</td>
</tr>
<tr>
<td></td>
<td>Heat-stable toxin (ST)</td>
<td>Overactivates guanylate cyclase ((\dagger) cGMP) → (\dagger) resorption of NaCl and H(_2)O in gut</td>
<td></td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td>Edema toxin(^a)</td>
<td>Mimics adenylate cyclase ((\dagger) cAMP)</td>
<td>Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Cholera toxin(^a)</td>
<td>Overactivates adenylate cyclase ((\dagger) cAMP) by permanently activating G(_{\text{q}}) → (\dagger) Cl(^{−}) secretion in gut and H(_2)O efflux</td>
<td>Voluminous “rice-water” diarrhea</td>
</tr>
<tr>
<td><strong>Inhibit phagocytic ability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
<td>Pertussis toxin(^a)</td>
<td>Overactivates adenylate cyclase ((\dagger) cAMP) by disabling G(_{\text{q}}), impairing phagocytosis to permit survival of microbe</td>
<td>Whooping cough—child coughs on expiration and “whoops” on inspiration (toxin may not actually be a cause of cough; can cause “100-day cough” in adults)</td>
</tr>
<tr>
<td><strong>Inhibit release of neurotransmitter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td>Tetanospsamin(^a)</td>
<td>Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion</td>
<td>Toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord → spastic paralysis, risus sardonicus, trismus (lockjaw)</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Botulinum toxin(^a)</td>
<td></td>
<td>Toxin prevents release of stimulatory (ACh) signals at neuromuscular junction → flaccid paralysis (floppy baby)</td>
</tr>
</tbody>
</table>

\(^a\)An AB toxin (aka, two-component toxin [or three for anthrax]) with B enabling binding and triggering uptake (endocytosis) of the active A component. The A components are usually ADP ribosyltransferases; others have enzymatic activities as listed in chart.
### Bugs with exotoxins (continued)

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>TOxin</th>
<th>MECHANISM</th>
<th>MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lyse cell membranes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>Alpha toxin</td>
<td>Phospholipase (lecithinase) that degrades tissue and cell membranes</td>
<td>Degradation of phospholipids → myonecrosis (“gas gangrene”) and hemolysis (“double zone” of hemolysis on blood agar)</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Streptolysin O</td>
<td>Protein that degrades cell membrane</td>
<td>Lyses RBCs; contributes to β-hemolysis; host antibodies against toxin (ASO) used to diagnose rheumatic fever (do not confuse with immune complexes of poststreptococcal glomerulonephritis)</td>
</tr>
</tbody>
</table>

#### Superantigens causing shock

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>TOxin</th>
<th>MECHANISM</th>
<th>MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Toxic shock syndrome toxin (TSST-1)</td>
<td>Cross-links β region of TCR to MHC: class II on APCs outside of the antigen binding site → overwhelming release of IL-1, IL-2, IFN-γ, and TNF-α → shock</td>
<td>Toxic shock syndrome: fever, rash, shock; other toxins cause scalded skin syndrome (exfoliative toxin) and food poisoning (heat-stable enterotoxin)</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Erythrogenic exotoxin A</td>
<td></td>
<td>Toxic shock–like syndrome: fever, rash, shock; scarlet fever</td>
</tr>
</tbody>
</table>

### Endotoxin

LPS found in outer membrane of gram − bacteria (both cocci and rods). Composed of O antigen + core polysaccharide + lipid A (the toxic component).

Released upon cell lysis or by living cells by blebs detaching from outer surface membrane (vs exotoxin, which is actively secreted).

Three main effects: macrophage activation (TLR4/CD14), complement activation, and tissue factor activation.

**ENDOTOXINS:**

- Edema
- Nitric oxide
- DIC/Death
- Outer membrane
- TNF-α
- O-antigen + core polysaccharide + lipid A
- eXtremely heat stable
- IL-1 and IL-6
- Neutrophil chemotaxis
- Shock

![Endotoxin Diagram](image-url)
Gram-positive lab algorithm

Gram (purple/blue)

Bacilli
- Aerobic
  - Listeria
  - Bacillus
  - Corynebacterium

Cocci
- Anaerobic
  - Clostridium
    - C. Cutit bacterium (formerly Propionibacterium)

Branching filaments

Catalase

Streptococcus
- Hemolysis
  - Optochin sensitivity and bile solubility
  - Bacitracin sensitivity
  - Growth in 6.5% NaCl

Staphylococcus
- Coagulase
  - Novobiocin sensitivity

S aureus

Gram-positive cocci antibiotic tests

**Staphylococci**
- NOvobiocin—*S. saprophyticus* is Resistant;
  *S. epidermidis* is Sensitive.

On the office’s “staph” retreat, there was NO StRESs.

**Streptococci**
- Optochin—*Viridans* is Resistant; *Pneumoniae* is Sensitive.

- Bacitracin—group B strep are Resistant; group A strep are Sensitive.

*OVRPS* (overpass).

*B-BRAS.*
α-hemolytic bacteria

Gram \( \oplus \) cocci. Partial reduction of hemoglobin causes greenish or brownish color without clearing around growth on blood agar. Include the following organisms:

- *Streptococcus pneumoniae* (catalase \( \ominus \) and optochin sensitive)
- Viridans streptococci (catalase \( \ominus \) and optochin resistant)

β-hemolytic bacteria

Gram \( \oplus \) cocci. Complete lysis of RBCs → clear area surrounding colony on blood agar. Include the following organisms:

- *Staphylococcus aureus* (catalase and coagulase)
- *Streptococcus pyogenes*—group A strep (catalase \( \ominus \) and bacitracin sensitive)
- *Streptococcus agalactiae*—group B strep (catalase \( \ominus \) and bacitracin resistant)

Staphylococcus aureus

Gram \( \oplus \), β-hemolytic, catalase \( \ominus \), coagulase \( \ominus \) cocci in clusters. Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares, ears, axilla, and groin. Causes:

- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—tissue shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).
- MRSA (methicillin-resistant *S. aureus*)—important cause of serious nosocomial and community-acquired infections; resistant to methicillin and nafcillin because of altered penicillin-binding protein.

TSST-1 is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation.

Staphylococcal toxic shock syndrome (TSS)—fever, vomiting, rash, desquamation, shock, end-organ failure. TSS results in ↑ AST, ↑ ALT, ↑ bilirubin. Associated with prolonged use of vaginal tampons or nasal packing.

Compare with *Streptococcus pyogenes* TSS (a toxic shock–like syndrome associated with painful skin infection).

*S. aureus* food poisoning due to ingestion of preformed toxin → short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable → not destroyed by cooking.

Bad staph (*aureus*) make coagulase and toxins. Forms fibrin clot around self → abscess.

Staphylococcus epidermidis

Gram \( \oplus \), catalase \( \ominus \), coagulase \( \ominus \), urease \( \ominus \) cocci in clusters. Novobiocin sensitive. Does not ferment mannitol (vs *S. aureus*).

Normal flora of skin; contaminates blood cultures.

Infects prosthetic devices (eg, hip implant, heart valve) and IV catheters by producing adherent biofilms.
**Staphylococcus saprophyticus**
Gram +, catalase +, coagulase −, urease + cocci in clusters. Novobiocin resistant.
Normal flora of female genital tract and perineum.
Second most common cause of uncomplicated UTI in young women (most common is *E. coli*).

**Streptococcus pneumoniae**
Gram +, lancet-shaped diplococci. Encapsulated. IgA protease. Optochin sensitive. Most common cause of:
- Meningitis
- Otitis media (in children)
- Pneumonia
- Sinusitis
Pneumococcus is associated with “rusty” sputum, sepsis in patients with sickle cell disease, and asplenic patients.
No virulence without capsule.
MOPS commonly spread pneumonia.

**Viridans group streptococci**
Gram +, α-hemolytic cocci. Resistant to optochin, differentiating them from *S. pneumoniae* which is α-hemolytic but optochin sensitive. Normal flora of the oropharynx.
*Streptococcus mutans* and *S. mitis* cause dental caries.
*S. sanguinis* makes dextrans that bind to fibrin-platelet aggregates on damaged heart valves, causing subacute bacterial endocarditis.
Viridans group strep live in the mouth, because they are not afraid of-the-chin (op-to-chin resistant).
*Sanguinis* = blood. Think, “there is lots of blood in the heart” (endocarditis).

**Streptococcus pyogenes (group A streptococci)**
Gram + cocci in chains. Group A strep cause:
- Pyogenic—pharyngitis, cellulitis, impetigo (“honey-crusted” lesions), erysipelas
- Toxigenic—scarlet fever, toxic shock-like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis
Bacitracin sensitive, β-hemolytic, pyrrolidonyl arylamidase (PYR) +. Hyaluronic acid capsule and M protein inhibit phagocytosis. Antibodies to M protein enhance host defenses against *S. pyogenes* but can give rise to rheumatic fever. ASO titer or anti-DNase B antibodies indicate recent *S. pyogenes* infection.
Pharyngitis can result in rheumatic “pfever” and glomerulonephritis.
Strains causing impetigo can induce glomerulonephritis.
Scarlet fever—blanching, sandpaper-like body rash, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin +).
**Streptococcus agalactiae (group B streptococci)**

Gram + coccii, bacitracin resistant, β-hemolytic, colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in **babies**. Produces CAMP factor, which enlarges the area of hemolysis formed by *S aureus*. (Note: CAMP stands for the authors of the test, not cyclic AMP.) Hippurate test +. **PYR ⊖.**

Screen pregnant women at 35–37 weeks of gestation with rectal and vaginal swabs. Patients with + culture receive intrapartum penicillin prophylaxis.

**Streptococcus bovis**

Gram + coccii, colonizes the gut. *S gallolyticus* (*S bovis* biotype 1) can cause bacteremia and subacute endocarditis and is associated with colon cancer.

**Enterococci**

Gram + coccii. Enterococci (*E faecalis* and *E faecium*) are normal colonic flora that are penicillin G resistant and cause UTI, biliary tract infections, and subacute endocarditis (following GI/GU procedures). Catalase ⊖, **PYR +**, variable hemolysis. VRE (vancomycin-resistant enterococci) are an important cause of nosocomial infection.

**Bacillus anthracis**

Gram +, spore-forming rod that produces anthrax toxin. The only bacterium with a polypeptide capsule (contains d-glutamate). Colonies show a halo of projections, sometimes referred to as “medusa head” appearance.

**Cutaneous anthrax**

Painless papule surrounded by vesicles → ulcer with black eschar (A) (painless, necrotic) → uncommonly progresses to bacteremia and death.

**Pulmonary anthrax**

Inhalation of spores → flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis, and shock. Also known as woolsorter’s disease. CXR may show widened mediastinum.
**Bacillus cereus**
Gram $\oplus$ rod. Causes food poisoning. Spores survive cooking rice (also known as reheated rice syndrome). Keeping rice warm results in germination of spores and enterotoxin formation. Emetic type usually seen with rice and pasta. Nausea and vomiting within 1–5 hr. Caused by cereulide, a preformed toxin. Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hr.

**Clostridia (with exotoxins)**
Gram $\oplus$, spore-forming, obligate anaerobic rods.

**C tetani**
Produces tetanospasmin, an exotoxin causing tetanus. Tetanus toxin (and botulinum toxin) are proteases that cleave SNARE proteins for neurotransmitters. Blocks release of inhibitory neurotransmitters, GABA and glycine, from Renshaw cells in spinal cord. Causes spastic paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin), opisthotonos (spasms of spinal extensors). Prevent with tetanus vaccine. Treat with antitoxin $+/−$ vaccine booster, antibiotics, diazepam (for muscle spasms), and wound debridement.

**C botulinum**
Produces a heat-labile toxin that inhibits ACh release at the neuromuscular junction, causing botulism. In adults, disease is caused by ingestion of preformed toxin. In babies, ingestion of spores (eg, in honey) leads to disease (floppy baby syndrome). Treat with human botulinum immunoglobulin. Symptoms of botulism (the 4 D’s): Diplopia, Dysarthria, Dysphagia, Dyspnea. *Botulinum* is from bad bottles of food, juice, and honey (causes a descending flaccid paralysis). Local botox injections used to treat focal dystonia, achalasia, and muscle spasms. Also used for cosmetic reduction of facial wrinkles.

**C perfringens**
Produces $\alpha$ toxin (lecinthinase, a phospholipase) that can cause myonecrosis (gas gangrene $\mathbb{A}$: presents as soft tissue crepitus) and hemolysis. Spores can survive in undercooked food; when ingested, bacteria release heat-labile enterotoxin $\rightarrow$ food poisoning. Perfringens perforates a gangrenous leg.

**C difficile**
Produces 2 toxins. Toxin A, an enterotoxin, binds to brush border of gut and alters fluid secretion. Toxin B, a cytotoxin, disrupts cytoskeleton via actin depolymerization. Both toxins lead to diarrhea $\rightarrow$ pseudomembranous colitis $\mathbb{F}$. Often $2^\circ$ to antibiotic use, especially clindamycin or ampicillin; associated with PPIs. Diagnosed by PCR or antigen detection of one or both toxins in stool. Difficile causes diarrhea. Treatment: metronidazole or oral vancomycin. For recurrent cases, consider repeating prior regimen, fidaxomicin, or fecal microbiota transplant.
**Corynebacterium diphtheriae**


Symptoms include pseudomembranous pharyngitis (grayish-white membrane) with lymphadenopathy, myocarditis, and arrhythmias.

Lab diagnosis based on gram ⊕ rods with metachromatic (blue and red) granules and ⊕ Elek test for toxin.

Toxoid vaccine prevents diphtheria.

**Listeria monocytogenes**

Gram ⊕, facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, via transplacental transmission, or by vaginal transmission during birth. Grows well at refrigeration temperatures (4°–10°C; “cold enrichment”).

Forms “rocket tails” (red in A) via actin polymerization that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Characteristic tumbling motility in broth.

Can cause amnionitis, septicemia, and spontaneous abortion in pregnant women; granulomatosis infanti septica; neonatal meningitis; meningitis in immunocompromised patients; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin.

**Nocardia vs Actinomyces**

Both are gram ⊕ and form long, branching filaments resembling fungi.

<table>
<thead>
<tr>
<th>Nocardia</th>
<th>Actinomyces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobe</td>
<td>Anaerobe</td>
</tr>
<tr>
<td>Acid fast (weak) A</td>
<td>Not acid fast B</td>
</tr>
<tr>
<td>Found in soil</td>
<td>Normal oral, reproductive, and GI flora</td>
</tr>
<tr>
<td>Causes pulmonary infections in immunocompromised (can mimic TB but with ⊕ PPD); cutaneous infections after trauma in immunocompetent; can spread to CNS</td>
<td>Causes oral/facial abscesses that drain through sinus tracts; often associated with dental caries/ extraction and other maxillofacial trauma; forms yellow “sulfur granules”; can also cause PID with IUDs</td>
</tr>
<tr>
<td>Treat with sulfonamides (TMP-SMX)</td>
<td>Treat with penicillin</td>
</tr>
<tr>
<td>Treatment is a SNAP: Sulfonamides—Nocardia; Actinomyces—Penicillin</td>
<td></td>
</tr>
</tbody>
</table>
**Mycobacteria**

*Mycobacterium tuberculosis* (TB, often resistant to multiple drugs).  
*M. avium–intracellulare* (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs). Prophylaxis with azithromycin when CD4+ count < 50 cells/mm³.  
*M. scrofulaceum* (cervical lymphadenitis in children).  
*M. marinum* (hand infection in aquarium handlers).  
All mycobacteria are acid-fast organisms (pink rods; arrows in **A**).

**Tuberculosis**

TB symptoms include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis.  
Cord factor creates a “serpentine cord” appearance in virulent *M. tuberculosis* strains; activates macrophages (promoting granuloma formation) and induces release of TNF-α.  
Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

PPD ⊕ if current infection or past exposure.  
PPD ⊖ if no infection and in sarcoidosis or HIV infection (especially with low CD4+ cell count).  
Interferon-γ release assay (IGRA) has fewer false positives from BCG vaccination.  
Caseating granulomas with central necrosis and Langhans giant cell (single example in **A**) are characteristic of 2° tuberculosis.
Leprosy (Hansen disease)

Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—“glove and stocking” loss of sensation) and cannot be grown in vitro. Diagnosed via skin biopsy or tissue PCR. Reservoir in United States: armadillos.

Hansen disease has 2 forms (many cases fall temporarily between two extremes):

- **Lepromatous**—presents diffusely over the skin, with leonine (lion-like) facies, and is communicable (high bacterial load); characterized by low cell-mediated immunity with a humoral Th2 response. Lepromatous form can be lethal.
- **Tuberculoid**—limited to a few hypoesthetic, hairless skin plaques; characterized by high cell-mediated immunity with a largely Th1-type immune response and low bacterial load.

Treatment: dapsone and rifampin for tuberculoid form; clofazimine is added for lepromatous form.

---

**Gram-negative lab algorithm**

*Gram* (pink)

- **Diplococci**
  - *N. gonorrheae*
  - *M. catarrhalis*

- **Cocobacilli**
  - *Haemophilus influenzae*
  - *Pasteurella*
  - *Franciscella tularensis*

- **Comma-shaped rods**
  - *Campylobacter jejuni*
  - *Vibrio cholerae*
  - *Helicobacter pylori*

- **Lactose fermentation**
  - *Shigella*
  - *Salmonella*

- **Oxidase**
  - *Citrobacter*
  - *Klebsiella*
  - *Escherichia coli*
  - *Enterobacter*

- **H₂S production on TSI agar**
  - *Pseudomonas*
  - *Proteus*

Important tests are in **bold**. Important pathogens are in **bold italics**.
**Neisseria**

Gram − diplococci. Metabolize glucose and produce IgA proteases. Contain lipooligosaccharides (LOS) with strong endotoxin activity. *N. gonorrhoeae* is often intracellular (within neutrophils).

**Gonococci**

- No polysaccharide capsule
- Maltose not fermented
- No vaccine due to antigenic variation of pilus proteins
- Sexually or perinatally transmitted
- Causes gonorrhea, septic arthritis, neonatal conjunctivitis (2–5 days after birth), pelvic inflammatory disease (PID), and Fitz-Hugh–Curtis syndrome
- Condoms ↓ sexual transmission, erythromycin eye ointment prevents neonatal blindness
- Treatment: ceftriaxone (+ azithromycin or doxycycline, for possible chlamydial coinfection)

**Meningococci**

- Polysaccharide capsule
- Maltose fermentation
- Vaccine (type B vaccine not widely available)
- Transmitted via respiratory and oral secretions
- Causes meningococcemia with petechial hemorrhages and gangrene of toes, meningitis, Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC, shock)
- Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts
- Treatment: ceftriaxone or penicillin G

**Haemophilus influenzae**

Small gram − (coccobacillary) rod. Aerosol transmission. Nontypeable (unencapsulated) strains are the most common cause of mucosal infections (otitis media, conjunctivitis, bronchitis) as well as invasive infections since the vaccine for capsular type b was introduced. Produces IgA protease.

- Culture on chocolate agar, which contains factors V (NAD+) and X (hematin) for growth; can also be grown with *S. aureus*, which provides factor V via RBC hemolysis.
- *HaEMOPhilus* causes Epiglottitis (endoscopic appearance in A) can be “cherry red” in children; “thumb sign” on lateral neck x-ray B, Meningitis, Otitis media, and Pneumonia.
- Treatment: amoxicillin +/- clavulanate for mucosal infections; ceftriaxone for meningitis; rifampin prophylaxis for close contacts.

Vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age. Does not cause the flu (influenza virus does).
**Bordetella pertussis**

Gram −, aerobic coccobacillus. Virulence factors include pertussis toxin (disables Gs), adenylate cyclase toxin († cAMP), and tracheal cytotoxin. Three clinical stages:
- Catarrhal—low-grade fevers, Coryza.
- Paroxysmal—paroxysms of intense cough followed by inspiratory “woooP” (“whooping cough”), posttussive vomiting.
- Convalescent—gradual recovery of chronic cough.
Prevented by Tdap, DTaP vaccines. May be mistaken as viral infection due to lymphocytic infiltrate resulting from immune response.

**Legionella pneumophila**


**Pseudomonas aeruginosa**

*Aeruginosa*—aerobic; motile, gram − rod. Non-lactose fermenting. Oxidase +. Frequently found in water. Has a grape-like odor. **PSEUDOMONAS** is associated with:
- Pneumonia, Sepsis, Ecthyma gangrenosum, UTIs, Diabetes, Osteomyelitis.
- Mucoid polysaccharide capsule, Otis externa (swimmer’s ear), Nosocomial infections (eg, catheters, equipment), Addicts (drug abusers), Skin infections (eg, hot tub folliculitis, wound infection in burn victims).
- Mucoid polysaccharide capsule may contribute to chronic pneumonia in cystic fibrosis patients due to biofilm formation.
- Produces PEEP. Phospholipase C (degrades cell membranes); Endotoxin (fever, shock); Exotoxin A (inactivates EF-2). Pigments: pyoverdine and pyocyanin (blue-green pigment also generates reactive oxygen species).
- Corneal ulcers/keratitis in contact lens wearers/
- minor eye trauma.
- **Ecthyma gangrenosum**—rapidly progressive, necrotic cutaneous lesion caused by *Pseudomonas* bacteremia. Typically seen in immunocompromised patients. Treatments include “CAMPFIRE” drugs:
  - Carbapenems
  - Aminoglycosides
  - Monobactams
  - Polymyxins (eg, polymyxin B, colistin)
  - Fluoroquinolones (eg, ciprofloxacin, levofloxacin)
  - ThIRD- and fourth-generation cephalosporins (eg, ceftazidime, cefepime)
  - Extended-spectrum penicillins (eg, piperacillin, ticarcillin).
Salmonella vs Shigella  
Both *Salmonella* and *Shigella* are gram-negative rods, non-lactose fermenters, oxidase-positive, and can invade the GI tract via M cells of Peyer patches.

<table>
<thead>
<tr>
<th></th>
<th><em>Salmonella typhi</em></th>
<th><em>Salmonella spp.</em> (except <em>S. typhi</em>)</th>
<th><em>Shigella</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reservoirs</strong></td>
<td>Humans only</td>
<td>Humans and animals</td>
<td>Humans only</td>
</tr>
<tr>
<td><strong>Spread</strong></td>
<td>Can disseminate hematogenously</td>
<td>Can disseminate hematogenously</td>
<td>Cell to cell; no hematogenous spread</td>
</tr>
<tr>
<td><strong>H₂S production</strong></td>
<td>Yes (salmon swim)</td>
<td>Yes (salmon swim)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Flagella</strong></td>
<td>Endotoxin; Vi capsule</td>
<td>Endotoxin</td>
<td>Endotoxin; Shiga toxin (enterotoxin)</td>
</tr>
<tr>
<td><strong>Virulence factors</strong></td>
<td>High—large inoculum required; acid-labile (inactivated by gastric acids)</td>
<td>High</td>
<td>Low—very small inoculum required; acid stable (resistant to gastric acids)</td>
</tr>
<tr>
<td><strong>Infectious dose (ID₅₀)</strong></td>
<td>Prolongs duration</td>
<td>Prolongs duration</td>
<td>Shortens duration</td>
</tr>
<tr>
<td><strong>Effect of Antibiotics on fecal excretion</strong></td>
<td>Primarily monocytes</td>
<td>PMNs in disseminated disease</td>
<td>Primarily PMN infiltration</td>
</tr>
<tr>
<td><strong>GI Manifestations</strong></td>
<td>Constipation, followed by diarrhea</td>
<td>Diarrhea (possibly bloody)</td>
<td>Bloody diarrhea (bacillary dysentery)</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td>Oral vaccine contains live attenuated <em>S. typhi</em> IM vaccine contains Vi capsular polysaccharide</td>
<td>No vaccine</td>
<td>No vaccine</td>
</tr>
<tr>
<td><strong>Unique Properties</strong></td>
<td>* Causes typhoid fever (rose spots on abdomen, constipation, abdominal pain, fever); treat with ceftriaxone or fluoroquinolone * Carrier state with gallbladder colonization</td>
<td>* Poultry, eggs, pets, and turtles are common sources * Antibiotics not indicated * Gastroenteritis is usually caused by nontyphoidal <em>Salmonella</em></td>
<td>* Four F’s: Fingers, Flies, Food, Feces * In order of decreasing severity (less toxin produced): <em>S. dysenteriae</em>, <em>S. flexneri</em>, <em>S. boydii</em>, <em>S. sonnei</em> * Invasion of M cells is key to pathogenicity: organisms that produce little toxin can cause disease</td>
</tr>
</tbody>
</table>

Yersinia enterocolitica  
Gram-negative rod. Usually transmitted from pet feces (e.g., puppies), contaminated milk, or pork. Causes acute diarrhea or pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis).

Lactose-fermenting enteric bacteria  
Fermentation of lactose → pink colonies on MacConkey agar. Examples include *Citrobacter*, *Klebsiella*, *E. coli*, *Enterobacter*, and *Serratia* (weak fermenter). *E. coli* produces β-galactosidase, which breaks down lactose into glucose and galactose. **Lactose is key.**

Test with MacConKEE’s agar.

EMB agar—lactose fermenters grow as purple/black colonies. *E. coli* grows colonies with a green sheen.
**Escherichia coli**
Gram \( \ominus \) rod. *E. coli* virulence factors: fimbriae—cystitis and pyelonephritis (P-pili), K capsule—pneumonia, neonatal meningitis, LPS endotoxin—septic shock.

<table>
<thead>
<tr>
<th>STRAIN</th>
<th>TOxin AND MECHANISM</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteroinvasive <em>E. coli</em></td>
<td>Microbe invades intestinal mucosa and causes necrosis and inflammation.</td>
<td>EIEC is Invasive; dysentery. Clinical manifestations similar to <em>Shigella</em>.</td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em></td>
<td>Produces heat-labile and heat-stable enterotoxins. No inflammation or invasion.</td>
<td>ETEC; Traveler’s diarrhea (watery).</td>
</tr>
<tr>
<td>Enteropathogenic <em>E. coli</em></td>
<td>No toxin produced. Adheres to apical surface, flattens villi, prevents absorption.</td>
<td>Diarrhea, usually in children (think EPEC and Pediatrics).</td>
</tr>
<tr>
<td>Enterohemorrhagic <em>E. coli</em></td>
<td>O157:H7 is most common serotype in US. Often transmitted via undercooked meat, raw leafy vegetables. Shiga-like toxin causes <strong>hemolytic-uremic syndrome</strong>: triad of anemia, thrombocytopenia, and acute renal failure due to microthrombi forming on damaged endothelium → mechanical hemolysis (with schistocytes on peripheral blood smear), platelet consumption, and ↓ renal blood flow.</td>
<td>Dysentery (toxin alone causes necrosis and inflammation). Does not ferment sorbitol (vs other <em>E. coli</em>). Hemorrhagic, Hamburgers, Hemolytic-uremic syndrome.</td>
</tr>
</tbody>
</table>

**Klebsiella**
Gram \( \ominus \) rod; intestinal flora that causes lobar pneumonia in alcoholics and diabetics when aspirated. Very mucoid colonies caused by abundant polysaccharide capsules. Dark red “currant jelly” sputum (blood/mucus). Also cause of nosocomial UTIs. Associated with evolution of multidrug resistance (MDR).

5 A’s of Klebsiella:
- Aspiration pneumonia
- Abscess in lungs and liver
- Alcoholics
- Diabetics
- “CurrAnt jelly” sputum

**Campylobacter jejuni**
Gram \( \ominus \), comma or S shaped (with polar flagella) oxidase \( \oplus \), grows at 42°C (“*Campylobacter* likes the hot campfire”). Major cause of bloody diarrhea, especially in children. Fecal-oral transmission through person-to-person contact or via ingestion of undercooked contaminated poultry or meat, unpasteurized milk. Contact with infected animals (dogs, cats, pigs) is also a risk factor. Common antecedent to Guillain-Barré syndrome and reactive arthritis.
**Vibrio cholerae**

Gram-, flagellated, comma shaped, oxidase+, grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates Gs, cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high ID₅₀) unless host has a gastric acidity. Transmitted via ingestion of contaminated water or uncooked food (eg, raw shellfish). Treat promptly with oral rehydration solution.

**Helicobacter pylori**

Curved, flagellated (motile), gram-, rod that is triple+: catalase+, oxidase+, and urease+ (can use urea breath test or fecal antigen test for diagnosis). Urease produces ammonia, creating an alkaline environment, which helps H. pylori survive in acidic mucosa. Colonizes mainly antrum of stomach; causes gastritis and peptic ulcers (especially duodenal). Risk factor for peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma.

Most common initial treatment is triple therapy: Amoxicillin (metronidazole if penicillin allergy) + Clarithromycin + Proton pump inhibitor; Antibiotics Cure P. pylori.

**Spirochetes**

Spiral-shaped bacteria with axial filaments. Includes Borrelia (big size), Leptospira, and Treponema. Only Borrelia can be visualized using aniline dyes (Wright or Giemsa stain) in light microscopy due to size. Treponema is visualized by dark-field microscopy or direct fluorescent antibody (DFA) microscopy.

**Lyme disease**

Caused by Borrelia burgdorferi, which is transmitted by the ixodes deer tick (also vector for Anaplasma spp. and protozoa Babesia). Natural reservoir is the mouse (and important to tick life cycle).

Common in northeastern United States.

Stage 1—early localized: erythema migrans (typical “bulls-eye” configuration is pathognomonic but not always present), flu-like symptoms.

Stage 2—early disseminated: secondary lesions, carditis, AV block, facial nerve (Bell) palsy, migratory myalgias/transient arthritis.

Stage 3—late disseminated: encephalopathy, chronic arthritis.

A Key Lyme pie to the FACE: Facial nerve palsy (typically bilateral) Arthritis Cardiac block Erythema migrans Treatment: doxycycline (1st line); amoxicillin and cefuroxime in pregnant women and children.
**Leptospira interrogans**  Spirochete with hook-shaped ends found in water contaminated with animal urine.

**Leptospirosis**—flu-like symptoms, myalgias (classically of calves), jaundice, photophobia with conjunctival suffusion (erythema without exudate). Prevalent among surfers and in tropics (eg, Hawaii).

**Weil disease** (icterohemorrhagic leptospirosis)—severe form with jaundice and azotemia from liver and kidney dysfunction, fever, hemorrhage, and anemia.

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**Syphilis**

**Primary syphilis** Localized disease presenting with painless chancre A. If available, use dark-field microscopy to visualize treponemes in fluid from chancre B. VDRL ⊕ in ~ 80%.

**Secondary syphilis** Disseminated disease with constitutional symptoms, maculopapular rash C (including palms D and soles), condylomata lata E (smooth, painless, wart-like white lesions on genitals), lymphadenopathy, patchy hair loss; also confirmable with dark-field microscopy. Serologic testing: VDRL/RPR (nonspecific), confirm diagnosis with specific test (eg, FTA-ABS). Secondary syphilis = Systemic. Latent syphilis (⊕ serology without symptoms) may follow.

**Tertiary syphilis** Gummas F (chronic granulomas), aortitis (vasa vasorum destruction), neurosyphilis (tabes dorsalis, “general paresis”), Argyll Robertson pupil (constricts with accommodation but is not reactive to light; also called “prostitute’s pupil” since it accommodates but does not react). Signs: broad-based ataxia, ⊖ Romberg, Charcot joint, stroke without hypertension. For neurosyphilis: test spinal fluid with VDRL, FTA-ABS, and PCR.

**Congenital syphilis** Presents with facial abnormalities such as rhagades (linear scars at angle of mouth, black arrow in G), snuffles (nasal discharge, red arrow in H), saddle nose, notched (Hutchinson) teeth I, mulberry molars, and short maxilla; saber shins; CN VIII deafness. To prevent, treat mother early in pregnancy, as placental transmission typically occurs after first trimester.
VDRL false positives  VDRL detects nonspecific antibody that reacts with beef cardiolipin. Quantitative, inexpensive, and widely available test for syphilis (sensitive but not specific). False-Positive results on VDRL with:
- Pregnancy
- Viral infection (eg, EBV, hepatitis)
- Drugs
- Rheumatic fever
- Lupus and leprosy

Jarisch-Herxheimer reaction  Flu-like syndrome (fever, chills, headache, myalgia) after antibiotics are started; due to killed bacteria (usually spirochetes) releasing toxins.

Gardnerella vaginalis  A pleomorphic, gram-variable rod involved in bacterial vaginosis. Presents as a gray vaginal discharge with a fishy smell; nonpainful (vs vaginitis). Associated with sexual activity, but not sexually transmitted. Bacterial vaginosis is also characterized by overgrowth of certain anaerobic bacteria in vagina. Clue cells (vaginal epithelial cells covered with Gardnerella) have stippled appearance along outer margin (arrow in A). Treatment: metronidazole or clindamycin.

Chlamydiae  Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:
- Elementary body (small, dense) is “Infectious” and Enters cell via Endocytosis; transforms into reticulate body.
- Reticulate body Replicates in cell by fission; Reorganizes into elementary bodies.

- Chlamydia trachomatis causes reactive arthritis (Reiter syndrome), neonatal and follicular adult conjunctivitis A, nongonococcal urethritis, and PID.
- Chlamydia pneumoniae and Chlamydia psittaci cause atypical pneumonia; transmitted by aerosol.

- Clamydia = cloak (intracellular).
- C psittaci—has an avian reservoir (parrots), causes atypical pneumonia.

Lab diagnosis: PCR, nucleic acid amplification test. Cytoplasmic inclusions (reticulate bodies) seen on Giemsa or fluorescent antibody–stained smear.
The chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering β-lactam antibiotics ineffective.
### Chlamydia trachomatis serotypes

<table>
<thead>
<tr>
<th>Types A, B, and C</th>
<th>Chronic infection, cause blindness due to follicular conjunctivitis in Africa.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types D–K</td>
<td>Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with eosinophilia, neonatal conjunctivitis (1–2 weeks after birth).</td>
</tr>
<tr>
<td>Types L1, L2, and L3</td>
<td>Lymphogranuloma venereum—small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (buboes). Treat with doxycycline.</td>
</tr>
</tbody>
</table>

### Zoonotic bacteria

<table>
<thead>
<tr>
<th>Species</th>
<th>Disease</th>
<th>Transmission and source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplasma spp.</td>
<td>Anaplasmosis</td>
<td>Ixodes ticks (live on deer and mice)</td>
</tr>
<tr>
<td>Bartonella spp.</td>
<td>Cat scratch disease, bacillary angiomatosis</td>
<td>Cat scratch</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>Lyme disease</td>
<td>Ixodes ticks (live on deer and mice)</td>
</tr>
<tr>
<td>Borrelia recurrentis</td>
<td>Relapsing fever</td>
<td>Louse (recurrent due to variable surface antigens)</td>
</tr>
<tr>
<td>Brucella spp.</td>
<td>Brucellosis/undulant fever</td>
<td>Unpasteurized dairy</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Bloody diarrhea</td>
<td>Feces from infected pets/animals; contaminated meats/foods/hands</td>
</tr>
<tr>
<td>Chlamyphila psittaci</td>
<td>Psittacosis</td>
<td>Parrots, other birds</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>Q fever</td>
<td>Aerosols of cattle/sheep amniotic fluid</td>
</tr>
<tr>
<td>Ehrlichia chaffeensis</td>
<td>Ehrlichiosis</td>
<td>Amblyomma (Lone Star tick)</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>Tularemia</td>
<td>Ticks, rabbits, deer flies</td>
</tr>
<tr>
<td>Leptospira spp.</td>
<td>Leptospirosis</td>
<td>Animal urine in water; recreational water use</td>
</tr>
<tr>
<td>Mycobacterium leprae</td>
<td>Leprosy</td>
<td>Humans with lepromatous leprosy; armadillo (rare)</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>Cellulitis, osteomyelitis</td>
<td>Animal bite, cats, dogs</td>
</tr>
<tr>
<td>Rickettsia prowazekii</td>
<td>Epidemic typhus</td>
<td>Human to human via human body louse</td>
</tr>
<tr>
<td>Rickettsia rickettsii</td>
<td>Rocky Mountain spotted fever</td>
<td>Dermacentor (dog tick)</td>
</tr>
<tr>
<td>Rickettsia typhi</td>
<td>Endemic typhus</td>
<td>Fleas</td>
</tr>
<tr>
<td>Salmonella spp. (except S typhi)</td>
<td>Diarrhea (which may be bloody), vomiting, fever, abdominal cramps</td>
<td>Reptiles and poultry</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>Plague</td>
<td>Fleas (rats and prairie dogs are reservoirs)</td>
</tr>
</tbody>
</table>
### Rickettsial diseases and vector-borne illnesses

**Rocky Mountain spotted fever**
- *Rickettsia rickettsii*, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists and ankles and then spreads to trunk, palms, and soles.
- Classic triad—headache, fever, rash (vasculitis).
- Palms and soles rash is seen in Coxsackievirus A infection (hand, foot, and mouth disease), Rocky Mountain spotted fever, and 2nd Syphilis (you drive CARS using your palms and soles).

**Typhus**
- Endemic (fleas)—*R typhi*.
- Epidemic (human body louse)—*R prowazekii*.
- Rash starts centrally and spreads out, sparing palms and soles.

### Rash Rare

**Ehrlichiosis**
- *Ehrlichia*, vector is tick. Monocytes with morulae (mulberry-like inclusions) in cytoplasm.
- MEGA berry—
  - Monocytes = Ehrlichiosis
  - Granulocytes = Anaplasmosis

**Anaplasmosis**
- *Anaplasma*, vector is tick. Granulocytes with morulae in cytoplasm.

**Q fever**
- Q fever is Queer because it has no rash or vector and its causative organism can survive outside in its endospore form. Not in the *Rickettsia* genus, but closely related.

### Mycoplasma pneumoniae
- Classic cause of atypical “walking” pneumonia (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate). X-ray looks worse than patient. High titer of cold agglutinins (IgM), which can agglutinate RBCs. Grown on Eaton agar.
- Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* have no cell wall).
- No cell wall. Not seen on Gram stain.
- Pleomorphic A
- Bacterial membrane contains sterols for stability.
- Mycoplasmal pneumonia is more common in patients < 30 years old.
- Frequent outbreaks in military recruits and prisons.
- *Mycoplasma* gets cold without a coat (cell wall).
### Systemic mycoses

All of the following can cause pneumonia and can disseminate.

All are caused by dimorphic fungi: **cold** (20°C) = mold; **heat** (37°C) = yeast. Only exception is *Coccidioides*, which is a spherule (not yeast) in tissue.

Systemic mycoses can form granulomas (like TB); cannot be transmitted person-to-person (unlike TB).

Treatment: fluconazole or itraconazole for **local** infection; amphotericin B for **systemic** infection.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endemic Location</th>
<th>Pathologic Features</th>
<th>Unique Signs/Symptoms</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histoplasmosis</strong></td>
<td>Mississippi and Ohio River Valleys</td>
<td>Macrophage filled with <em>Histoplasma</em> (smaller than RBC)</td>
<td>Palatal/tongue ulcers, splenomegaly</td>
<td>Histo hides (within macrophages) Bird (eg, starlings) or bat droppings Diagnosis via urine/serum antigen</td>
</tr>
<tr>
<td><strong>Blastomycosis</strong></td>
<td>Eastern and Central US</td>
<td>Broad-based budding of <em>Blastomyces</em> (same size as RBC)</td>
<td>Inflammatory lung disease, can disseminate to skin/bone Verrucous skin lesions can simulate SCC Forms granulomatous nodules</td>
<td>Blasto buds broadly</td>
</tr>
<tr>
<td><strong>Coccidioidomycosis</strong></td>
<td>Southwestern US, California</td>
<td>Spherule (much larger than RBC) filled with endospores of <em>Coccidioides</em></td>
<td>Disseminates to skin/bone Erythema nodosum (desert bumps) or multiforme Arthralgias (desert rheumatism) Can cause meningitis</td>
<td></td>
</tr>
<tr>
<td><strong>Paracoccidioidomycosis</strong></td>
<td>Latin America</td>
<td>Budding yeast of <em>Paracoccidioides</em> with “captain’s wheel” formation (much larger than RBC)</td>
<td>Similar to blastomycosis, males &gt; females</td>
<td>Paracoccidio parasails with the captain’s wheel all the way to Latin America</td>
</tr>
</tbody>
</table>
**Cutaneous mycoses**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea (dermatophytes)</td>
<td>Clinical name for dermatophyte (cutaneous fungal) infections. Dermatophytes include Microsporum, Trichophyton, and Epidermophyton. Branching septate hyphae visible on KOH preparation with blue fungal stain. Associated with pruritus.</td>
</tr>
<tr>
<td>Tinea capitis</td>
<td>Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling.</td>
</tr>
<tr>
<td>Tinea corporis</td>
<td>Occurs on torso. Characterized by erythematous scaling rings (“ringworm”) and central clearing. Can be acquired from contact with an infected cat or dog.</td>
</tr>
<tr>
<td>Tinea cruris</td>
<td>Occurs in inguinal area. Often does not show the central clearing seen in tinea corporis.</td>
</tr>
</tbody>
</table>
| Tinea pedis                      | Three varieties:  
  - Interdigital  
  - Moccasin distribution  
  - Vesicular type                                                                                                                                     |
| Tinea unguium                    | Onychomycosis; occurs on nails.                                                                                                                                                                               |
| Tinea (pityriasis) versicolor     | Caused by Malassezia spp. (Pityrosporum spp.), a yeast-like fungus (not a dermatophyte despite being called tinea). Degradation of lipids produces acids that damage melanocytes and cause hypopigmented, hyperpigmented, and/or pink patches. Less pruritic than dermatophytes.  
  Can occur any time of year, but more common in summer (hot, humid weather). “Spaghetti and meatballs” appearance on microscopy.  
  Treatment: selenium sulfide, topical and/or oral antifungal medications.                                                                                   |
Opportunistic fungal infections

**Candida albicans**  
*a* _alb*sa* = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C, germ tubes at 37°C.  
Systemic or superficial fungal infection. Causes oral and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, endocarditis (IV drug users), disseminated candidiasis (especially in neutropenic patients), chronic mucocutaneous candidiasis.  
Treatment: oral fluconazole/topical azole for vaginal; nystatin, fluconazole, or echinocandins for oral/esophageal; fluconazole, echinocandins, or amphotericin B for systemic.

**Aspergillus fumigatus**  
Monomorphic septate hyphae that branch at 45°.  
Causes invasive aspergillosis in immunocompromised patients, neutrophil dysfunction (eg, chronic granulomatous disease).  
Can cause aspergillomas in pre-existing lung cavities, especially after TB infection.  
Some species of _Aspergillus_ produce aflatoxins (associated with hepatocellular carcinoma).  
**Allergic bronchopulmonary aspergillosis (ABPA)** —hypersensitivity response associated with asthma and cystic fibrosis; may cause bronchiecstasy and eosinophilia.

**Cryptococcus neoformans**  
Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Culture on Sabouraud agar. Highlighted with India ink (clear halo) and mucicarmine (red inner capsule). Latex agglutination test detects polysaccharide capsular antigen and is more specific.  
Causes cryptococcosis, cryptococcal meningitis, cryptococcal encephalitis (“soap bubble” lesions in brain), primarily in immunocompromised.  
Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.

**Mucor and Rhizopus spp.**  
Irregular, broad, nonseptate hyphae branching at wide angles.  
Causes mucormycosis, mostly in ketoacidotic diabetic and/or neutropenic patients (eg, leukemia).  
Inhalation of spores —fungi proliferate in blood vessel walls, penetrate cribiform plate, and enter brain. Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face; may have cranial nerve involvement.  
Treatment: surgical debridement, amphotericin B or isavuconazole.
**Pneumocystis jirovecii**

Causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia. Yeast-like fungus (originally classified as protozoan). Most infections are asymptomatic. Immunosuppression (eg, AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on CXR/CT, with pneumatoceles. Diagnosed by lung biopsy or lavage. Disc-shaped yeast seen on methenamine silver stain of lung tissue.

Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis only), atovaquone. Start prophylaxis when CD4+ count drops to < 200 cells/mm³ in HIV patients.

---

**Sporothrix schenckii**

Sporotrichosis. Dimorphic, *cigar*-shaped budding yeast that grows in branching hyphae with *rosettes* of conidia; lives on vegetation. When spores are traumatically introduced into the skin, typically by a thorn ("rose gardener's disease"), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis). Disseminated disease possible in immunocompromised host.

Treatment: itraconazole or potassium iodide.

Think of a *rose gardener* who smokes a *cigar* and *pot.*
Protozoa—gastrointestinal infections

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Giardia lamblia</em></td>
<td><strong>Giardiasis</strong>—bloating, flatulence, foul-smelling, fatty diarrhea (often seen in campers/hikers)—think fat-rich Ghirardelli chocolates for fatty stools of <em>Giardia</em></td>
<td>Cysts in water</td>
<td>Multinucleated trophozoites (\text{A}) or cysts (\text{B}) in stool, antigen detection</td>
<td>Metronidazole</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td><strong>Amebiasis</strong>—bloody diarrhea (dyentery), liver abscess (&quot;anchovy paste&quot; exudate), RUQ pain; histology of colon biopsy shows flask-shaped ulcers</td>
<td>Cysts in water</td>
<td>Serology, antigen testing, and/or trophozoites (with engulfed RBCs (\text{C}) in the cytoplasm) or cysts with up to 4 nuclei in stool (\text{D}); <em>Entamoeba</em> Eats Erythrocytes</td>
<td>Metronidazole; paromomycin or iodoquinol for asymptomatic cyst passers</td>
</tr>
</tbody>
</table>
| *Cryptosporidium* | **Severe diarrhea in AIDS**  
Mild disease (watery diarrhea) in immunocompetent hosts | Oocysts in water | Oocysts on acid-fast stain \(\text{E}\), antigen detection | Prevention (by filtering city water supplies); nitazoxanide in immunocompetent hosts |
## Protozoa—CNS infections

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxoplasma gondii</strong></td>
<td>Immunocompetent: mononucleosis-like symptoms, ○ heterophile antibody test. Reactivation in AIDS → brain abscesses usually seen as multiple ring-enhancing lesions on MRI A. Congenital toxoplasmosis: classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications.</td>
<td>Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant women should avoid cats)</td>
<td>Serology, biopsy (tachyzoite) B</td>
<td>Sulfadiazine + pyrimethamine</td>
</tr>
<tr>
<td><strong>Naegleria fowleri</strong></td>
<td>Rapidly fatal meningoencephalitis</td>
<td>Swimming in warm freshwater (think Nalgene bottle filled with fresh water containing Naegleria); enters via cribriform plate</td>
<td>Amoebas in CSF C</td>
<td>Amphotericin B has been effective for a few survivors</td>
</tr>
<tr>
<td><strong>Trypanosoma brucei</strong></td>
<td><strong>African sleeping sickness</strong>—enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma</td>
<td>Tsetse fly, a painful bite</td>
<td>Trypomastigote in blood smear D</td>
<td>Suramin for blood-borne disease or melarsoprol for CNS penetration (“I sure am mellow when I'm sleeping”; remember melatonin helps with sleep)</td>
</tr>
</tbody>
</table>

![Image A](image1)

![Image B](image2)

![Image C](image3)

![Image D](image4)
### Protozoa—hematologic infections

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmodium</td>
<td></td>
<td></td>
<td>Blood smear: trophozoite</td>
<td>Chloroquine (for sensitive species), which blocks Plasmodium heme polymerase; if resistant, use mefloquine or atovaquone/proguanil</td>
</tr>
<tr>
<td>P vivax/ovale</td>
<td>Malaria—fever, headache, anemia, splenomegaly</td>
<td>Anopheles mosquito</td>
<td>form within RBC A, schizont containing merozoites; red granules (Schüffner stippling) B throughout RBC cytoplasm seen with P vivax/ovale</td>
<td>If life-threatening, use intravenous quinidine or artesunate (test for G6PD deficiency) For P vivax/ovale, add primaquine for hypnozoite (test for G6PD deficiency)</td>
</tr>
<tr>
<td>P falciparum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P malariae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babesia</td>
<td>Babesiosis—fever and hemolytic anemia; predominantly in northeastern United States; asplenia ↑ risk of severe disease</td>
<td>Ixodes tick (same as Borrelia burgdorferi of Lyme disease; may often coinfect humans)</td>
<td>Blood smear: ring form [C1], “Maltese cross” [C2], PCR</td>
<td>Atovaquone + azithromycin</td>
</tr>
</tbody>
</table>

**Protozoa—hematologic infections**

- **Plasmodium**
  - **P vivax/ovale**
  - **P falciparum**
  - **P malariae**

**Malaria**
- Fever, headache, anemia, splenomegaly
- **P vivax/ovale**—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver
- **P falciparum**—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs
- **P malariae**—72-hr cycle (quartan)

**Anopheles** mosquito

**Plasmodium heme polymerase**

**Chloroquine** (for sensitive species), which blocks

**Mefloquine** or **atovaquone/proguanil**

**Intravenous quinidine** or **artesunate** (test for G6PD deficiency)

**Primaquine** for hypnozoite (test for G6PD deficiency)

**Babesiosis**
- Fever and hemolytic anemia; predominantly in northeastern United States; asplenia ↑ risk of severe disease

**Ixodes tick** (same as *Borrelia burgdorferi* of Lyme disease; may often coinfect humans)

**Blood smear**: ring form [C1], “Maltese cross” [C2], PCR

**Atovaquone** + azithromycin
Protozoa—others

<table>
<thead>
<tr>
<th>ORGANISM</th>
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<th>DIAGNOSIS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypanosoma cruzi</td>
<td>Chagas disease—dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America</td>
<td>Triatomite (&quot;kissing&quot;) bug, a type of reduvid bug, deposits feces in a painless bite (much like a kiss)</td>
<td>Trypomastigote in blood smear</td>
<td>Benzimidazole or nifurtimox; cruzing in my Benz, with a fur coat on</td>
</tr>
<tr>
<td>Leishmania donovani</td>
<td>Visceral leishmaniasis (kala-azar)—spiking fevers, hepatosplenomegaly, pancytopenia</td>
<td>Sandfly</td>
<td>Macrophages containing amastigotes</td>
<td>Amphotericin B, sodium stibogluconate</td>
</tr>
<tr>
<td></td>
<td>Cutaneous leishmaniasis—skin ulcers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sexually transmitted infections

| Trichomonas vaginalis | Vaginitis—foul-smelling, greenish discharge; itching and burning; do not confuse with Gardnerella vaginalis, a gram-variable bacterium associated with bacterial vaginosis | Sexual (cannot exist outside human because it cannot form cysts) | Trophozoites (motile) on wet mount; “strawberry cervix” | Metronidazole for patient and partner (prophylaxis) |

Nematode routes of infection

Ingested—Enterobius, Ascaris, Toxocara, Trichinella, Trichuris
Cutaneous—Strongyloides, Ancylostoma, Necator
Bites—Loa loa, Onchocerca volvulus, Wuchereria bancrofti

You’ll get sick if you EATTT these!
These get into your feet from the SANd.
Lay LOW to avoid getting bitten.
### Nematodes (roundworms)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobius vermicularis</em> (pinworm)</td>
<td>Causes anal pruritus (diagnosed by seeing egg via the tape test)</td>
<td>Fecal-oral</td>
<td>Pyrantel pamoate or <strong>bendazoles</strong> (because worms are bendy)</td>
</tr>
<tr>
<td><em>Ascaris lumbricoides</em> (giant roundworm)</td>
<td>May cause obstruction at ileocecal valve, biliary obstruction, intestinal perforation, migrates from nose/mouth</td>
<td>Fecal-oral; knobby-coated, oval eggs seen in feces under microscope</td>
<td><strong>Bendazoles</strong></td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em> (threadworm)</td>
<td>Autoinfection: rarely, some larvae may penetrate the intestinal wall to enter the bloodstream without leaving the body</td>
<td>Larvae in soil penetrate skin; rhabditiform larvae seen in feces under microscope</td>
<td><strong>Ivermectin</strong> or <strong>bendazoles</strong></td>
</tr>
<tr>
<td><em>Ancylostoma duodenale, Necator americanus</em> (hookworms)</td>
<td>Cause anemia by sucking blood from intestinal wall Cutaneous larva migrans—pruritic, serpiginous rash from walking barefoot on contaminated beach</td>
<td>Larvae penetrate skin</td>
<td><strong>Bendazoles or pyrantel pamoate</strong></td>
</tr>
</tbody>
</table>
| *Trichinella spiralis*                  | Larvae enter bloodstream, encyst in striated muscle → muscle inflammation  
Trichinosis—fever, vomiting, nausea, periorbital edema, myalgia | Undercooked meat (especially pork); fecal-oral (less likely) | **Bendazoles**                                                            |
| *Trichuris trichiura* (whipworm)       | Often asymptomatic; loose stools, anemia, rectal prolapse in children (heavy infection) | Fecal-oral                                                                 | **Bendazoles**                                                            |
| **Tissue**                             |                                                                         |                                                                              |                                                                           |
| *Toxocara canis*                       | Visceral larva migrans—nematodes migrate to blood through intestinal wall → inflammation and damage. Often affects heart (myocarditis), liver, eyes (visual impairment, blindness), and CNS (seizures, coma) | Fecal-oral                                                                 | **Bendazoles**                                                            |
| *Onchocerca volvulus*                  | Skin changes, loss of elastic fibers, and river blindness (black flies, black skin nodules, “black sight”); allergic reaction to microfilaria possible | Female blackfly                                                            | **Ivermectin** (ivermectin for river blindness)                           |
| *Loa loa*                              | Swelling in skin, worm in conjunctiva                                   | Deer fly, horse fly, mango fly                                              | **Diethylcarbamazine**                                                    |
| *Wuchereria bancrofti*                 | Lymphatic filariasis (elephantiasis)—worms invade lymph nodes → inflammation → lymphedema C; symptom onset after 9 mo–1 yr | Female mosquito                                                            | **Diethylcarbamazine**                                                    |
### Cestodes (tapeworms)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taenia solium A</td>
<td>Intestinal tapeworm</td>
<td>Ingestion of larvae encysted in undercooked pork</td>
<td>Praziqanantel</td>
</tr>
<tr>
<td></td>
<td>Cysticercosis,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>neurocysticercosis (cystic CNS lesions,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>seizures)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diphyllobothrium latum</td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency</td>
<td>Ingestion of larvae in raw freshwater fish</td>
</tr>
<tr>
<td></td>
<td>(tapeworm competes for B&lt;sub&gt;12&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in intestine) × megaloblastic anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echinococcus</td>
<td>Hydatid cysts ('eggshell calcification')</td>
<td>Ingestion of eggs in food contaminated with dog</td>
<td>Albendazole</td>
</tr>
<tr>
<td>granulosus C</td>
<td>in liver</td>
<td>feces</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cyst rupture can cause anaphylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sheep are an intermediate host</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Image of Taenia solium](image1.png)

### Trematodes (flukes)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
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<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosoma A</td>
<td>Liver and spleen enlargement (S mansoni,</td>
<td>Snails are intermediate host;</td>
<td>Praziqanantel</td>
</tr>
<tr>
<td></td>
<td>egg with lateral spine, fibrosis,</td>
<td>cercariae penetrate skin of humans in contact with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inflammation, portal hypertension</td>
<td>contaminated fresh water (eg, swimming or bathing)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic infection with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S haematobium (egg with terminal spine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>can lead to squamous cell carcinoma of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>the bladder (painless hematuria) and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pulmonary hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonorchis sinensis</td>
<td>Biliary tract inflammation</td>
<td>Undercooked fish</td>
<td>Praziqanantel</td>
</tr>
</tbody>
</table>
### Ectoparasites

**Sarcoptes scabiei**

- Mite burrow into stratum corneum and cause **scabies**—pruritus (worse at night) and serpiginous burrows (lines) in webspace of hands and feet.

- Common in children, crowded populations (jails, nursing homes); transmission through skin-to-skin contact (most common) or via fomites.

- Treatment: permethrin cream, washing/drying all clothing/bedding, treat close contacts.

**Pediculus humanus/Phthirus pubis**

- Blood-sucking lice that cause intense pruritus with associated excoriations, commonly on scalp and neck (head lice) or waistband and axilla (body lice).


- Treatment includes pyrethroids, malathion, or ivermectin lotion, and nit combing. Children with head lice can be treated at home without interrupting school attendance.

### Parasite hints

<table>
<thead>
<tr>
<th>ASSOCIATIONS</th>
<th>ORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary tract disease, cholangiocarcinoma</td>
<td><em>Clonorchis sinensis</em></td>
</tr>
<tr>
<td>Brain cysts, seizures</td>
<td><em>Taenia solium</em> (neurocysticercosis)</td>
</tr>
<tr>
<td>Hematuria, squamous cell bladder cancer</td>
<td><em>Schistosoma haematobium</em></td>
</tr>
<tr>
<td>Liver (hydatid) cysts</td>
<td><em>Echinococcus granulosus</em></td>
</tr>
<tr>
<td>Microcytic anemia</td>
<td><em>Ancylostoma, Necator</em></td>
</tr>
<tr>
<td>Myalgias, peri orbital edema</td>
<td><em>Trichinella spiralis</em></td>
</tr>
<tr>
<td>Perianal pruritus</td>
<td><em>Enterobius</em></td>
</tr>
<tr>
<td>Portal hypertension</td>
<td><em>Schistosoma mansoni, Schistosoma japonicum</em></td>
</tr>
<tr>
<td>Vitamin B₁₂ deficiency</td>
<td><em>Diphyllobothrium latum</em></td>
</tr>
</tbody>
</table>
Viral structure—general features

Viral genetics

**Recombination**
Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.

**Reassortment**
When viruses with segmented genomes (eg, influenza virus) exchange genetic material. For example, the 2009 novel H1N1 influenza A pandemic emerged via complex viral reassortment of genes from human, swine, and avian viruses. Has potential to cause antigenic shift.

**Complementation**
When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein, the nonmutated virus “complements” the mutated one by making a functional protein that serves both viruses. For example, hepatitis D virus requires the presence of replicating hepatitis B virus to supply HBsAg, the envelope protein for HDV.

**Phenotypic mixing**
Occurs with simultaneous infection of a cell with 2 viruses. Genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the tropism (infectivity) of the hybrid virus. However, the progeny from this infection have a type A coat that is encoded by its type A genetic material.

**DNA viral genomes**
All DNA viruses have dsDNA genomes except Parvoviridae (ssDNA).
All are linear except papilloma-, polyoma-, and hepadnaviruses (circular).

**RNA viral genomes**
All RNA viruses have ssRNA genomes except Reoviridae (dsRNA).
⊕ stranded RNA viruses: I went to a retro (retrovirus) toga (togavirus) party, where I drank flavored (flavivirus) Corona (coronavirus) and ate hippie (hepevirus) California (calicivirus) pickles (picornavirus).

All are ssRNA, except “repeato-virus” (reovirus) is dsRNA.

All are dsDNA (like our cells), except “part-of-a-virus” (parvovirus) is ssDNA.
Parvus = small.
**Naked viral genome infectivity**

Purified nucleic acids of most dsDNA (except poxviruses and HBV) and $\odot$ strand ssRNA ($\approx$ mRNA) viruses are infectious. Naked nucleic acids of $\odot$ strand ssRNA and dsRNA viruses are not infectious. They require polymerases contained in the complete virion.

---

**Viral envelopes**

Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.

**Naked** (nonenveloped) viruses include Papillomavirus, Adenovirus, Parvovirus, Polyomavirus, Calicivirus, Picornavirus, Reovirus, and Hepevirus.

DNA = PAPP, RNA = CPR and hepevirus.

Give PAPP smears and CPR to a naked hippie (hepevirus).

---

**DNA virus characteristics**

Some general rules—all DNA viruses:

<table>
<thead>
<tr>
<th>GENERAL RULE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are HHAPPPPy viruses</td>
<td>Hepadna, Herpes, Adeno, Pox, Parvo, Papilloma, Polyoma.</td>
</tr>
<tr>
<td>Are double stranded</td>
<td>Except parvo (single stranded).</td>
</tr>
<tr>
<td>Have linear genomes</td>
<td>Except papilloma and polyoma (circular, supercoiled) and hepadna (circular, incomplete).</td>
</tr>
<tr>
<td>Are icosahedral</td>
<td>Except pox (complex).</td>
</tr>
<tr>
<td>Replicate in the nucleus</td>
<td>Except pox (carries own DNA-dependent RNA polymerase).</td>
</tr>
<tr>
<td>DNA viruses</td>
<td>All replicate in the nucleus (except poxvirus). “Pox is out of the box (nucleus).”</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>VIRAL FAMILY</strong></td>
<td><strong>ENVELOPE</strong></td>
</tr>
<tr>
<td>Herpesviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Poxvirus</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepadnavirus</td>
<td>Yes</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>No</td>
</tr>
<tr>
<td>Papillomavirus</td>
<td>No</td>
</tr>
<tr>
<td>Polyomavirus</td>
<td>No</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>No</td>
</tr>
</tbody>
</table>

**Herpesviruses** Enveloped, DS, and linear viruses

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>ROUTE OF TRANSMISSION</th>
<th>CLINICAL SIGNIFICANCE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus-1</td>
<td>Respiratory secretions, saliva</td>
<td>Gingivostomatitis, keratoconjunctivitis A, herpes labialis B, herpetic whitlow on finger, temporal lobe encephalitis, esophagitis, erythema multiforme.</td>
<td>Most commonly latent in trigeminal ganglia. Most common cause of sporadic encephalitis, can present as altered mental status, seizures, and/or aphasia.</td>
</tr>
<tr>
<td>Herpes simplex virus-2</td>
<td>Sexual contact, perinatal</td>
<td>Herpes genitalis C, neonatal herpes.</td>
<td>Most commonly latent in sacral ganglia. Viral meningitis more common with HSV-2 than with HSV-1.</td>
</tr>
<tr>
<td>Varicella-Zoster virus (HHV-3)</td>
<td>Respiratory secretions</td>
<td>Varicella-zoster (chickenpox D, shingles E), encephalitis, pneumonia. Most common complication of shingles is post-herpetic neuralgia.</td>
<td>Latent in dorsal root or trigeminal ganglia; CN V1 branch involvement can cause herpes zoster ophthalmicus.</td>
</tr>
</tbody>
</table>
### Herpesviruses (continued)

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>ROUTE OF TRANSMISSION</th>
<th>CLINICAL SIGNIFICANCE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epstein-Barr virus (HHV-4)</strong></td>
<td>Respiratory secretions, saliva; aka “kissing disease,” (common in teens, young adults)</td>
<td><strong>Mononucleosis</strong>—fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior cervical nodes). Avoid contact sports until resolution due to risk of splenic rupture. Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients.</td>
<td></td>
</tr>
<tr>
<td><strong>Cytomegalovirus (HHV-5)</strong></td>
<td>Congenital transfusion, sexual contact, saliva, urine, transplant</td>
<td><strong>Mononucleosis</strong> (⊕ Monospot) in immunocompetent patients; infection in immunocompromised, especially pneumonia in transplant patients; esophagitis; AIDS retinitis (“sightomegalovirus”): hemorrhage, cotton-wool exudates, vision loss. Congenital CMV</td>
<td></td>
</tr>
<tr>
<td><strong>Human herpesviruses 6 and 7</strong></td>
<td>Saliva</td>
<td>Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash. <strong>Roseola</strong>: fever first, <strong>Rosy</strong> (rash) later. HHV-7—less common cause of roseola.</td>
<td></td>
</tr>
<tr>
<td><strong>Human herpesvirus 8</strong></td>
<td>Sexual contact</td>
<td>Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules representing vascular proliferations. Can also affect GI tract and lungs.</td>
<td></td>
</tr>
</tbody>
</table>

---

**Epstein-Barr virus (HHV-4)**

- **Respiratory secretions, saliva; aka “kissing disease,”** (common in teens, young adults)
- **Mononucleosis**—fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior cervical nodes). Avoid contact sports until resolution due to risk of splenic rupture. Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients.
- Infections B cells through CD21.
- Atypical lymphocytes on peripheral blood smear — not infected B cells but reactive cytotoxic T cells.
- ⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs.
- Use of amoxicillin in mononucleosis can cause characteristic maculopapular rash.

**Cytomegalovirus (HHV-5)**

- **Congenital transfusion, sexual contact, saliva, urine, transplant**
- **Mononucleosis** (⊕ Monospot) in immunocompetent patients; infection in immunocompromised, especially pneumonia in transplant patients; esophagitis; AIDS retinitis (“sightomegalovirus”): hemorrhage, cotton-wool exudates, vision loss. Congenital CMV
- Infected cells have characteristic “owl eye” intranuclear inclusions. Latent in mononuclear cells.

**Human herpesviruses 6 and 7**

- **Saliva**
- **Roseola infantum** (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash. **Roseola**: fever first, **Rosy** (rash) later. HHV-7—less common cause of roseola.

**Human herpesvirus 8**

- **Sexual contact**
- Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules representing vascular proliferations. Can also affect GI tract and lungs.
**HSV identification**

Viral culture for skin/genitalia.
CSF PCR for herpes encephalitis.
Tzanck test—a smear of an opened skin vesicle to detect multinucleated giant cells commonly seen in HSV-1, HSV-2, and VZV infection. PCR of skin lesions is test of choice.
**Tzanck** heavens I do not have herp.es.
Intranuclear eosinophilic Cowdry A inclusions also seen with HSV-1, HSV-2, VZV.

---

**Receptors used by viruses**

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>Integrins (heparan sulfate)</td>
</tr>
<tr>
<td>EBV</td>
<td>CD21</td>
</tr>
<tr>
<td>HIV</td>
<td>CD4, CXCR4, CCR5</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>P antigen on RBCs</td>
</tr>
<tr>
<td>Rabies</td>
<td>Nicotinic AChR</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>ICAM-1</td>
</tr>
</tbody>
</table>
### RNA viruses

<table>
<thead>
<tr>
<th>VIRAL FAMILY</th>
<th>ENVELOPE</th>
<th>RNA STRUCTURE</th>
<th>CAPSID SYMMETRY</th>
<th>MEDICAL IMPORTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoviruses</td>
<td>No</td>
<td>DS linear 10–12 segments</td>
<td>Icosahedral (double)</td>
<td>Coltivirus — Colorado tick fever (sight).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rotavirus — cause of fatal diarrhea in children</td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>No</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>Poliovirus — polio-Salk/Sabin vaccines — IPV/OPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Echovirus — aseptic meningitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rhinovirus — “common cold”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coxsackievirus — aseptic meningitis; herpangina</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(mouth blisters, fever); hand, foot, and mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>disease; myocarditis; pericarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HAV — acute viral hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PERCH</td>
</tr>
<tr>
<td>Hepevirus</td>
<td>No</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>HEV</td>
</tr>
<tr>
<td>Caliciviruses</td>
<td>No</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>Norovirus — viral gastroenteritis</td>
</tr>
<tr>
<td>Flaviviruses</td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>HCV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yellow fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dengue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>St. Louis encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>West Nile virus — meningoencephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zika virus</td>
</tr>
<tr>
<td>Togaviruses</td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>Rubella</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Western and Eastern equine encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chikungunya virus</td>
</tr>
<tr>
<td>Retroviruses</td>
<td>Yes</td>
<td>SS ⊕ linear 2 copies</td>
<td>Icosahedral (HTLV), complex and conical (HIV)</td>
<td>Have reverse transcriptase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HTLV — T-cell leukemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HIV — AIDS</td>
</tr>
<tr>
<td>Coronaviruses</td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Helical</td>
<td>“Common cold,” SARS, MERS</td>
</tr>
<tr>
<td>Orthomyxoviruses</td>
<td>Yes</td>
<td>SS ⊕ linear 8 segments</td>
<td>Helical</td>
<td>Influenza virus</td>
</tr>
<tr>
<td>Paramyxoviruses</td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Helical</td>
<td>Parainfluenza — croup</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsegmented</td>
<td></td>
<td>RSV — bronchiolitis in babies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Measles, Mumps</td>
</tr>
<tr>
<td>Rhabdoviruses</td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Helical</td>
<td>Rabies</td>
</tr>
<tr>
<td>Filoviruses</td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Helical</td>
<td>Ebola/Marburg hemorrhagic fever — often fatal.</td>
</tr>
<tr>
<td>Arenaviruses</td>
<td>Yes</td>
<td>SS ⊕ and ⊕ circular 2 segments</td>
<td>Helical</td>
<td>LCMV — lymphocytic choriomeningitis virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lassa fever encephalitis — spread by rodents</td>
</tr>
<tr>
<td>Bunyaviruses</td>
<td>Yes</td>
<td>SS ⊕ circular 3 segments</td>
<td>Helical</td>
<td>California encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sandfly/Rift Valley fevers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crimean-Congo hemorrhagic fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hantavirus — hemorrhagic fever, pneumonia</td>
</tr>
<tr>
<td>Delta virus</td>
<td>Yes</td>
<td>SS ⊕ circular</td>
<td>Uncertain</td>
<td>HDV is a “defective” virus that requires the presence of HBV to replicate</td>
</tr>
</tbody>
</table>

SS, single-stranded; DS, double-stranded; ⊕, positive sense; ⊖, negative sense; a = arbovirus, arthropod borne (mosquitoes, ticks).
**Negative-stranded viruses**
Must transcribe ⨯ strand to ⊕. Virion brings its own RNA-dependent RNA polymerase. They include Arenaviruses, Bunyaviruses, Paramyxoviruses, Orthomyxoviruses, Filoviruses, and Rhabdoviruses.

Always Bring Polymerase Or Fail Replication.

**Segmented viruses**
All are RNA viruses. They include Bunyaviruses, Orthomyxoviruses (influenza viruses), Arenaviruses, and Reoviruses.

BOAR.

**Picornavirus**
Includes Poliovirus, Echovirus, Rhinovirus, Coxsackievirus, and HAV. RNA is translated into 1 large polypeptide that is cleaved by proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV). All are enteroviruses except rhinovirus and HAV.

PicoRNAvirus = small RNA virus.
PERCH on a "peak" (pico).

**Rhinovirus**
A picornavirus. Nonenveloped RNA virus. Cause of common cold; > 100 serologic types. Acid labile—destroyed by stomach acid; therefore, does not infect the GI tract (unlike the other picornaviruses).

Rhino has a runny nose.

**Yellow fever virus**
A flavivirus (also an arbovirus) transmitted by Aedes mosquitoes. Virus has a monkey or human reservoir. Symptoms: high fever, black vomitus, and jaundice. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy.

Flavi = yellow, jaundice.

**Rotavirus**
Segmented dsRNA virus (a reovirus). Most important global cause of infantile gastroenteritis. Major cause of acute diarrhea in the United States during winter, especially in day care centers, kindergartens. Villous destruction with atrophy leads to ↓ absorption of Na⁺ and loss of K⁺.

ROTAvirus = Right Out The Anus.
CDC recommends routine vaccination of all infants except those with a history of intussusception or SCID.
### Influenza viruses

Orthomyxoviruses. Enveloped, ssRNA viruses with 8-segment genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S. aureus*, *S. pneumoniae*, and *H. influenzae*.

Reformulated vaccine (“the flu shot”) contains viral strains most likely to appear during the flu season, due to the virus’ rapid genetic change. Killed viral vaccine is most frequently used. Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally.

<table>
<thead>
<tr>
<th>Genetic/antigenic shift</th>
<th>Causes pandemics. Reassortment of viral genome segments, such as when segments of human flu A virus reassort with swine flu A virus.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Genetic/antigenic drift</th>
<th>Causes epidemics. Minor (antigenic drift) changes based on random mutation in hemagglutinin or neuraminidase genes.</th>
</tr>
</thead>
</table>

### Rubella virus

A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, maculopapular rash that starts on face and spreads centrifugally to involve trunk and extremities.

Causes mild disease in children but serious congenital disease (a ToRCHeS infection). Congenital rubella findings include “blueberry muffin” appearance due to dermal extramedullary hematopoiesis.
Paramyxoviruses

Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, measles, RSV, and human metapneumovirus, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants. Palivizumab for Paramyxovirus (RSV) Prophylaxis in Preemies.

Croup (acute laryngotracheobronchitis)

Caused by parainfluenza viruses, which are paramyxoviruses. Virus membrane contains hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Results in a “seal-like” barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on x-ray. Severe croup can result in pulsus paradoxus due to upper airway obstruction.

Measles (rubeola) virus

A paramyxovirus that causes measles. Usual presentation involves prodromal fever with cough, coryza, and conjunctivitis, then eventually Koplik spots (bright red spots with blue-white center on buccal mucosa), followed 1–2 days later by a maculopapular rash that starts at the head/neck and spreads downward. Lymphadenitis with Warthin-Finkeldey giant cells (fused lymphocytes) in a background of paracortical hyperplasia. Possible sequelae:
- SSPE (subacute sclerosing panencephalitis, occurring years later)
- Encephalitis (1:2000)
- Giant cell pneumonia (rare except in immunosuppressed)

3 C’s of measles:
- Cough
- Coryza
- Conjunctivitis

Vitamin A supplementation can reduce morbidity and mortality from measles, particularly in malnourished children.

Mumps virus

A paramyxovirus that causes mumps, uncommon due to effectiveness of MMR vaccine. Symptoms: Parotitis, Orchitis (inflammation of testes), aseptic Meningitis, and Pancreatitis. Can cause sterility (especially after puberty).

Mumps makes your parotid glands and testes as big as POM-Poms.
Rabies virus

Bullet-shaped virus. Negri bodies (cytoplasmic inclusions) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has a long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity. Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors. Progression of disease: fever, malaise → agitation, photophobia, hydrophobia, hypersalivation → paralysis, coma → death.

Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (e.g., bat caves) also possible.

Ebola virus

A filovirus that targets endothelial cells, phagocytes, hepatocytes. Following an incubation period of up to 21 days, presents with abrupt onset of flu-like symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock. Diagnosed with RT-PCR within 48 hr of symptom onset. High mortality rate.

Transmission requires direct contact with bodily fluids, fomites (including dead bodies), infected bats or primates (apes/monkeys); high incidence of nosocomial infection. Supportive care, no definitive treatment. Strict isolation of infected individuals and barrier practices for health care workers are key to preventing transmission.

Zika virus

A flavivirus most commonly transmitted by Aedes mosquito bites. Causes conjunctivitis, low-grade pyrexia, and itchy rash in 20% of cases. Can lead to congenital microcephaly or miscarriage if transmitted in utero. Diagnose with RT-PCR or serology. Sexual and vertical transmission possible. Outbreaks more common in tropical and subtropical climates. Supportive care, no definitive treatment.
### Hepatitis viruses

Signs and symptoms of all hepatitis viruses: episodes of fever, jaundice, ↑ALT and AST. Naked viruses (HAV and HEV) lack an envelope and are not destroyed by the gut: the **vowels hit your bowels**. HBV DNA polymerase has DNA- and RNA-dependent activities. Upon entry into nucleus, the polymerase completes the partial dsDNA. Host RNA polymerase transcribes mRNA from viral DNA to make viral proteins. The DNA polymerase then reverse transcribes viral RNA to DNA, which is the genome of the progeny virus.

HCV lacks 3′-5′ exonuclease activity → no proofreading ability → variation in antigenic structures of HCV envelope proteins. Host antibody production lags behind production of new mutant strains of HCV.

<table>
<thead>
<tr>
<th>Virus</th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAMILY</strong></td>
<td>RNA picornavirus</td>
<td>DNA hepatavirus</td>
<td>RNA flavivirus</td>
<td>RNA deltavirus</td>
<td>RNA hepevirus</td>
</tr>
<tr>
<td><strong>TRANSMISSION</strong></td>
<td>Fecal-oral (shellfish, travelers, day care)</td>
<td>Parenteral (Blood), sexual (Baby-making), perinatal (Birth)</td>
<td>Primarily blood (IDVU, post-transfusion)</td>
<td>Parenteral, sexual, perinatal</td>
<td>Fecal-oral, especially waterborne</td>
</tr>
<tr>
<td><strong>INCUBATION</strong></td>
<td>Short (weeks)</td>
<td>Long (months)</td>
<td>Long</td>
<td>Superinfection (HDV after HBV) = short</td>
<td>Short</td>
</tr>
<tr>
<td><strong>CLINICAL COURSE</strong></td>
<td>Asymptomatic (usually), Acute</td>
<td>Initially like serum sickness (fever, arthralgias, rash); may progress to cirrhoma</td>
<td>May progress to Cirrhosis or Carcinoma</td>
<td>Similar to HBV</td>
<td>Fulminant hepatitis in Expectant (pregnant) women</td>
</tr>
<tr>
<td><strong>PROGNOSIS</strong></td>
<td>Good</td>
<td>Adults → mostly full resolution; neonates → worse prognosis</td>
<td>Majority develop stable, Chronic hepatitis C</td>
<td>Superinfection → worse prognosis</td>
<td>High mortality in pregnant women</td>
</tr>
<tr>
<td><strong>HCC RISK</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>LIVER BIOPSY</strong></td>
<td>Hepatocyte swelling, monocyte infiltration, Councilman bodies</td>
<td>Granular eosinophilic “ground glass” appearance; cytotoxic T cells mediate damage</td>
<td>Lymphoid aggregates with focal areas of macrovesicular steatosis</td>
<td>Similar to HBV</td>
<td>Patchy necrosis</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>No carrier state (“Alone”)</td>
<td>Carrier state common</td>
<td>Carrier state very common</td>
<td>Defective virus, Depends on HBV HBsAg coat for entry into hepatocytes</td>
<td>Enteric, Epidemic, no carrier state</td>
</tr>
</tbody>
</table>
### Extrahepatic manifestations of hepatitis B and C

<table>
<thead>
<tr>
<th></th>
<th><strong>Hepatitis B</strong></th>
<th><strong>Hepatitis C</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td>Aplastic anemia</td>
<td>Essential mixed cryoglobulinemia, † risk B-cell NHL, ITP, autoimmune hemolytic anemia</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
<td>Membranous GN &gt; membranoproliferative GN</td>
<td>Membranoproliferative GN &gt; membranous GN</td>
</tr>
<tr>
<td><strong>VASCULAR</strong></td>
<td>Polyarteritis nodosa</td>
<td>Leukocytoclastic vasculitis</td>
</tr>
<tr>
<td><strong>DERMATOLOGIC</strong></td>
<td></td>
<td>Sporadic porphyria cutanea tarda, lichen planus</td>
</tr>
<tr>
<td><strong>ENDOCRINE</strong></td>
<td></td>
<td>† risk of diabetes mellitus, autoimmune hypothyroidism</td>
</tr>
</tbody>
</table>

† indicates increased risk.
**Hepatitis serologic markers**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-HAV (IgM)</strong></td>
<td>IgM antibody to HAV; best test to detect acute hepatitis A.</td>
</tr>
<tr>
<td><strong>Anti-HAV (IgG)</strong></td>
<td>IgG antibody indicates prior HAV infection and/or prior vaccination; protects against reinfection.</td>
</tr>
<tr>
<td><strong>HBsAg</strong></td>
<td>Antigen found on surface of HBV; indicates hepatitis B infection.</td>
</tr>
<tr>
<td><strong>Anti-HBs</strong></td>
<td>Antibody to HBsAg; indicates immunity to hepatitis B due to vaccination or recovery from infection.</td>
</tr>
<tr>
<td><strong>HBcAg</strong></td>
<td>Antibody associated with core of HBV.</td>
</tr>
<tr>
<td><strong>Anti-HBc</strong></td>
<td>Antibody to HBcAg; IgM = acute/recent infection; IgG = prior exposure or chronic infection. IgM anti-HBc may be the sole marker of infection during window period.</td>
</tr>
<tr>
<td><strong>HBeAg</strong></td>
<td>Secreted by infected hepatocyte into circulation. Not part of mature HBV virion. Indicates active viral replication and therefore high transmissibility and poorer prognosis.</td>
</tr>
<tr>
<td><strong>Anti-HBe</strong></td>
<td>Antibody to HBeAg; indicates low transmissibility.</td>
</tr>
</tbody>
</table>

---

**Table of Hepatitis Serologic Markers**

<table>
<thead>
<tr>
<th></th>
<th>HbsAg</th>
<th>Anti-HBs</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>Anti-HBc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>IgM</td>
</tr>
<tr>
<td>Window</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IgM</td>
</tr>
<tr>
<td>Chronic HBV (high infectivity)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>IgG</td>
</tr>
<tr>
<td>Chronic HBV (low infectivity)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>IgG</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td>IgG</td>
</tr>
<tr>
<td>Immunized</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Diagram:**

- **Incubation period:**
  - HBsAg
  - DNA polymerase
- **Prodrome, acute disease:**
  - HBeAg
  - DNA polymerase
  - e antigen
  - Core antigen
- **Convalescence:**
  - Early
  - Anti-HBc
  - Anti-HBe
  - Anti-HBs
  - Anti-HBc
- **Late:**
  - Anti-HBc
- **Symptoms:**
  - SGPT (ALT)

---

**Level of detection:**

- **0-1 months after exposure:**
  - HBsAg
- **2-5 months after exposure:**
  - HBeAg
  - Window period
- **6-8 months after exposure:**
  - Anti-HBe
HIV

Presumptive diagnosis made with HIV-1/2 Ag/Ab immunoassays. These immunoassays detect viral p24 Ag capsid protein and IgG Abs to HIV-1/2. Very high sensitivity/specificity. ⊕ tests are confirmed with HIV-1/2 Ab-differentiation immunoassays which determine whether patient has HIV-1 or HIV-2.

If inconclusive differentiation assay, an HIV-1 nucleic acid amplification test (NAAT) is performed; if the NAAT is ⊗, patient had false positive initial Ag/Ab immunoassay.

Viral load tests determine the amount of viral RNA in the plasma. High viral load associated with poor prognosis. Also use viral load to monitor effect of drug therapy. Use HIV genotyping to determine appropriate therapy.

AIDS diagnosis ≤ 200 CD4+ cells/mm³ (normal: 500–1500 cells/mm³). HIV ⊗ with AIDS-defining condition (eg, Pneumocystis pneumonia) or CD4+ percentage < 14%.

Western blot tests are no longer recommended by the CDC for confirmatory testing. HIV-1/2 Ag/Ab testing is not recommended in babies with suspected HIV due to maternally transferred antibody. Use HIV viral load instead.

Diploid genome (2 molecules of RNA).

The 3 structural genes (protein coded for):
- **env** (gp120 and gp41):
  - Formed from cleavage of gp160 to form envelope glycoproteins.
  - gp120—attachment to host CD4+ T cell.
  - gp41—fusion and entry.
- **gag** (p24 and p17)—capsid and matrix proteins, respectively.
- **pol**—reverse transcriptase, aspartate protease, integrase.

Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity.

Heterozygous CCR5 mutation = slower course.

HIV diagnosis

Enzyme proteins acquired through budding from host cell plasma membrane.
Dashed lines on CD4+ count axis indicate moderate immunocompromise (<400 CD4+ cells/mm³) and when AIDS-defining illnesses emerge (<200 CD4+ cells/mm³).

Most patients who do not receive treatment eventually die of complications of HIV infection.

Four stages of untreated infection:
1. Flu-like (acute)
2. Feeling fine (latent)
3. Falling count
4. Final crisis

During clinical latency phase, virus replicates in lymph nodes.
### Common diseases of HIV-positive adults

As CD4+ cell count ↓, risks of reactivation of past infections (eg, TB, HSV, shingles), dissemination of bacterial infections and fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas ↑.

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>PRESENTATION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4+ cell count &lt; 500/mm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Oral thrush</td>
<td>Scrapable white plaque, pseudohyphae on microscopy</td>
</tr>
<tr>
<td>EBV</td>
<td>Oral hairy leukoplakia</td>
<td>Unscrapable white plaque on lateral tongue</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi sarcoma</td>
<td>Biopsy with lymphocytic inflammation</td>
</tr>
<tr>
<td>HPV</td>
<td>Squamous cell carcinoma, commonly of anus (men who have sex with men) or cervix (women)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4+ cell count &lt; 200/mm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea</td>
<td>Oval yeast cells within macrophages</td>
</tr>
<tr>
<td>HIV</td>
<td>Dementia</td>
<td></td>
</tr>
<tr>
<td>JC virus (reactivation)</td>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Nondenfacing areas of demyelination on MRI</td>
</tr>
<tr>
<td>Pneumocystis jirovecii</td>
<td>Pneumocystis pneumonia</td>
<td>“Ground-glass” opacities on CXR</td>
</tr>
<tr>
<td><strong>CD4+ cell count &lt; 100/mm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>Hemoptysis, pleuritic pain</td>
<td>Cavitation or infiltrates on chest imaging</td>
</tr>
<tr>
<td>Bartonella henselae</td>
<td>Bacillary angiomatosis</td>
<td>Biopsy with neutrophilic inflammation</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Esophagitis</td>
<td>White plaques on endoscopy; yeast and pseudohyphae on biopsy</td>
</tr>
<tr>
<td>CMV</td>
<td>Retinitis, esophagitis, colitis, pneumonitis, encephalitis</td>
<td>Linear ulcers on endoscopy, cotton-wool spots on fundoscopy; biopsy reveals cells with intranuclear (owl eye) inclusion bodies</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Meningitis</td>
<td>Encapsulated yeast on India ink stain or capsular antigen ⊕</td>
</tr>
<tr>
<td>Cryptosporidium spp.</td>
<td>Chronic, watery diarrhea</td>
<td>Acid-fast oocysts in stool</td>
</tr>
<tr>
<td>EBV</td>
<td>B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma)</td>
<td>CNS lymphoma—ring enhancing, may be solitary (vs Toxoplasma)</td>
</tr>
<tr>
<td>Mycobacterium avium–intracellular, Mycobacterium avium complex</td>
<td>Nonspecific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis</td>
<td></td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>Brain abscesses</td>
<td>Multiple ring-enhancing lesions on MRI</td>
</tr>
</tbody>
</table>
Prions

Prion diseases are caused by the conversion of a normal (predominantly α-helical) protein termed prion protein (PrP\textsubscript{c}) to a β-pleated form (PrP\textsubscript{sc}), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). PrP\textsubscript{sc} resists protease degradation and facilitates the conversion of still more PrP\textsubscript{c} to PrP\textsubscript{sc}. Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of PrP\textsubscript{sc} results in spongiform encephalopathy and dementia, ataxia, and death.

**Creutzfeldt-Jakob disease**—rapidly progressive dementia, typically sporadic (some familial forms).

**Bovine spongiform encephalopathy**—also known as “mad cow disease.”

**Kuru**—acquired prion disease noted in tribal populations practicing human cannibalism.

---

### MICROBIOLOGY—SYSTEMS

#### Normal flora: dominant

Neonates delivered by C-section have no flora but are rapidly colonized after birth.

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>MICROORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td><em>S. epidermidis</em></td>
</tr>
<tr>
<td>Nose</td>
<td><em>S. epidermidis</em>; colonized by <em>S. aureus</em></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Viridans group streptococci</td>
</tr>
<tr>
<td>Dental plaque</td>
<td><em>S. mutans</em></td>
</tr>
<tr>
<td>Colon</td>
<td><em>B. fragilis &gt; E. coli</em></td>
</tr>
<tr>
<td>Vagina</td>
<td><em>Lactobacillus</em>; colonized by <em>E. coli</em> and group B strep</td>
</tr>
</tbody>
</table>

#### Bugs causing food-borne illness

*S. aureus* and *B. cereus* food poisoning starts quickly and ends quickly.

<table>
<thead>
<tr>
<th>MICROORGANISM</th>
<th>SOURCE OF INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. cereus</em></td>
<td>Reheated rice. “Food poisoning from reheated rice? Be serious!” (<em>B. cereus</em>)</td>
</tr>
<tr>
<td><em>C. botulinum</em></td>
<td>Improperly canned foods (toxins), raw honey (spores)</td>
</tr>
<tr>
<td><em>C. perfringens</em></td>
<td>Reheated meat</td>
</tr>
<tr>
<td><em>E. coli O157:H7</em></td>
<td>Undercooked meat</td>
</tr>
<tr>
<td><em>L. monocytogenes</em></td>
<td>Deli meats, soft cheeses</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Poultry, meat, and eggs</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Meats, mayonnaise, custard; preformed toxin</td>
</tr>
<tr>
<td><em>V. parahaemolyticus</em> and <em>V. vulnificus</em>(^a)</td>
<td>Contaminated seafood</td>
</tr>
</tbody>
</table>

\(^a\) *V. vulnificus* can also cause wound infections from contact with contaminated water or shellfish.
**Bugs causing diarrhea**

### Bloody diarrhea

- **Campylobacter**
  - Comma- or S-shaped organisms; growth at 42°C

- **E histolytica**
  - Protozoan; amebic dysentery; liver abscess

- **Enterohemorrhagic E coli**
  - O157:H7; can cause HUS; makes Shiga-like toxin

- **Salmonella (non-typhoidal)**
  - Lactose ⊝; flagellar motility; has animal reservoir, especially poultry and eggs

- **Shigella**
  - Lactose ⊝; very low ID₅₀; produces Shiga toxin (human reservoir only); bacillary dysentery

- **Y enterocolitica**
  - Day care outbreaks; pseudoappendicitis

### Watery diarrhea

- **C difficile**
  - Pseudomembranous colitis; associated with antibiotics and PPIs; occasionally bloody diarrhea

- **C perfringens**
  - Also causes gas gangrene

- **Enterotoxigenic E coli**
  - Travelers’ diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins

- **Protozoa**
  - Giardia, Cryptosporidium

- **V cholerae**
  - Comma-shaped organisms; rice-water diarrhea; often from infected seafood

- **Viruses**
  - Rotavirus, norovirus, enteric adenovirus

### Common causes of pneumonia

<table>
<thead>
<tr>
<th><strong>Neonates (&lt; 4 wk)</strong></th>
<th><strong>Children (4 wk–18 yr)</strong></th>
<th><strong>Adults (18–40 yr)</strong></th>
<th><strong>Adults (40–65 yr)</strong></th>
<th><strong>Elderly</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococci</td>
<td>Viruses (RSV)</td>
<td>Mycoplasma</td>
<td>S pneumoniae</td>
<td>S pneumoniae</td>
</tr>
<tr>
<td>E coli</td>
<td><strong>Mycoplasma</strong></td>
<td><strong>C pneumoniae</strong></td>
<td><strong>H influenzae</strong></td>
<td>Influenza virus</td>
</tr>
<tr>
<td></td>
<td><strong>C trachomatis</strong></td>
<td><strong>S pneumoniae</strong></td>
<td><strong>Anaerobes</strong></td>
<td>Anaerobes</td>
</tr>
<tr>
<td></td>
<td>(infants–3 yr)</td>
<td><strong>Viruses (eg, influenza)</strong></td>
<td>Viruses</td>
<td>H influenzae</td>
</tr>
<tr>
<td></td>
<td><strong>C pneumoniae</strong></td>
<td></td>
<td></td>
<td>Gram ⊝ rods</td>
</tr>
<tr>
<td></td>
<td>(school-aged children)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>S pneumoniae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Runts May Cough</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Chunky Sputum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Special groups

- **Alcoholic**
  - Klebsiella, anaerobes usually due to aspiration (eg, Peptostreptococcus, Fusobacterium, Prevotella, Bacteroides)

- **IV drug users**
  - S pneumoniae, S aureus

- **Aspiration**
  - Anaerobes

- **Atypical**
  - Mycoplasma, Chlamydia, Legionella, viruses (RSV, CMV, influenza, adenovirus)

- **Cystic fibrosis**
  - Pseudomonas, S aureus, S pneumoniae, Burkholderia cepacia

- **Immunocompromised**
  - S aureus, enteric gram ⊝ rods, fungi, viruses, P jirovecii (with HIV)

- **Nosocomial (hospital acquired)**
  - S aureus, Pseudomonas, other enteric gram ⊝ rods

- **Postviral**
  - S pneumoniae, S aureus, H influenzae
### Common causes of meningitis

<table>
<thead>
<tr>
<th>Newborn (0–6 mo)</th>
<th>Children (6 mo–6 yr)</th>
<th>6–60 yr</th>
<th>60 yr +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococci</td>
<td><em>S. pneumoniae</em></td>
<td><em>S. pneumoniae</em></td>
<td><em>S. pneumoniae</em></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td><em>N. meningitidis</em></td>
<td><em>N. meningitidis</em> (#1 in teens)</td>
<td>Gram − rods</td>
</tr>
<tr>
<td><em>Listeria</em></td>
<td><em>H. influenzae</em> type b</td>
<td>Enteroviruses</td>
<td><em>Listeria</em></td>
</tr>
<tr>
<td></td>
<td>Enteroviruses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Give ceftriaxone and vancomycin empirically (add ampicillin if *Listeria* is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackie virus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: *Cryptococcus* spp.

Note: Incidence of *H. influenzae* meningitis has greatly due to conjugate *H. influenzae* vaccinations. Today, cases are usually seen in unimmunized children.

### Cerebrospinal fluid findings in meningitis

<table>
<thead>
<tr>
<th>Opening Pressure</th>
<th>Cell Type</th>
<th>Protein</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>↑</td>
<td>↑ PMNs</td>
<td>↑</td>
</tr>
<tr>
<td>Fungal/TB</td>
<td>↑</td>
<td>↑ lymphocytes</td>
<td>↑</td>
</tr>
<tr>
<td>Viral</td>
<td>Normal/↑</td>
<td>↑ lymphocytes</td>
<td>Normal/↑</td>
</tr>
</tbody>
</table>

### Infections causing brain abscess

Most commonly viridans streptococci and *Staphylococcus aureus*. If dental infection or extraction precedes abscess, oral anaerobes commonly involved.

Multiple abscesses are usually from bacteremia; single lesions from contiguous sites: otitis media and mastoiditis → temporal lobe and cerebellum; sinusitis or dental infection → frontal lobe. *Toxoplasma* reactivation in AIDS.

### Osteomyelitis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Associated Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assume if no other information is available</td>
<td><em>S. aureus</em> (most common overall)</td>
</tr>
<tr>
<td>Sexually active</td>
<td><em>Neisseria gonorrhoeae</em> (rare), septic arthritis more common</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td><em>Salmonella</em> and <em>S. aureus</em></td>
</tr>
<tr>
<td>Prosthetic joint replacement</td>
<td><em>S. aureus</em> and <em>S. epidermidis</em></td>
</tr>
<tr>
<td>Vertebral involvement</td>
<td><em>S. aureus</em>, <em>Mycobacterium tuberculosis</em> (Pott disease)</td>
</tr>
<tr>
<td>Cat and dog bites</td>
<td><em>Pasteurella multocida</em></td>
</tr>
<tr>
<td>IV drug abuse</td>
<td><em>S. aureus</em>; also <em>Pseudomonas, Candida</em></td>
</tr>
</tbody>
</table>

Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate common but nonspecific. Radiographs are insensitive early but can be useful in chronic osteomyelitis (A, left). MRI is best for detecting acute infection and detailing anatomic involvement (A, right).
**Urinary tract infections**

Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts. Ten times more common in women (shorter urethras colonized by fecal flora). Other predisposing factors: obstruction, kidney surgery, catheterization, GU malformation, diabetes, pregnancy. Males—infants with congenital defects, vesicoureteral reflux. Elderly—enlarged prostate.

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>FEATURES</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| *Escherichia coli*       | Leading cause of UTI. Colonies show strong pink lactose-fermentation on MacConkey agar. | Diagnostic markers:  
  ⊕ Leukocyte esterase = evidence of WBC activity.  
  ⊕ Nitrite test = reduction of urinary nitrates by bacterial species (eg, *E. coli*).  
  ⊕ Urease test = urease-producing bugs (eg, *S. saprophyticus*, *Proteus*, *Klebsiella*). |
| *Staphylococcus saprophyticus* | 2nd leading cause of UTI in sexually active women. |          |
| *Klebsiella pneumoniae*  | 3rd leading cause of UTI. Large mucoid capsule and viscous colonies. |          |
| *Serratia marcescens*    | Some strains produce a red pigment; often nosocomial and drug resistant. |          |
| *Enterococcus*           | Often nosocomial and drug resistant. |          |
| *Proteus mirabilis*      | Motility causes “swarming” on agar; associated with struvite stones. |          |
| *Pseudomonas aeruginosa* | Blue-green pigment and fruity odor; usually nosocomial and drug resistant. |          |

**Common vaginal infections**

<table>
<thead>
<tr>
<th></th>
<th><strong>Bacterial vaginosis</strong></th>
<th><strong>Trichomonas vaginitis</strong></th>
<th><strong>Candida vulvo-vaginitis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIGNS AND SYMPTOMS</strong></td>
<td>No inflammation</td>
<td>Inflammation (“strawberry cervix”)</td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>Thin, white discharge</td>
<td>Frothy, yellow-green, foul-smelling discharge</td>
<td>Thick, white, “cottage cheese” discharge</td>
</tr>
<tr>
<td></td>
<td>with fishy odor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LAB FINDINGS</strong></td>
<td>Clue cells</td>
<td>Motile trichomonads</td>
<td>Pseudohyphae</td>
</tr>
<tr>
<td></td>
<td>pH &gt; 4.5</td>
<td>pH &gt; 4.5</td>
<td>pH normal (4.0–4.5)</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Metronidazole or clindamycin</td>
<td>Metronidazole</td>
<td>Azoles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat sexual partner(s)</td>
<td></td>
</tr>
</tbody>
</table>
ToRCHes infections

Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via delivery (especially HSV-2). Nonspecific signs common to many ToRCHes infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth retardation. Other important infectious agents include Streptococcus agalactiae (group B streptococci), E. coli, and Listeria monocytogenes—all causes of meningitis in neonates. Parvovirus B19 causes hydrops fetalis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Modes of Maternal Transmission</th>
<th>Maternal Manifestations</th>
<th>Neonatal Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasma gondii</td>
<td>Cat feces or ingestion of undercooked meat</td>
<td>Usually asymptomatic; lymphadenopathy (rarely)</td>
<td>Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, +/- “blueberry muffin” rash.</td>
</tr>
<tr>
<td>Rubella</td>
<td>Respiratory droplets</td>
<td>Rash, lymphadenopathy, polyarthritis, polyarthralgia</td>
<td>Classic triad: abnormalities of eye (cataract) and ear (deafness) and congenital heart disease (PDA); +/- “blueberry muffin” rash. “I (eye) ♥ ruby (rubella) earrings.”</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Sexual contact, organ transplants</td>
<td>Usually asymptomatic; mononucleosis-like illness</td>
<td>Hearing loss, seizures, petechial rash, “blueberry muffin” rash, chorioretinitis, periventricular calcifications</td>
</tr>
<tr>
<td>HIV</td>
<td>Sexual contact, needlestick</td>
<td>Variable presentation depending on CD4+ cell count</td>
<td>Recurrent infections, chronic diarrhea</td>
</tr>
<tr>
<td>Herpes simplex virus-2</td>
<td>Skin or mucous membrane contact</td>
<td>Usually asymptomatic; herpetic (vesicular) lesions</td>
<td>Meningoencephalitis, herpetic (vesicular) lesions</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Sexual contact</td>
<td>Chancere (1°) and disseminated rash (2°) are the two stages likely to result in fetal infection</td>
<td>Often results in stillbirth, hydrops fetalis; if child survives, presents with facial abnormalities (eg, notched teeth, saddle nose, short maxilla), saber shins, CN VIII deafness</td>
</tr>
</tbody>
</table>


### Red rashes of childhood

<table>
<thead>
<tr>
<th>AGENT</th>
<th>ASSOCIATED SYNDROME/DISEASE</th>
<th>CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxsackievirus type A</td>
<td>Hand-foot-mouth disease</td>
<td>Oval-shaped vesicles on palms and soles (A); vesicles and ulcers in oral mucosa</td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>Roseola (exanthem subitum)</td>
<td>Asymptomatic rose-colored macules appear on body after several days of high fever; can present with febrile seizures; usually affects infants</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Measles (rubella)</td>
<td>Confluent rash beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Erythema infectiosum (fifth disease)</td>
<td>“Slapped cheek” rash on face (B) (can cause hydrops fetalis in pregnant women)</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Rubella</td>
<td>Pink macules and papules begin at head and move down, remain discrete (C) fine desquamating truncal rash; postauricular lymphadenopathy</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Scarlet fever</td>
<td>Flushed cheeks and circumoral pallor (D) on the face; erythematous, sandpaper-like rash from neck to trunk and extremities; fever and sore throat</td>
</tr>
<tr>
<td>Varicella-Zoster virus</td>
<td>Chickenpox</td>
<td>Vesicular rash begins on trunk; spreads to face (D) and extremities with lesions of different stages</td>
</tr>
</tbody>
</table>

![Image of rash examples](image-url)
### Sexually transmitted infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Features</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Opportunistic infections, Kaposi sarcoma, lymphoma</td>
<td>HIV</td>
</tr>
<tr>
<td>Chancroid</td>
<td>Painful genital ulcer with exudate, inguinal adenopathy</td>
<td><em>Haemophilus ducreyi</em> (it’s so painful, you “do cry”)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Urethritis, cervicitis, epididymitis, conjunctivitis, reactive arthritis, PID</td>
<td><em>Chlamydia trachomatis</em> (D–K)</td>
</tr>
<tr>
<td>Condylomata acuminata</td>
<td>Genital warts, koilocytes</td>
<td>HPV-6 and -11</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>Painful penile, vulvar, or cervical vesicles and ulcers; can cause systemic symptoms such as fever, headache, myalgia</td>
<td>HSV-2, less commonly HSV-1</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge</td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td>Granuloma inguinale (Donovanosis)</td>
<td>Painless, beefy red ulcer that bleeds readily on contact Uncommon in US</td>
<td><em>Klebsiella (Calymmatobacterium) granulomatis</em>; cytoplasmic Donovan bodies (bipolar staining) seen on microscopy</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Jaundice</td>
<td>HBV</td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
<td>Infection of lymphatics; painless genital ulcers, painful lymphadenopathy (ie, buboes)</td>
<td><em>C trachomatis</em> (L1–L3)</td>
</tr>
<tr>
<td>Primary syphilis</td>
<td>Painless chancre</td>
<td><em>Treponema pallidum</em></td>
</tr>
<tr>
<td>Secondary syphilis</td>
<td>Fever, lymphadenopathy, skin rashes, condylomata lata</td>
<td></td>
</tr>
<tr>
<td>Tertiary syphilis</td>
<td>Gummas, tabs dorsalis, general paresis, aortitis, Argyll Robertson pupil</td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>Vaginitis, strawberry cervix, motile in wet prep</td>
<td><em>Trichomonas vaginalis</em></td>
</tr>
</tbody>
</table>
Pelvic inflammatory disease

Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute).

*C. trachomatis*—most common bacterial STI in the United States.

Signs include cervical motion tenderness, adnexal tenderness, purulent cervical discharge.

PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions.

Can lead to perihepatitis (*Fitz-Hugh–Curtis syndrome*)—infection and inflammation of liver capsule and "violin string" adhesions of peritoneum to liver.

---

**Nosocomial infections**

*E. coli* (UTI) and *S. aureus* (wound infection) are the two most common causes.

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>PATHOGEN</th>
<th>UNIQUE SIGNS/SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use</td>
<td><em>Clostridium difficile</em></td>
<td>Watery diarrhea, leukocytosis</td>
</tr>
<tr>
<td>Aspiration (2* to altered mental status, old age)</td>
<td>Polymicrobial, gram − bacteria, often anaerobes</td>
<td>Right lower lobe infiltrate or right upper/middle lobe (patient recumbent); purulent malodorous sputum</td>
</tr>
<tr>
<td>Decubitus ulcers, surgical wounds, drains</td>
<td><em>S. aureus</em> (including MRSA), gram − anaerobes (<em>Bacteroides, Prevotella, Fusobacterium</em>)</td>
<td>Erythema, tenderness, induration, drainage from surgical wound sites</td>
</tr>
<tr>
<td>Intravascular catheters</td>
<td><em>S. aureus</em> (including MRSA), <em>S. epidermidis</em> (long term), <em>Enterobacter</em></td>
<td>Erythema, induration, tenderness, drainage from access sites</td>
</tr>
<tr>
<td>Mechanical ventilation, endotracheal intubation</td>
<td>Late onset: <em>P. aeruginosa</em>, <em>Klebsiella</em>, <em>Acinetobacter</em>, <em>S. aureus</em></td>
<td>New infiltrate on CXR, ↑ sputum production; sweet odor (<em>Pseudomonas</em>)</td>
</tr>
<tr>
<td>Renal dialysis unit, needlestick</td>
<td>HBV, HCV</td>
<td></td>
</tr>
<tr>
<td>Urinary catheterization</td>
<td><em>Proteus spp, E. coli, Klebsiella</em> (infections in your PECker)</td>
<td>Dysuria, leukocytosis, flank pain or costovertebral angle tenderness</td>
</tr>
<tr>
<td>Water aerosols</td>
<td><em>Legionella</em></td>
<td>Signs of pneumonia, GI symptoms (diarrhea, nausea, vomiting), neurologic abnormalities</td>
</tr>
</tbody>
</table>
### Bugs affecting unvaccinated children

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>FINDINGS/LABS</th>
<th>PATHOGEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Beginning at head and moving down with postauricular lymphadenopathy</td>
<td>Rubella virus</td>
</tr>
<tr>
<td></td>
<td>Beginning at head and moving down; rash preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa</td>
<td>Measles virus</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>Microbe colonizes nasopharynx</td>
<td><em>H. influenzae</em> type b</td>
</tr>
<tr>
<td></td>
<td>Can also lead to myalgia and paralysis</td>
<td>Poliovirus</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epiglottitis</td>
<td>Fever with dysphagia, drooling, and difficulty breathing due to edematous “cherry red” epiglottis; “thumbprint sign” on x-ray</td>
<td><em>H. influenzae</em> type b (also capable of causing epiglottitis in fully immunized children)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Grayish oropharyngeal exudate (“pseudomembranes” may obstruct airway); painful throat</td>
<td><em>Corynebacterium diphteriae</em> (elaborates toxin that causes necrosis in pharynx, cardiac, and CNS tissue)</td>
</tr>
</tbody>
</table>

### Bug hints

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>ORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asplenic patient (due to surgical splenectomy or autosplenectomy, eg, chronic sickle cell disease)</td>
<td>Encapsulated microbes, especially SHiN (<em>S. pneumoniae</em> &gt;&gt; <em>H. influenzae</em> type b &gt;&gt; <em>N. meningitidis</em>)</td>
</tr>
<tr>
<td>Branching rods in oral infection, sulfur granules</td>
<td><em>Actinomyces israelii</em></td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Catalase + microbes, especially <em>S. aureus</em></td>
</tr>
<tr>
<td>“Currant jelly” sputum</td>
<td><em>Klebsiella</em></td>
</tr>
<tr>
<td>Dog or cat bite</td>
<td><em>Pasteurella multocida</em></td>
</tr>
<tr>
<td>Facial nerve palsy (typically bilateral)</td>
<td><em>Borrelia burgdogeri</em> (Lyme disease)</td>
</tr>
<tr>
<td>Fungal infection in diabetic or immunocompromised patient</td>
<td><em>Mucor</em> or <em>Rhizopus</em> spp.</td>
</tr>
<tr>
<td>Health care provider</td>
<td>HBV, HCV (from needlestick)</td>
</tr>
<tr>
<td>Neutropenic patients</td>
<td><em>Candida albicans</em> (systemic), <em>Aspergillus</em></td>
</tr>
<tr>
<td>Organ transplant recipient</td>
<td>CMV</td>
</tr>
<tr>
<td>PAS ⊕</td>
<td><em>Tropheryma whippelii</em> (Whipple disease)</td>
</tr>
<tr>
<td>Pediatric infection</td>
<td><em>Haemophilus influenzae</em> (including epiglottitis)</td>
</tr>
<tr>
<td>Pneumonia in cystic fibrosis, burn infection</td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>Pus, empyema, abscess</td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>Rash on hands and feet</td>
<td><em>Coxsackie A virus</em>, <em>Treponema pallidum</em>, <em>Rickettsia rickettsii</em></td>
</tr>
<tr>
<td>Sepsis/meningitis in newborn</td>
<td>Group B strep</td>
</tr>
<tr>
<td>Surgical wound</td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>Traumatic open wound</td>
<td><em>Clostridium perfringens</em></td>
</tr>
</tbody>
</table>
Antimicrobial therapy

**Penicillin G, V**

Penicillin G (IV and IM form), penicillin V (oral). Prototype β-lactam antibiotics.

**MECHANISM**

**CLINICAL USE**
Mostly used for gram ⊕ organisms (S pneumoniae, S pyogenes, Actinomyces). Also used for gram ⊕ cocci (mainly N meningitidis) and spirochetes (namely T pallidum). Bactericidal for gram ⊕ cocci, gram ⊕ rods, and spirochetes. β-lactamase sensitive.

**ADVERSE EFFECTS**
Hypersensitivity reactions, direct Coombs ⊕ hemolytic anemia, drug-induced interstitial nephritis.

**RESISTANCE**
β-lactamase cleaves the β-lactam ring. Mutations in penicillin-binding proteins.
### Penicillinase-sensitive penicillins

**Mechanism**
Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by β-lactamase.

**Coverage**
Penicillinase-sensitive penicillins are AMpolished penicillin. Amoxicillin has greater oral bioavailability than ampicillin.

**Clinical Use**

**Adverse Effects**
Hypersensitivity reactions, rash, pseudomembranous colitis.

**Mechanism of Resistance**
Penicillinase (a type of β-lactamase) cleaves β-lactam ring.

### Penicillinase-resistant penicillins

**Mechanism**
Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of β-lactamase to β-lactam ring.

**Clinical Use**
*S. aureus* (except MRSA). “Use naf (nafcillin) for staph.”

**Adverse Effects**
Hypersensitivity reactions, interstitial nephritis.

**Mechanism of Resistance**
MRSA has altered penicillin-binding protein target site.

### Antipseudomonal penicillins

**Mechanism**
Same as penicillin. Extended spectrum. Penicillinase sensitive; use with β-lactamase inhibitors.

**Clinical Use**
Pseudomonas spp. and gram-negative rods.

**Adverse Effects**
Hypersensitivity reactions.

### β-lactamase inhibitors

Include Clavulanic acid, Avibactam, Sulbactam, Tazobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β-lactamase (penicillinase).

**CAST.**
### Cephalosporins

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Organisms typically not covered by 1st–4th generation cephalosporins are \textit{LAME}: \textit{Listeria}, \textit{Atypicals} (Chlamydia, Mycoplasma), MRSA, and \textit{Enterococci}.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>1st generation (cefazolin, cephalexin)—gram $\oplus$ cocci, \textit{Proteus mirabilis}, \textit{E coli}, \textit{Klebsiella pneumoniae}. Cefazolin used prior to surgery to prevent \textit{S aureus} wound infections.</td>
</tr>
<tr>
<td></td>
<td>1st generation—\textit{PEcK}.</td>
</tr>
<tr>
<td></td>
<td>2nd grader wear fake fox fur to tea parties.</td>
</tr>
<tr>
<td></td>
<td>2nd generation—\textit{HENS PEcK}.</td>
</tr>
<tr>
<td></td>
<td>Can cross blood-brain barrier.</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone—meningitis, gonorrhea, disseminated Lyme disease.</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime—\textit{Pseudomonas}.</td>
</tr>
<tr>
<td></td>
<td>3rd generation (ceftriaxone, cefotaxime, cefpodoxime, ceftazidime)—serious gram $\ominus$ infections resistant to other $\beta$-lactams.</td>
</tr>
<tr>
<td></td>
<td>4th generation (cefepime)—gram $\ominus$ organisms, with $\Dagger$ activity against \textit{Pseudomonas} and gram $\ominus$ organisms.</td>
</tr>
<tr>
<td></td>
<td>5th generation (ceftaroline)—broad gram $\ominus$ and gram $\ominus$ organism coverage; unlike 1st–4th generation cephalosporins, ceftaroline covers \textit{Listeria}, MRSA, and \textit{Enterococcus faecalis}—does not cover \textit{Pseudomonas}.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Low rate of cross-reactivity even in penicillin-allergic patients. $\Dagger$ nephrotoxicity of aminoglycosides.</td>
</tr>
<tr>
<td>MECHANISM OF RESISTANCE</td>
<td>Inactivated by cephalosporinases (a type of $\beta$-lactamase). Structural change in penicillin-binding proteins (transpeptidases).</td>
</tr>
</tbody>
</table>
### Carbapenems

**Doripenem, Imipenem, Meropenem, Ertapenem (DIME antibiotics are given when there is a 10/10 [life-threatening] infection).**

| MECHANISM | Imipenem is a broad-spectrum, β-lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to inactivation of drug in renal tubules. With imipenem, “the kill is lastin’ with cilastatin.” Newer carbapenems include ertapenem (limited Pseudomonas coverage) and doripenem. |
| CLINICAL USE | Gram + cocci, gram − rods, and anaerobes. Wide spectrum and significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a risk of seizures and is stable to dehydropeptidase I. |
| ADVERSE EFFECTS | GI distress, rash, and CNS toxicity (seizures) at high plasma levels. |

### Monobactams

**Aztreonam**

| CLINICAL USE | Gram − rods only—no activity against gram + rods or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides. |
| ADVERSE EFFECTS | Usually nontoxic; occasional GI upset. |

### Vancomycin

| MECHANISM | Inhibits cell wall peptidoglycan formation by binding D-Ala-D-Ala portion of cell wall precursors. Bactericidal against most bacteria (bacteriostatic against *C difficile*). Not susceptible to β-lactamases. |
| CLINICAL USE | Gram + bugs only—serious, multidrug-resistant organisms, including MRSA, *S epidermidis*, sensitive *Enterococcus* species, and *Clostridium difficile* (oral dose for pseudomembranous colitis). |
| ADVERSE EFFECTS | Well tolerated in general—but NOT trouble free. Nephrotoxicity, Otoxicity, Thrombophlebitis, diffuse flushing—**red man syndrome** (largely preventable by pretreatment with antihistamines and slow infusion rate), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). |

| MECHANISM OF RESISTANCE | Occurs in bacteria (eg, *Enterococcus*) via amino acid modification of D-Ala-D-Ala to D-Ala-D-Lac. “If you Lack a D-Ala (dollar), you can’t ride the van (vancomycin).” |
Protein synthesis inhibitors

Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected. All are bacteriostatic, except aminoglycosides (bactericidal) and linezolid (variable).

30S inhibitors
- Aminoglycosides
- Tetracyclines

50S inhibitors
- Chloramphenicol, Clindamycin
- Erythromycin (macrolides)
- Linezolid

“Buy AT 30, CCEL (sell) at 50.”

Aminoglycosides
- Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.

**MECHANISM**
Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require O₂ for uptake; therefore ineffective against anaerobes.

**CLINICAL USE**

**ADVERSE EFFECTS**
Nephrotoxicity, Neuromuscular blockade, Otoxicity (especially when used with loop diuretics). Teratogen.

**MECHANISM OF RESISTANCE**
Bacterial transferase enzymes inactivate the drug by acetylation, phosphorylation, or adenylation.

“Mean” (aminoglycoside) GNATS caNNOT kill anaerobes.
### Tetracyclines

- **Tetracycline, doxycycline, minocycline.**

#### MECHANISM

Bacteriostatic; bind to 30S and prevent attachment of aminoseryl-tRNA. Limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk (Ca\(^{2+}\)), antacids (Ca\(^{2+}\) or Mg\(^{2+}\)), or iron-containing preparations because divalent cations inhibit drugs' absorption in the gut.

#### CLINICAL USE

*Borrelia burgdorferi, M pneumoniae.* Drugs' ability to accumulate intracellularly makes them very effective against *Rickettsia* and *Chlamydia*. Also used to treat acne. Doxycycline effective against MRSA.

#### ADVERSE EFFECTS


#### MECHANISM OF RESISTANCE

4\(^{t}\) uptake or 4\(^{t}\) efflux out of bacterial cells by plasmid-encoded transport pumps.

### Glycylcyclines

- **Tigecycline.**

#### MECHANISM


#### CLINICAL USE

Broad-spectrum anaerobic, gram - , and gram + coverage. Multidrug-resistant organisms (MRSA, VRE) or infections requiring deep tissue penetration.

#### ADVERSE EFFECTS

GI symptoms: nausea, vomiting.

### Chloramphenicol

#### MECHANISM

Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic.

#### CLINICAL USE

Meningitis (*Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*) and rickettsial diseases (eg, Rocky Mountain spotted fever [*Rickettsia rickettsii*]). Limited use due to toxicity but often still used in developing countries because of low cost.

#### ADVERSE EFFECTS

Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronosyltransferase).

#### MECHANISM OF RESISTANCE

Plasmid-encoded acetyltransferase inactivates the drug.

### Clindamycin

#### MECHANISM

Blocks peptide transfer (translocation) at 50S ribosomal subunit. Bacteriostatic.

#### CLINICAL USE

Anaerobic infections (eg, *Bacteroides* spp., *Clostridium perfringens*) in aspiration pneumonia, lung abscesses, and oral infections. Also effective against invasive group A streptococcal infection. Treats anaerobic infections above the diaphragm vs metronidazole (anaerobic infections below diaphragm).

#### ADVERSE EFFECTS

Pseudomembranous colitis (*C difficile* overgrowth), fever, diarrhea.
### Oxazolidinones

<table>
<thead>
<tr>
<th>Linezolid.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
</tr>
<tr>
<td><strong>MECHANISM OF RESISTANCE</strong></td>
</tr>
</tbody>
</table>

### Macrolides

<table>
<thead>
<tr>
<th>Azithromycin, clarithromycin, erythromycin.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
</tr>
<tr>
<td><strong>MECHANISM OF RESISTANCE</strong></td>
</tr>
</tbody>
</table>

### Polymyxins

<table>
<thead>
<tr>
<th>Colistin (polymyxin E), polymyxin B.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
</tr>
</tbody>
</table>
### Sulfonamides

**Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine.**

**MECHANISM**

Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).

**CLINICAL USE**

Gram +, gram −, Nocardia. TMP-SMX for simple UTI.

**ADVERSE EFFECTS**

Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, Stevens-Johnson syndrome, kernicterus in infants, displace other drugs from albumin (eg, warfarin).

**MECHANISM OF RESISTANCE**

Altered enzyme (bacterial dihydropteroate synthase), ↓ uptake, or ↑ PABA synthesis.

---

### Dapsone

**MECHANISM**

Similar to sulfonamides, but structurally distinct agent.

**CLINICAL USE**

Leprosy (lepromatous and tuberculoid), *Pneumocystis jirovecii* prophylaxis.

**ADVERSE EFFECTS**

Hemolysis if G6PD deficient, methemoglobinemia.

---

### Trimethoprim

**MECHANISM**

Inhibits bacterial dihydrofolate reductase. Bacteriostatic.

**CLINICAL USE**

Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMP-SMX]), causing sequential block of folate synthesis. Combination used for UTIs, *Shigella, Salmonella, Pneumocystis jirovecii* pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis.

**ADVERSE EFFECTS**

Megaloblastic anemia, leukopenia, granulocytopenia, which may be avoided with coadministration of folinic acid. TMP Treats Marrow Poorly.
### Fluoroquinolones

**MECHANISM**
Inhibit prokaryotic enzymes topoisomerase II (DNA gyrase) and topoisomerase IV.
Bactericidal. Must not be taken with antacids.

**CLINICAL USE**
Gram - rods of urinary and GI tracts (including *Pseudomonas*), some gram + organisms, otitis externa.

**ADVERSE EFFECTS**
GI upset, superinfections, skin rashes, headache, dizziness. Less commonly, can cause leg cramps and myalgias.
Contraindicated in pregnant women, nursing mothers, and children < 18 years old due to possible damage to cartilage. Some may prolong QT interval.
May cause tendonitis or tendon rupture in people > 60 years old and in patients taking prednisone. Ciprofloxacin inhibits cytochrome P-450.

**MECHANISM OF RESISTANCE**
Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.

**Fluoroquinolones hurt attachments to your bones.**

### Daptomycin

**MECHANISM**
Lipopeptide that disrupts cell membranes of gram + cocci by creating transmembrane channels.

**CLINICAL USE**
*S aureus* skin infections (especially MRSA), bacteremia, endocarditis, VRE. Not used for pneumonia (avidly binds to and is inactivated by surfactant).

**ADVERSE EFFECTS**
Myopathy, rhabdomyolysis.

### Metronidazole

**MECHANISM**
Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal.

**CLINICAL USE**
Treats *Giardia, Entamoeba, Trichomonas, Gardnerella vaginalis, Anaerobes (Bacteroides, C difficile)*. Can be used in place of amoxicillin in *H pylori* “triple therapy” in case of penicillin allergy.

**ADVERSE EFFECTS**
Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.

**GET GAP on the Metro with metronidazole!**
Treats anaerobic infection below the diaphragm vs clindamycin (anaerobic infections above diaphragm).
### Antimycobacterial drugs

<table>
<thead>
<tr>
<th>BACTERIUM</th>
<th>PROPHYLAXIS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em></td>
<td>Isoniazid</td>
<td>Rifampin, Isoniazid, Pyrazinamide, Ethambutol (RIPE for treatment)</td>
</tr>
<tr>
<td><em>M. avium—intracellulare</em></td>
<td>Azithromycin, rifabutin</td>
<td>More drug resistant than <em>M. tuberculosis</em>. Azithromycin or clarithromycin + ethambutol. Can add rifabutin or ciprofloxacin.</td>
</tr>
<tr>
<td><em>M. leprae</em></td>
<td>N/A</td>
<td>Long-term treatment with dapsone and rifampin for tuberculoid form. Add clofazimine for lepromatous form.</td>
</tr>
</tbody>
</table>

#### MYCOBACTERIAL CELL

**MYCINIC ACID SYNTHESIS**
- Isoniazid

**ARABINOGLACTAN SYNTHESIS** (arabinosyl transferase)
- Ethambutol

**INTRACELLULAR** (unclear mechanism)
- Rifampin
- Pyrazinamide

**mRNA SYNTHESIS** (DNA-dependent RNA polymerase)

**Rifamycins**

- Rifampin, rifabutin.

**MECHANISM**
- Inhibit DNA-dependent RNA polymerase.

**CLINICAL USE**
- *Mycobacterium tuberculosis*: delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with *H. influenzae* type b.

**ADVERSE EFFECTS**
- Minor hepatotoxicity and drug interactions († cytochrome P-450); orange body fluids (nonhazardous side effect). Rifabutin favored over rifampin in patients with HIV infection due to less cytochrome P-450 stimulation.

**MECHANISM OF RESISTANCE**
- Mutations reduce drug binding to RNA polymerase. Monotherapy rapidly leads to resistance.

**Rifampin’s 4 R’s**:
- RNA polymerase inhibitor
- Ramps up microsomal cytochrome P-450
- Red/orange body fluids
- Rapid resistance if used alone

**Rifampin ramps up cytochrome P-450, but rifabutin does not.**
### Isoniazid

**MECHANISM**
- Synthesis of mycolic acids. Bacterial catalase-peroxidase (encoded by KatG) needed to convert INH to active metabolite.

**CLINICAL USE**
- *Mycobacterium tuberculosis*. The only agent used as solo prophylaxis against TB. Also used as monotherapy for latent TB.

**ADVERSE EFFECTS**
- Hepatotoxicity, P-450 inhibition, drug-induced SLE, anion gap metabolic acidosis, vitamin B₆ deficiency (peripheral neuropathy, sideroblastic anemia). Administer with pyridoxine (B₆).

**MECHANISM OF RESISTANCE**
- Mutations leading to underexpression of KatG.

---

### Pyrazinamide

**MECHANISM**
- Mechanism uncertain. Pyrazinamide is a prodrug that is converted to the active compound pyrazinoic acid. Works best at acidic pH (eg, in host phagolysosomes).

**CLINICAL USE**
- *Mycobacterium tuberculosis*.

**ADVERSE EFFECTS**
- Hyperuricemia, hepatotoxicity.

---

### Ethambutol

**MECHANISM**
- Carbohydrate polymerization of mycobacterium cell wall by blocking arabinosyltransferase.

**CLINICAL USE**
- *Mycobacterium tuberculosis*.

**ADVERSE EFFECTS**
- Optic neuropathy (red-green color blindness). Pronounce “eyethambutol.”

---

### Streptomycin

**MECHANISM**
- Interferes with 30S component of ribosome.

**CLINICAL USE**
- *Mycobacterium tuberculosis* (2nd line).

**ADVERSE EFFECTS**
- Tinnitus, vertigo, ataxia, nephrotoxicity.
Antimicrobial prophylaxis

<table>
<thead>
<tr>
<th>CLINICAL SCENARIO</th>
<th>MEDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk for endocarditis and undergoing surgical or dental procedures</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Exposure to gonorrhea</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>History of recurrent UTIs</td>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Exposure to meningococcal infection</td>
<td>Ceftriaxone, ciprofloxacin, or rifampin</td>
</tr>
<tr>
<td>Pregnant woman carrying group B strep</td>
<td>Intrapartum penicillin G or ampicillin</td>
</tr>
<tr>
<td>Prevention of gonococcal conjunctivitis in newborn</td>
<td>Erythromycin ointment on eyes</td>
</tr>
<tr>
<td>Prevention of postsurgical infection due to S. aureus</td>
<td>Cefazolin</td>
</tr>
<tr>
<td>Prophylaxis of strep pharyngitis in child with prior rheumatic fever</td>
<td>Benzathine penicillin G or oral penicillin V</td>
</tr>
<tr>
<td>Exposure to syphilis</td>
<td>Benzathine penicillin G</td>
</tr>
</tbody>
</table>

Prophylaxis in HIV patients

<table>
<thead>
<tr>
<th>CD4 COUNT</th>
<th>PROPHYLAXIS</th>
<th>INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 200 cells/mm³</td>
<td>TMP-SMX</td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td>CD4 &lt; 100 cells/mm³</td>
<td>TMP-SMX</td>
<td>Pneumocystis pneumonia and toxoplasmosis</td>
</tr>
<tr>
<td>CD4 &lt; 50 cells/mm³</td>
<td>Azithromycin or clarithromycin</td>
<td>Mycobacterium avium complex</td>
</tr>
</tbody>
</table>

Treatment of highly resistant bacteria

MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline, doxycycline.
VRE: linezolid and streptogramins (quinupristin, dalfopristin).
Multi-drug-resistant P. aeruginosa, multi-drug-resistant Acinetobacter baumanni: polymyxins B and E (colistin).

Antifungal therapy

**LANOSTEROL SYNTHESIS**
- Terbinafine

**ERGOSTEROL SYNTHESIS**
- Azoles: Clotrimazole, Fluconazole, Itraconazole, Ketoconazole, Micronazole, Voriconazole

**CELL WALL SYNTHESIS**
- Echinocandins: Anidulafungin, Caspofungin, Micafungin

**CELL MEMBRANE INTEGRITY**
- Polyenes: Amphotericin B, Nystatin

**NUCLEIC ACID SYNTHESIS**
- Flucytosine
### Amphotericin B

**MECHANISM**
Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes.

**Amphotericin** "tears" holes in the fungal membrane by forming pores.

**CLINICAL USE**

**ADVERSE EFFECTS**
Fever/chills ("shake and bake"), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis ("amphotericible"). Hydration ↓ nephrotoxicity. Liposomal amphotericin ↓ toxicity.

### Nystatin

**MECHANISM**
Same as amphotericin B. Topical use only as too toxic for systemic use.

**CLINICAL USE**
“Swish and swallow” for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

### Flucytosine

**MECHANISM**
Inhibits DNA and RNA biosynthesis by conversion to 5-fluorouracil by cytosine deaminase.

**CLINICAL USE**
Systemic fungal infections (especially meningitis caused by *Cryptococcus*) in combination with amphotericin B.

**ADVERSE EFFECTS**
Bone marrow suppression.

### Azoles

Clotrimazole, fluconazole, isavuconazole, itraconazole, ketoconazole, miconazole, voriconazole.

**MECHANISM**
Inhibit fungal sterol (ergosterol) synthesis by inhibiting the cytochrome P-450 enzyme that converts lanosterol to ergosterol.

**CLINICAL USE**
Local and less serious systemic mycoses. Fluconazole for chronic suppression of cryptococcal meningitis in AIDS patients and candidal infections of all types. Itraconazole for *Blastomyces, Coccidioides, Histoplasma*. Clotrimazole and miconazole for topical fungal infections. Voriconazole for *Aspergillus* and some *Candida*. Isavuconazole for serious *Aspergillus* and *Mucor* infections.

**ADVERSE EFFECTS**
Testosterone synthesis inhibition (gynecomastia, especially with ketoconazole), liver dysfunction (inhibits cytochrome P-450).

### Terbinafine

**MECHANISM**
Inhibits the fungal enzyme squalene epoxidase.

**CLINICAL USE**
Dermatophytoes (especially onychomycosis—fungal infection of finger or toe nails).

**ADVERSE EFFECTS**
GI upset, headaches, hepatotoxicity, taste disturbance.
### Echinocandins

**MECHANISM**
Inhibit cell wall synthesis by inhibiting synthesis of β-glucan.

**CLINICAL USE**
Invasive aspergillosis, Candida.

**ADVERSE EFFECTS**
GI upset, flushing (by histamine release).

### Griseofulvin

**MECHANISM**
Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (eg, nails).

**CLINICAL USE**
Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).

**ADVERSE EFFECTS**
Teratogenic, carcinogenic, confusion, headaches, disulfiram-like reaction, ↑ cytochrome P-450 and warfarin metabolism.

### Antiprotozoal therapy

**Pyrimethamine** (toxoplasmosis), suramin and melarsoprol (*Trypanosoma brucei*), nifurtimox (*T cruzi*), sodium stibogluconate (leishmaniasis).

### Anti-mite/lice therapy

**Permethrin** (inhibits Na+ channel deactivation → neuronal membrane depolarization), malathion (acetylcholinesterase inhibitor), lindane (blocks GABA channels → neurotoxicity). Used to treat scabies (*Sarcoptes scabiei*) and lice (*Pediculus* and *Pthirus*).

**Treat PML** (Pesty Mites and Lice) with **PML** (Permethrin, Malathion, Lindane), because they NAG you (Na, AChE, GABA blockade).

### Chloroquine

**MECHANISM**
Blocks detoxification of heme into hemozoin. Heme accumulates and is toxic to plasmodia.

**CLINICAL USE**
Treatment of plasmodial species other than *P falciparum* (frequency of resistance in *P falciparum* is too high). Resistance due to membrane pump that ↓ intracellular concentration of drug. Treat *P falciparum* with artemether/lumefantrine or atovaquone/proguanil. For life-threatening malaria, use quinidine in US (quinine elsewhere) or artesunate.

**ADVERSE EFFECTS**
Retinopathy; pruritus (especially in dark-skinned individuals).

### Antihelminthic therapy

**Pyrantel pamoate**, Ivermectin, Mebendazole (microtubule inhibitor), Praziquantel, Diethylcarbamazine. Helminths get PIMP’D.
Oseltamivir, zanamivir

**MECHANISM**
Inhibit influenza neuraminidase → release of progeny virus.

**CLINICAL USE**
Treatment and prevention of both influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness.

Acyclovir, famciclovir, valacyclovir

**MECHANISM**
Guanosine analogs. Monophosphorylated by HSV/VZV thymidine kinase and not phosphorylated in uninfected cells → few adverse effects. Triphosphate formed by cellular enzymes. Preferentially inhibit viral DNA polymerase by chain termination.

**CLINICAL USE**
HSV and VZV. Weak activity against EBV. No activity against CMV. Used for HSV-induced mucocutaneous and genital lesions as well as for encephalitis. Prophylaxis in immunocompromised patients. No effect on latent forms of HSV and VZV. Valacyclovir, a prodrug of acyclovir, has better oral bioavailability. For herpes zoster, use famciclovir.

**ADVERSE EFFECTS**
Obstructive crystalline nephropathy and acute renal failure if not adequately hydrated.

**MECHANISM OF RESISTANCE**
Mutated viral thymidine kinase.
### Ganciclovir

**MECHANISM**
5'-monophosphate formed by a CMV viral kinase. Guanosine analog. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase.

**CLINICAL USE**
CMV, especially in immunocompromised patients. Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability.

**ADVERSE EFFECTS**
Bone marrow suppression (leukopenia, neutropenia, thrombocytopenia), renal toxicity. More toxic to host enzymes than acyclovir.

**MECHANISM OF RESISTANCE**
Mutated viral kinase.

### Foscarnet

**MECHANISM**
Viral DNA/RNA polymerase inhibitor and HIV reverse transcriptase inhibitor. Binds to pyrophosphate-binding site of enzyme. Does not require any kinase activation.

**CLINICAL USE**
CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.

**ADVERSE EFFECTS**
Nephrotoxicity, electrolyte abnormalities (hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, hypomagnesemia) can lead to seizures.

**MECHANISM OF RESISTANCE**
Mutated DNA polymerase.

### Cidofovir

**MECHANISM**
Preferentially inhibits viral DNA polymerase. Does not require phosphorylation by viral kinase.

**CLINICAL USE**
CMV retinitis in immunocompromised patients; acyclovir-resistant HSV. Long half-life.

**ADVERSE EFFECTS**
Nephrotoxicity (coadminister with probenecid and IV saline to ↓ toxicity).
HIV therapy

Highly active antiretroviral therapy (HAART): often initiated at the time of HIV diagnosis. Strongest indication for patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm³), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and preferably an integrase inhibitor.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3′ OH group). Tenofovir is a nucleotide; the others are nucleosides. All need to be phosphorylated to be active.</td>
<td>Bone marrow suppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), peripheral neuropathy, lactic acidosis (nucleosides), anemia (ZDV), pancreatitis (didanosine).</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td></td>
<td></td>
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<tr>
<td>Lamivudine (3TC)</td>
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<td></td>
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<tr>
<td>Stavudine (d4T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>ZDV can be used for general prophylaxis and during pregnancy to ↓ risk of fetal transmission. Have you dined (vudine) with my nucleic (nucleosides) family?</td>
<td>Abacavir contraindicated if patient has HLA-B*5701 mutation due to ↑ risk of hypersensitivity.</td>
</tr>
<tr>
<td>Zidovudine (ZDV, formerly AZT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Bind to reverse transcriptase at site different from NRTIs. Do not require phosphorylation to be active or compete with nucleotides.</td>
<td>Rash and hepatotoxicity are common to all NNRTIs. Vivid dreams and CNS symptoms are common with efavirenz. Delavirdine and efavirenz are contraindicated in pregnancy.</td>
</tr>
<tr>
<td>Efavirenz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>Assembly of virions depends on HIV-1 protease (pol gene), which cleaves the polypeptide products of HIV mRNA into their functional parts. Thus, protease inhibitors prevent maturation of new viruses.</td>
<td>Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy (Cushing-like syndrome). Nephropathy, hematuria, thrombocytopenia (indinavir).</td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
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<tr>
<td>Darunavir</td>
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<tr>
<td>Fosamprenavir</td>
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<tr>
<td>Indinavir</td>
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<tr>
<td>Lopinavir</td>
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<tr>
<td>Ritonavir</td>
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<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Integrase inhibitors</strong></td>
<td>Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.</td>
<td>↑ creatine kinase.</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fusion inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Binds gp41, inhibiting viral entry.</td>
<td>Skin reaction at injection sites. Enfuvirtide inhibits fusion.</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gp120.</td>
<td>Maraviroc inhibits docking.</td>
</tr>
</tbody>
</table>
Interferons

**MECHANISM**
Glycoproteins normally synthesized by virus-infected cells, exhibiting a wide range of antiviral and antitumoral properties.

**CLINICAL USE**
Chronic HBV and HVC, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma, multiple sclerosis, chronic granulomatous disease.

**ADVERSE EFFECTS**
Flu-like symptoms, depression, neutropenia, myopathy.

Hepatitis C therapy

Chronic HCV infection is treated with different combinations of the following drugs; none is approved as monotherapy. Ribavirin also used to treat RSV (palivizumab preferred in children).

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir</td>
<td>Viral phosphoprotein (NS5A) inhibitor; NS5A plays important role in replication.</td>
<td>Hemolytic anemia, severe teratogen.</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Inhibits synthesis of guanine nucleotides by competitively inhibiting inosine monophosphate dehydrogenase.</td>
<td>Photosensitivity reactions, rash.</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>HCV protease (NS3/4A); prevents viral replication.</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Inhibits HCV RNA-dependent RNA polymerase (NS5B) acting as a chain terminator.</td>
<td>Fatigue, headache, nausea.</td>
</tr>
</tbody>
</table>

Disinfection and sterilization

Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of all microbes including spores (sterilization).

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoclave</td>
<td>Pressurized steam at &gt; 120°C. Sporicidal. May not reliably inactivate prions.</td>
</tr>
<tr>
<td>Alcohols</td>
<td>Denature proteins and disrupt cell membranes. Not sporicidal.</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Denatures proteins and disrupts cell membranes. Not sporicidal.</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Oxidizes and denatures proteins. Sporicidal.</td>
</tr>
<tr>
<td>Iodine and iodophors</td>
<td>Halogenation of DNA, RNA, and proteins. May be sporicidal.</td>
</tr>
<tr>
<td>Quaternary amines</td>
<td>Impair permeability of cell membranes. Not sporicidal.</td>
</tr>
</tbody>
</table>

Antimicrobials to avoid in pregnancy

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>Kernicterus</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Cartilage damage</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Embryotoxicity</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Discolored teeth, inhibition of bone growth</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Gray baby syndrome</td>
</tr>
</tbody>
</table>

SAFe Children Take Really Good Care.
“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.”
—Friedrich Nietzsche

“You cannot separate passion from pathology any more than you can separate a person’s spirit from his body.”
—Richard Selzer

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis.
Cellular adaptations
Reversible changes that can be physiologic (eg, uterine enlargement during pregnancy) or pathologic (eg, myocardial hypertrophy \( \Rightarrow \) systemic HTN to prevent injury). If stress is excessive or persistent, adaptations can progress to cell injury (eg, significant LV hypertrophy \( \Rightarrow \) injury to myofibrils \( \Rightarrow \) HF).

Hypertrophy
\( \uparrow \) structural proteins and organelles \( \Rightarrow \) \( \uparrow \) in size of cells.

Hyperplasia
Controlled proliferation of stem cells and differentiated cells \( \Rightarrow \) \( \uparrow \) in number of cells. Excessive stimulation \( \Rightarrow \) pathologic hyperplasia (eg, endometrial hyperplasia), which may progress to dysplasia and cancer.

Atrophy
\( \downarrow \) in tissue mass due to \( \downarrow \) in size (\( \downarrow \) cytoskeleton degradation via ubiquitin-proteasome pathway and autophagy, \( \downarrow \) protein synthesis) and/or number of cells (apoptosis). Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.

Metaplasia
Reprogramming of stem cells \( \Rightarrow \) replacement of one cell type by another that can adapt to a new stress. Usually due to exposure to an irritant, such as gastric acid (\( \Rightarrow \) Barrett esophagus) or cigarette smoke (\( \Rightarrow \) respiratory ciliated columnar epithelium replaced by stratified squamous epithelium). May progress to dysplasia \( \Rightarrow \) malignant transformation with persistent insult (eg, Barrett esophagus \( \Rightarrow \) esophageal adenocarcinoma). Metaplasia of connective tissue can also occur (eg, myositis ossificans, the formation of bone within muscle after trauma).

Dysplasia
Disordered, precancerous epithelial cell growth. Characterized by loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, \( \uparrow \) nuclear:cytoplasmic ratio and clumped chromatin). Mild and moderate dysplasias (ie, do not involve entire thickness of epithelium) may regress with alleviation of inciting cause. Severe dysplasia usually becomes irreversible and progresses to carcinoma in situ. Usually preceded by persistent metaplasia or pathologic hyperplasia.
Cell injury

**Normal cell**
- Membrane blebbing
- Nuclear chromatin clumping

**Reversible**
- Cellular/mitochondrial swelling ($\downarrow$ ATP → $\downarrow$ activity of Na+/K+ and Ca²⁺ pumps)
- Ribosomal/polysomal detachment ($\downarrow$ protein synthesis)
- Membrane blebbing
- Nuclear chromatin clumping

**Irreversible**
- Rupture of lysosomes and autolysis
- Plasma membrane damage (degradation of membrane phospholipid) → leakage of cytosolic enzymes into serum, influx of Ca²⁺ activating lysosomal enzymes
- Mitochondrial permeability

**Cell death**
- Nucleus:
  - Pyknosis (condensation)
  - Karyorrhexis (fragmentation)
  - Karyolysis (fading)

- Rupture of lysosomes and autolysis
- Influx of Ca²⁺ activating lysosomal enzymes
- Mitochondrial permeability
Apoptosis

ATP-dependent programmed cell death.
Intrinsic and extrinsic pathways; both pathways activate caspases (cytosolic proteases) → cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.
Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis (nuclear shrinkage), and karyorrhexis (fragmentation caused by endonuclease-mediated cleavage).
Cell membrane typically remains intact without significant inflammation (unlike necrosis).
DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

**Intrinsic (mitochondrial) pathway**
Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (eg, IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (eg, radiation, toxins, hypoxia).
Regulated by Bcl-2 family of proteins. BAX and BAK are proapoptotic, while Bcl-2 and Bcl-xL are antiapoptotic.
BAX and BAK form pores in the mitochondrial membrane → release of cytochrome C from inner mitochondrial membrane into the cytoplasm → activation of caspases.
Bcl-2 keeps the mitochondrial membrane impermeable, thereby preventing cytochrome C release.
Bcl-2 overexpression (eg, follicular lymphoma t[14;18]) → caspase activation → tumorigenesis.

**Extrinsic (death receptor) pathway**
2 pathways:
- Ligand receptor interactions (FasL binding to Fas [CD95] or TNF-α binding to its receptor)
- Immune cell (cytotoxic T-cell release of perforin and granzyme B)
Fas-FasL interaction is necessary in thymic medullary negative selection. Mutations in Fas → numbers of circulating self-reacting lymphocytes due to failure of clonal deletion.
Defective Fas-FasL interactions cause autoimmune lymphoproliferative syndrome.
**Necrosis**

Enzymatic degradation and protein denaturation of cell due to exogenous injury → intracellular components leak. Inflammatory process (unlike apoptosis).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SEEN IN</th>
<th>DUE TO</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulative</td>
<td>Ischemia/infarcts in most tissues (except brain)</td>
<td>Ischemia or infarction; injury denatures enzymes → proteolysis blocked</td>
<td>Preserved cellular architecture (cell outlines seen), but nuclei disappear; cytoplasmic binding of eosin stain (→ eosinophilia; red/pink color)</td>
</tr>
<tr>
<td>Liquefactive</td>
<td>Bacterial abscesses, brain infarcts</td>
<td>Neutrophils release lysosomal enzymes that digest the tissue</td>
<td>Early: cellular debris and macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Late: cystic spaces and cavitation (brain)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neutrophils and cell debris seen with bacterial infection</td>
</tr>
<tr>
<td>Caseous</td>
<td>TB, systemic fungi (eg, <em>Histoplasma capsulatum</em>, Nocardia)</td>
<td>Macrophages wall off the infecting microorganism → granular debris</td>
<td>Fragmented cells and debris surrounded by lymphocytes and macrophages (granuloma)</td>
</tr>
<tr>
<td>Fat</td>
<td>Enzymatic: acute pancreatitis (saponification of peripancreatic fat) Nonenzymatic: traumatic (eg, injury to breast tissue)</td>
<td>Damaged cells release lipase, which breaks down triglycerides; liberated fatty acids bind calcium → saponification</td>
<td>Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with Ca²⁺) appears dark blue on H&amp;E stain</td>
</tr>
<tr>
<td>Fibrinoid</td>
<td>Immune reactions in vessels (eg, polyarteritis nodosa), preeclampsia, hypertensive emergency</td>
<td>Immune complexes combine with fibrin → vessel wall damage (type III hypersensitivity reaction)</td>
<td>Vessel walls are thick and pink</td>
</tr>
<tr>
<td>Gangrenous</td>
<td>Distal extremity and GI tract, after chronic ischemia</td>
<td>Dry: ischemia</td>
<td>Coagulative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wet: superinfection</td>
<td>Liquefactive superimposed on coagulative</td>
</tr>
</tbody>
</table>
Ischemia

Inadequate blood supply to meet demand. Mechanisms include arteriolar perfusion (e.g., atherosclerosis), venous drainage (e.g., testicular torsion, Budd-Chiari syndrome), and shock. Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>REGION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>ACA/MCA/PCA boundary areas&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart</td>
<td>Subendocardium (LV)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Straight segment of proximal tubule (medulla)</td>
</tr>
<tr>
<td></td>
<td>Thick ascending limb (medulla)</td>
</tr>
<tr>
<td>Liver</td>
<td>Area around central vein (zone III)</td>
</tr>
<tr>
<td>Colon</td>
<td>Splenic flexure,&lt;sup&gt;a&lt;/sup&gt; rectum&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Watershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion.

<sup>b</sup>Neurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (zones 3, 5, 6).

Types of infarcts

**Red infarct**

Red (hemorrhagic) infarcts occur in venous occlusion and tissues with multiple blood supplies, such as liver, lung, intestine, testes; reperfusion (e.g., after angioplasty). Reperfusion injury is due to damage by free radicals.

Red = reperfusion.

**Pale infarct**

Pale (anemic) infarcts occur in solid organs with a single (end-arterial) blood supply, such as heart, kidney, and spleen.
**Inflammation**

Response to eliminate initial cause of cell injury, to remove necrotic cells resulting from the original insult, and to initiate tissue repair. Divided into acute and chronic. The inflammatory response itself can be harmful to the host if the reaction is excessive (eg, septic shock), prolonged (eg, persistent infections such as TB), or inappropriate (eg, autoimmune diseases such as SLE).

<table>
<thead>
<tr>
<th>Cardinal signs</th>
<th>MECHANISM</th>
<th>MEDIATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rubor (redness), calor (warmth)</strong></td>
<td>Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow</td>
<td>Histamine, prostaglandins, bradykinin</td>
</tr>
<tr>
<td><strong>Tumor (swelling)</strong></td>
<td>Endothelial contraction/disruption (eg, from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ oncotic pressure</td>
<td>Endothelial contraction: leukotrienes (C₄, D₄, E₄), histamine, serotonin</td>
</tr>
<tr>
<td><strong>Dolor (pain)</strong></td>
<td>Sensitization of sensory nerve endings</td>
<td>Bradykinin, PGE₂</td>
</tr>
<tr>
<td><strong>Functio laesa (loss of function)</strong></td>
<td>Cardinal signs above impair function (eg, inability to make fist with hand that has cellulitis)</td>
<td></td>
</tr>
</tbody>
</table>

**Systemic manifestations (acute-phase reaction)**

| Fever | Pyrogens (eg, LPS) induce macrophages to release IL-1 and TNF → ↑ COX activity in perivascular cells of hypothalamus → ↑ PGE₂ → ↑ temperature set point. |
| Leukocytosis | Elevation of WBC count. Type of cell that is predominantly elevated depends on the inciting agent or injury (eg, bacteria → ↑ neutrophils). | Leukemoid reaction—severe elevation in WBC (> 40,000 cells/mm³) caused by some stressors or infections (eg, Clostridium difficile). |
| ↑ plasma acute-phase proteins | Factors whose serum concentrations change significantly in response to inflammation. Produced by the liver in both acute and chronic inflammatory states. | Notably induced by IL-6. |

**Acute phase reactants**

*More FFfSH in the C (sea).*

**POSITIVE (UPREGULATED)**

- **Ferritin**
  - Binds and sequesters iron to inhibit microbial iron scavenging.
- **Fibrinogen**
  - Coagulation factor; promotes endothelial repair; correlates with ESR.
- **Serum amyloid A**
  - Prolonged elevation can lead to amyloidosis.
- **Hepcidin**
  - ↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
- **C-reactive protein**
  - Opsonin; fixes complement and facilitates phagocytosis.
  - Measured clinically as a nonspecific sign of ongoing inflammation.

**NEGATIVE (DOWNREGULATED)**

- **Albumin**
  - Reduction conserves amino acids for positive reactants.
- **Transferrin**
  - Internalized by macrophages to sequester iron.
Erythrocyte sedimentation rate

Products of inflammation (eg, fibrinogen) coat RBCs and cause aggregation. The denser RBC aggregates fall at a faster rate within a pipette tube \( \uparrow \) ESR. Often co-tested with CRP levels.

<table>
<thead>
<tr>
<th>↑ ESR</th>
<th>↓ ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most anemias</td>
<td>Sickle cell anemia (altered shape)</td>
</tr>
<tr>
<td>Infections</td>
<td>Polycythemia (↑ RBCs “dilute” aggregation factors)</td>
</tr>
<tr>
<td>Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica)</td>
<td>HF</td>
</tr>
<tr>
<td>Cancer (eg, metastases, multiple myeloma)</td>
<td>Microcytosis</td>
</tr>
<tr>
<td>Renal disease (end-stage or nephrotic syndrome)</td>
<td>Hypofibrinogenemia</td>
</tr>
</tbody>
</table>

Acute inflammation

Transient and early response to injury or infection. Characterized by neutrophils in tissue, often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

Stimuli: Infections, trauma, necrosis, foreign bodies.

MEDIATORS: Toll-like receptors, arachidonic acid metabolites, neutrophils, eosinophils, antibodies (pre-existing), mast cells, basophils, complement, Hageman factor (factor XII).

Inflammasome—Cytoplasmic protein complex that recognizes products of dead cells, microbial products, and crystals (eg, uric acid crystals) \( \rightarrow \) activation of IL-1 and inflammatory response.

Components

- Vascular: vasodilation (\( \rightarrow \) ↑ blood flow and stasis) and ↑ endothelial permeability
- Cellular: extravasation of leukocytes (mainly neutrophils) from postcapillary venules and accumulation in the focus of injury followed by leukocyte activation
- To bring cells and proteins to site of injury or infection.
- Leukocyte extravasation has 4 steps: margination and rolling, adhesion, transmigration, and migration (chemoattraction).

Outcomes

- Resolution and healing (IL-10, TGF-β)
- Persistent acute inflammation (IL-8)
- Abscess (acute inflammation walled off by fibrosis)
- Chronic inflammation (antigen presentation by macrophages and other APCs \( \rightarrow \) activation of CD4+ Th cells)
- Scarring
- Macrophages predominate in the late stages of acute inflammation (peak 2–3 days after onset) and influence the outcome of acute inflammation by secreting cytokines.
Extravasation predominantly occurs at postcapillary venules. WBCs exit from blood vessels at sites of tissue injury and inflammation in 4 steps:

<table>
<thead>
<tr>
<th>STEP</th>
<th>VASCULATURE/STROMA</th>
<th>LEUKOCYTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Margination and rolling—defective in leukocyte adhesion deficiency type 2 (Sialyl-LewisX)</td>
<td>E-selectin (upregulated by TNF and IL-1)</td>
<td>Sialyl-LewisX</td>
</tr>
<tr>
<td></td>
<td>P-selectin (released from Weibel-Palade bodies)</td>
<td>Sialyl-LewisX</td>
</tr>
<tr>
<td></td>
<td>GlyCAM-1, CD34</td>
<td>L-selectin</td>
</tr>
<tr>
<td>2 Tight binding (adhesion)—defective in leukocyte adhesion deficiency type 1 (CD18 integrin subunit)</td>
<td>ICAM-1 (CD54)</td>
<td>CD11/18 integrins (LFA-1, Mac-1)</td>
</tr>
<tr>
<td></td>
<td>VCAM-1 (CD106)</td>
<td>VLA-4 integrin</td>
</tr>
<tr>
<td>3 Diapedesis (transmigration)—WBC travels between endothelial cells and exits blood vessel</td>
<td>PECAM-1 (CD31)</td>
<td>PECAM-1 (CD31)</td>
</tr>
<tr>
<td>4 Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals</td>
<td>Chemotactic products released in response to bacteria: C5a, IL-8, LTB4, kallikrein, platelet-activating factor</td>
<td>Various</td>
</tr>
</tbody>
</table>
**Chronic inflammation**
Inflammation of prolonged duration characterized by infiltration of tissue by mononuclear cells (macrophages, lymphocytes, and plasma cells). Tissue destruction and repair (including angiogenesis and fibrosis) occur simultaneously. May or may not be preceded by acute inflammation.

**STIMULI**
Persistent infections (e.g., TB, T. pallidum, certain fungi and viruses) → type IV hypersensitivity, autoimmune diseases, prolonged exposure to toxic agents (e.g., silica) and foreign material.

**MEDIATORS**
Macrophages are the dominant cells. Chronic inflammation is the result of their interaction with T lymphocytes.
- Th1 cells secrete INF-γ → macrophage classical activation (proinflammatory)
- Th2 cells secrete IL-4 and IL-13 → macrophage alternative activation (repair and anti-inflammatory)

**OUTCOMES**
Scarring, amyloidosis and neoplastic transformation (e.g., chronic HCV infection → chronic inflammation → hepatocellular carcinoma; Helicobacter pylori infection → chronic gastritis → gastric adenocarcinoma).

**Granulomatous diseases**
Bacterial:
- Mycobacteria (tuberculosis, leprosy)
- Bartonella henselae (cat scratch disease)
- Listeria monocytogenes (granulomatosis infantiseptica)
- Treponema pallidum (3° syphilis)
Fungal: endemic mycoses (e.g., histoplasmosis)  
Parasitic: schistosomiasis
Chronic granulomatous disease
Autoinflammatory:
- Sarcoidosis
- Crohn disease
- Primary biliary cholangitis
- Subacute (de Quervain/granulomatous) thyroiditis
- Granulomatosis with polyanigitis (Wegener)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Giant cell (temporal) arteritis
- Takayasu arteritis
Foreign material: berylliosis, talcosis, hypersensitivity pneumonitis

Granulomas (a pattern of chronic inflammation) are composed of epithelioid cells (macrophages with abundant pink cytoplasm) with surrounding multinucleated giant cells and lymphocytes. Th1 cells secrete IFN-γ activating macrophages. TNF-α from macrophages induces and maintains granuloma formation. Anti-TNF drugs can cause sequestering granulomas to break down → disseminated disease. Always test for latent TB before starting anti-TNF therapy. Associated with hypercalcemia due to calcitriol (1,25-(OH)2 vitamin D3) production.
Caseating necrosis is more common with an infectious etiology (e.g., TB). Diagnosis of sarcoidosis requires noncaseating granulomas on biopsy.
### Types of calcification

<table>
<thead>
<tr>
<th>CA(^{2+}) DEPOSITION</th>
<th>Dystrophic calcification</th>
<th>Metastatic calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXTENT</strong></td>
<td>In abnormal tissues</td>
<td>In normal tissues</td>
</tr>
<tr>
<td></td>
<td>Tends to be localized (eg, calcific aortic stenosis)</td>
<td>Widespread (ie, diffuse, metastatic)</td>
</tr>
<tr>
<td></td>
<td>(\text{\textbf{A}}) shows dystrophic calcification (yellow star), and thick fibrotic wall (red arrows)</td>
<td>(\text{\textbf{B}}) shows metastatic calcifications of alveolar walls in acute pneumonitis (arrows)</td>
</tr>
<tr>
<td><strong>ASSOCIATED CONDITIONS</strong></td>
<td>TB (lung and pericardium) and other granulomatous infections, liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, congenital CMV, toxoplasmosis, rubella, psammoma bodies, CREST syndrome, atherosclerotic plaques can become calcified</td>
<td>Predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; (\uparrow \text{pH}) favors Ca(^{2+}) deposition) Nephrocalcinosis of collecting ducts may lead to nephrogenic diabetes insipidus and renal failure</td>
</tr>
<tr>
<td><strong>ETIOLOGY</strong></td>
<td>(2^\circ) to injury or necrosis</td>
<td>(2^\circ) to hypercalcemia (eg, (1^\circ) hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (eg, chronic renal failure with (2^\circ) hyperparathyroidism, long-term dialysis, calciphylaxis, multiple myeloma)</td>
</tr>
<tr>
<td><strong>SERUM CA(^{2+}) LEVELS</strong></td>
<td>Patients are usually normocalcemic</td>
<td>Patients usually have abnormal serum Ca(^{2+}) levels</td>
</tr>
</tbody>
</table>

---

### Lipofuscin

A yellow-brown “wear and tear” pigment \(\text{\textbf{A}}\) associated with normal aging. Formed by oxidation and polymerization of autophagocytosed organelar membranes. Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.
Free radical injury

Free radicals damage cells via membrane lipid peroxidation, protein modification, and DNA breakage. Initiated via radiation exposure (e.g., cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (e.g., inflammation), transition metals, WBC (e.g., neutrophils, macrophages) oxidative burst.

Free radicals can be eliminated by scavenging enzymes (e.g., catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (e.g., vitamins A, C, E), and certain metal carrier proteins (e.g., transferrin, ceruloplasmin).

Examples:
- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy
- Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into CCl₃ free radical → fatty liver [cell injury → ↓ apolipoprotein synthesis → fatty change], centrilobular necrosis)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

Scar formation

Occurs when repair cannot be accomplished by cell regeneration alone. Nonregenerated cells (2° to severe acute or chronic injury) are replaced by connective tissue. 70–80% of tensile strength regained at 3 months; little tensile strength regained thereafter.

<table>
<thead>
<tr>
<th>SCAR TYPE</th>
<th>Hypertrophic</th>
<th>Keloid</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLLAGEN SYNTHESIS</td>
<td>↑ (type III collagen)</td>
<td>↑↑↑ (disorganized types I and III collagen)</td>
</tr>
<tr>
<td>COLLAGEN ORGANIZATION</td>
<td>Parallel</td>
<td>Disorganized</td>
</tr>
<tr>
<td>EXTENT OF SCAR</td>
<td>Confined to borders of original wound</td>
<td>Extends beyond borders of original wound with “claw-like” projections typically on earlobes, face, upper extremities</td>
</tr>
<tr>
<td>RECURRENCE</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>PREDISPOSITION</td>
<td>None</td>
<td>↑ incidence in ethnic groups with darker skin</td>
</tr>
</tbody>
</table>
### Wound healing

<table>
<thead>
<tr>
<th>Tissue mediators</th>
<th>ROLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF</td>
<td>Stimulates angiogenesis</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Angiogenesis, fibrosis</td>
</tr>
<tr>
<td>VEGF</td>
<td>Stimulates angiogenesis</td>
</tr>
<tr>
<td>PDGF</td>
<td>Secreted by activated platelets and macrophages</td>
</tr>
<tr>
<td></td>
<td>Stimulates vascular remodeling and smooth muscle cell migration</td>
</tr>
<tr>
<td></td>
<td>Stimulates fibroblast growth for collagen synthesis</td>
</tr>
<tr>
<td>Metalloproteinases</td>
<td>Tissue remodeling</td>
</tr>
<tr>
<td>EGF</td>
<td>Stimulates cell growth via tyrosine kinases (eg, EGFR/ErbB1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHASE OF WOUND HEALING</th>
<th>EFFECTOR CELLS</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory (up to</td>
<td>Platelets, neutrophils, macrophages</td>
<td>Clot formation, vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later</td>
</tr>
<tr>
<td>3 days after wound)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative</td>
<td>Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages</td>
<td>Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts) Delayed wound healing in vitamin C deficiency and copper deficiency</td>
</tr>
<tr>
<td>(day 3–weeks after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wound)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remodeling</td>
<td>Fibroblasts</td>
<td>Type III collagen replaced by type I collagen, tensile strength of tissue Collagenases (require zinc to function) break down type III collagen Zinc deficiency → delayed wound healing</td>
</tr>
<tr>
<td>(1 week–6+ months after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wound)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Exudate vs transudate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exudate</td>
<td>Transudate</td>
<td></td>
</tr>
<tr>
<td>Cellular (cloudy)</td>
<td>Hypocellular (clear)</td>
<td></td>
</tr>
<tr>
<td>↑ protein (&gt; 2.9 g/dL)</td>
<td>↓ protein (&lt; 2.5 g/dL)</td>
<td></td>
</tr>
<tr>
<td>Due to:</td>
<td>Due to:</td>
<td></td>
</tr>
<tr>
<td>* Lymphatic obstruction (chylous)</td>
<td>* ↑ hydrostatic pressure (eg, HF, Na⁺ retention)</td>
<td></td>
</tr>
<tr>
<td>* Inflammation/infection</td>
<td>* ↑ oncotic pressure (eg, cirrhosis, nephrotic syndrome)</td>
<td></td>
</tr>
<tr>
<td>* Malignancy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Light criteria**

Fluid is exudative if ≥ 1 of the following criteria is met:

* Pleural effusion protein/serum protein ratio > 0.5
* Pleural effusion LDH/serum LDH ratio > 0.6
* Pleural effusion LDH > ½ of the upper limit of normal for serum LDH
Amyloidosis

Abnormal aggregation of proteins (or their fragments) into β-pleated linear sheets → insoluble fibrils → cellular damage and apoptosis. Amyloid deposits visualized by Congo red stain, polarized light (apple green birefringence), and H&E stain shows deposits in glomerular mesangial areas (white arrows), tubular basement membranes (black arrows).

<table>
<thead>
<tr>
<th>COMMON TYPES</th>
<th>FIBRIL PROTEIN</th>
<th>DESCRIPTION</th>
<th>MANIFESTATIONS (EXAMPLES)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary amyloidosis</td>
<td>AL (from Ig Light chains)</td>
<td>Seen in plasma cell disorders and multiple myeloma</td>
<td>Cardiac (eg, restrictive cardiomyopathy, arrhythmia)</td>
</tr>
<tr>
<td>Secondary amyloidosis</td>
<td>Serum Amyloid (AA)</td>
<td>Seen in chronic inflammatory conditions, eg, rheumatoid arthritis, IBD, familial Mediterranean fever, protracted infection</td>
<td>GI (eg, macroglossia, hepatomegaly)</td>
</tr>
<tr>
<td>Dialysis-related amyloidosis</td>
<td>β2-microglobulin</td>
<td>Seen in patients with ESRD and/or on long-term dialysis</td>
<td>Renal (eg, nephrotic syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hematologic (eg, easy bruising, splenomegaly)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neurologic (neuropathy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Musculoskeletal (carpal tunnel syndrome)</td>
</tr>
<tr>
<td><strong>Localized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>β-amyloid protein</td>
<td>Cleaved from amyloid precursor protein (APP)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>Islet amyloid polypeptide (IAPP)</td>
<td>Caused by deposition of amylin in pancreatic islets</td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>Calcitonin (A Cal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated atrial amyloidosis</td>
<td>ANP</td>
<td>Common in normal aging → risk of atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Systemic senile (age-related)</td>
<td>Normal (wild-type) transthyretin (TTR)</td>
<td>Seen predominantly in cardiac ventricles</td>
<td>Cardiac dysfunction more insidious than in AL amyloidosis</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Mutated transthyretin (ATTR)</td>
<td>Ventricular endomyocardium deposition → restrictive cardiomyopathy, arrhythmias</td>
<td>5% of African Americans are carriers of mutant allele</td>
</tr>
<tr>
<td>Familial amyloid cardiomyopathy</td>
<td>Mutated transthyretin (ATTR)</td>
<td>Due to transthyretin gene mutation</td>
<td></td>
</tr>
</tbody>
</table>

![Congo red stain](image1)

![Polarized light](image2)

![H&E stain](image3)
Neoplasia and neoplastic progression


| Normal cells | Normal cells with basal → apical polarity. See cervical example A, which shows normal cells and spectrum of dysplasia, as discussed below. |
| Dysplasia | Loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, nuclear:cytoplasmic ratio) A. |
| Carcinoma in situ/preinvasive | Irreversible severe dysplasia that involves the entire thickness of epithelium but does not penetrate the intact basement membrane. |
| Invasive carcinoma | Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin. |
| Metastasis | Spread to distant organ(s) via lymphatics or blood. “Seed and soil” theory of metastasis:  
  * Seed = tumor embolus.  
  * Soil = target organ is often the first-encountered capillary bed (eg, liver, lungs, bone, brain, etc). |

![Diagram of normal and dysplastic tissue](image_url)
**Tumor nomenclature**

Carcinoma implies epithelial origin, whereas sarcoma denotes mesenchymal origin. Both terms generally imply malignancy.  

Benign tumors are usually well differentiated, well demarcated, low mitotic activity, no metastasis, no necrosis.

Malignant tumors may show poor differentiation, erratic growth, local invasion, metastasis, and apoptosis. Upregulation of telomerase prevents chromosome shortening and cell death.

Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, eg, Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, eg, gastric tissue located in distal ileum in Meckel diverticulum).

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>BENIGN</th>
<th>MALIGNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium</td>
<td>Adenoma, papilloma</td>
<td>Adenocarcinoma, papillary carcinoma</td>
</tr>
<tr>
<td>Mesenchyme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood cells</td>
<td>Hemangiomia</td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td>Blood vessels</td>
<td></td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Striated muscle</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Melanocyte</td>
<td>Nevus/mole</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>

**Tumor grade vs stage**

Differentiation—degree to which a tumor resembles its tissue of origin. Well-differentiated tumors (often less aggressive) closely resemble their tissue of origin, whereas poorly differentiated tumors (often more aggressive) look almost nothing like their tissue of origin.

Anaplasia—complete lack of differentiation of cells in a malignant neoplasm.

Grade

Degree of cellular differentiation and mitotic activity on histology. Range from low grade (well differentiated) to high grade (poorly differentiated, undifferentiated or anaplastic).

Stage generally has more prognostic value than grade (eg, a high-stage yet low-grade tumor is usually worse than a low-stage yet high-grade tumor). Stage determines Survival.

Stage

Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathology (p) findings. Example: cT3N1M0

TNM staging system (Stage = Spread):

- **T** = Tumor size/invasiveness
- **N** = Node involvement
- **M** = Metastases

Each TNM factor has independent prognostic value; N and M are often most important.


### Paraneoplastic syndromes

<table>
<thead>
<tr>
<th>MANIFESTATION</th>
<th>DESCRIPTION/MECHANISM</th>
<th>MOST COMMONLY ASSOCIATED TUMOR(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and cutaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Progressive proximal muscle weakness, Gottron papules, heliotrope rash</td>
<td>Adenocarcinomas, especially ovarian</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Hyperpigmented velvety plaques in axilla and neck</td>
<td>Gastric adenocarcinoma and other visceral malignancies (but more commonly associated with obesity and insulin resistance)</td>
</tr>
<tr>
<td>Sign of Leser-Trélat</td>
<td>Sudden onset of multiple seborrheic keratoses</td>
<td>GI adenocarcinomas and other visceral malignancies</td>
</tr>
<tr>
<td>Hypertrophic osteoarthropathy</td>
<td>Abnormal proliferation of skin and bone at distal extremities → clubbing, arthralgia, joint effusions, periostosis of tubular bones</td>
<td>Adenocarcinoma of the lung</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>PTHrP</td>
<td>Squamous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>↑ 1,25-(OH)₂ vitamin D₃ (calcitriol)</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Hyponatremia (SIADH)</td>
<td>↑ ACTH</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia</td>
<td>↑ Erythropoietin</td>
<td>Pheochromocytoma, renal cell carcinoma, HCC, hemangioblastoma, leiomyoma</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>Anemia with low reticulocytes</td>
<td>Thymoma</td>
</tr>
<tr>
<td>Good syndrome</td>
<td>Hypogammaglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Trousseau syndrome</td>
<td>Migratory superficial thrombophlebitis</td>
<td></td>
</tr>
<tr>
<td>Nonbacterial thrombotic (marantic) endocarditis</td>
<td>Deposition of sterile platelet thrombi on heart valves</td>
<td>Adenocarcinomas, especially pancreatic</td>
</tr>
<tr>
<td><strong>Neuromuscular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-NMDA receptor encephalitis</td>
<td>Psychiatric disturbance, memory deficits, seizures, dyskinesias, autonomic instability, language dysfunction</td>
<td>Ovarian teratoma</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus ataxia syndrome</td>
<td>“Dancing eyes, dancing feet”</td>
<td>Neuroblastoma (children), small cell lung cancer (adults)</td>
</tr>
<tr>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Antibodies against antigens in Purkinje cells</td>
<td>Small cell lung cancer (anti-Hu), gynecologic and breast cancers (anti-Yo), and Hodgkin lymphoma (anti-Tr)</td>
</tr>
<tr>
<td>Paraneoplastic encephalomyelitis</td>
<td>Antibodies against Hu antigens in neurons</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>Antibodies against presynaptic (P/Q-type) Ca²⁺ channels at NMJ</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Antibodies against postsynaptic ACh receptors at NMJ</td>
<td>Thymoma</td>
</tr>
</tbody>
</table>
**Oncogenes**

Gain of function mutation converts proto-oncogene (normal gene) to oncogene → ↑ cancer risk. Need damage to only one allele of a proto-oncogene.

<table>
<thead>
<tr>
<th>GENE</th>
<th>GENE PRODUCT</th>
<th>ASSOCIATED NEOPLASM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Receptor tyrosine kinase</td>
<td>Lung adenocarcinoma (adenocarcinoma of the lung)</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>Tyrosine kinase</td>
<td>CML, ALL</td>
</tr>
<tr>
<td>BCL-2</td>
<td>Antiapoptotic molecule (inhibits apoptosis)</td>
<td>Follicular and diffuse large B cell lymphomas</td>
</tr>
<tr>
<td>BRAF</td>
<td>Serine/threonine kinase</td>
<td>Melanoma, non-Hodgkin lymphoma, papillary thyroid carcinoma</td>
</tr>
<tr>
<td>c-KIT</td>
<td>Cytokine receptor</td>
<td>Gastrointestinal stromal tumor (GIST)</td>
</tr>
<tr>
<td>c-MYC</td>
<td>Transcription factor</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>HER2/neu (c-erbB2)</td>
<td>Receptor tyrosine kinase</td>
<td>Breast and gastric carcinomas</td>
</tr>
<tr>
<td>JAK2</td>
<td>Tyrosine kinase</td>
<td>Chronic myeloproliferative disorders</td>
</tr>
<tr>
<td>KRAS</td>
<td>GTPase</td>
<td>Colon cancer, lung cancer, pancreatic cancer</td>
</tr>
<tr>
<td>MYCL1</td>
<td>Transcription factor</td>
<td>Lung tumor</td>
</tr>
<tr>
<td>N-myc (MYCN)</td>
<td>Transcription factor</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>RET</td>
<td>Receptor tyrosine kinase</td>
<td>MEN 2A and 2B, papillary thyroid carcinoma</td>
</tr>
</tbody>
</table>

**Tumor suppressor genes**

Loss of function → ↑ cancer risk; both (two) alleles of a tumor suppressor gene must be lost for expression of disease.

<table>
<thead>
<tr>
<th>GENE</th>
<th>GENE PRODUCT</th>
<th>ASSOCIATED CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Negative regulator of β-catenin/WNT pathway</td>
<td>Colorectal cancer (associated with FAP)</td>
</tr>
<tr>
<td>BRCA1/BRCA2</td>
<td>DNA repair protein</td>
<td>Breast, ovarian, and pancreatic cancer</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>p16, blocks G1 → S phase</td>
<td>Melanoma, pancreatic cancer</td>
</tr>
<tr>
<td>DCC</td>
<td>DCC—Deleted in Colon Cancer</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>SMAD4 (DPC4)</td>
<td>DPC—Deleted in Pancreatic Cancer</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>MEN1</td>
<td>Menin</td>
<td>Multiple Endocrine Neoplasia 1</td>
</tr>
<tr>
<td>NF1</td>
<td>Neurofibromin (Ras GTPase activating protein)</td>
<td>Neurofibromatosis type 1</td>
</tr>
<tr>
<td>NF2</td>
<td>Merlin (schwannomin) protein</td>
<td>Neurofibromatosis type 2</td>
</tr>
<tr>
<td>PTEN</td>
<td>Negatively regulates PI3k/AKT pathway</td>
<td>Breast, prostate, and endometrial cancer</td>
</tr>
<tr>
<td>Rb</td>
<td>Inhibits E2F, blocks G1 → S phase</td>
<td>Retinoblastoma, osteosarcoma</td>
</tr>
<tr>
<td>TP53</td>
<td>p53, activates p21, blocks G1 → S phase</td>
<td>Most human cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA cancer syndrome: Sarcoma, Breast, Leukemia, Adrenal gland)</td>
</tr>
<tr>
<td>TSC1</td>
<td>Hamartin protein</td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>TSC2</td>
<td>Tuberin protein</td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>VHL</td>
<td>Inhibits hypoxia inducible factor 1α</td>
<td>Von Hippel-Lindau disease</td>
</tr>
<tr>
<td>WT1</td>
<td>Transcription factor that regulates urogenital development</td>
<td>Wilms tumor (nephroblastoma)</td>
</tr>
</tbody>
</table>
### Oncogenic microbes

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Associated cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1st CNS lymphoma (in immunocompromised patients)</td>
</tr>
<tr>
<td>HBV, HCV</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>HPV</td>
<td>Cervical and penile/anal carcinoma (types 16, 18), head and neck cancer</td>
</tr>
<tr>
<td><em>H pylori</em></td>
<td>Gastric adenocarcinoma and MALT lymphoma</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Adult T-cell leukemia/Lymphoma</td>
</tr>
<tr>
<td>Liver fluke (<em>Clonorchis sinensis</em>)</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td><em>Schistosoma haematobium</em></td>
<td>Bladder cancer (squamous cell)</td>
</tr>
</tbody>
</table>

### Carcinogens

<table>
<thead>
<tr>
<th>TOXIN</th>
<th>EXPOSURE</th>
<th>ORGAN</th>
<th>IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxins (<em>Aspergillus</em>)</td>
<td>Stored grains and nuts</td>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Oncologic chemotherapy</td>
<td>Blood</td>
<td>Leukemia/lymphoma</td>
</tr>
<tr>
<td>Aromatic amines (eg, benzidine, 2-naphthylamine)</td>
<td>Textile industry (dyes), cigarette smoke (2-naphthylamine)</td>
<td>Bladder</td>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Herbicides (vineyard workers), metal smelting</td>
<td>Liver, Lung, Skin</td>
<td>Angiosarcoma, Lung cancer, Squamous cell carcinoma</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Old roofing material, shipyard workers</td>
<td>Lung</td>
<td>Bronchogenic carcinoma &gt; mesothelioma</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td></td>
<td>Bladder, Cervix, Esophagus, Kidney, Larynx, Lung, Pancreas</td>
<td>Transitional cell carcinoma, Squamous cell carcinoma, Squamous cell carcinoma/adenocarcinoma, Renal cell carcinoma, Squamous cell carcinoma, Squamous cell and small cell carcinoma, Pancreatic adenocarcinoma</td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
<td>Esophagus, Liver</td>
<td>Squamous cell carcinoma, Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td></td>
<td>Thyroid</td>
<td>Papillary thyroid carcinoma</td>
</tr>
<tr>
<td>Nitrosamines</td>
<td>Smoked foods</td>
<td>Stomach</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Radon</td>
<td>By-product of uranium decay, accumulates in basements</td>
<td>Lung</td>
<td>Lung cancer (2nd leading cause after cigarette smoke)</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Used to make PVC pipes (plumbers)</td>
<td>Liver</td>
<td>Angiosarcoma</td>
</tr>
</tbody>
</table>
Psammoma bodies

Laminated, concentric spherules with dystrophic calcification. PSaMMoma bodies are seen in:
- Papillary carcinoma of thyroid
- Serous papillary cystadenocarcinoma of ovary
- Meningioma
- Malignant Mesothelioma

Serum tumor markers

Tumor markers should not be used as the 1st tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is made via biopsy. Some can be associated with non-neoplastic conditions.

<table>
<thead>
<tr>
<th>MARKER</th>
<th>IMPORTANT ASSOCIATIONS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP).</td>
<td>Exclude hepatic origin by checking LFTs and GGT levels.</td>
</tr>
<tr>
<td>α-fetoprotein</td>
<td>Hepatocellular carcinoma, Endodermal sinus (yolk sac) tumor, Mixed germ cell tumor, Ataxia-telangiectasia, Neural tube defects. (HE-MAN is the alpha male!)</td>
<td>Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.</td>
</tr>
<tr>
<td>β-hCG</td>
<td>Hydatidiform moles and Choriocarinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.</td>
<td>Produced by syncytiotrophoblasts of the placenta.</td>
</tr>
<tr>
<td>CA 15-3/CA 27-29</td>
<td>Breast cancer.</td>
<td></td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreatic adenocarcinoma.</td>
<td></td>
</tr>
<tr>
<td>CA 125</td>
<td>Ovarian cancer.</td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Medullary thyroid carcinoma (alone and in MEN2A, MEN2B).</td>
<td></td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Neuroendocrine tumors.</td>
<td>Can be used as an indicator of tumor burden.</td>
</tr>
<tr>
<td>LDH</td>
<td>Testicular germ cell tumors, ovarian dysgerminoma, other cancers.</td>
<td>Can be used as an indicator of tumor burden.</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate cancer.</td>
<td>Prostate-specific antigen. Can also be elevated in BPH and prostatitis. Questionable risk/benefit for screening. Surveillance marker for recurrent disease after prostatectomy.</td>
</tr>
</tbody>
</table>
Important immunohistochemical stains

Determine primary site of origin for metastatic tumors and characterize tumors that are difficult to classify. Can have prognostic and predictive value.

<table>
<thead>
<tr>
<th>STAIN</th>
<th>TARGET</th>
<th>EXAMPLES IDENTIFIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages)</td>
<td>Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma)</td>
</tr>
<tr>
<td>S-100</td>
<td>Neural crest cells</td>
<td>Melanoma, schwannoma, Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>DesMin</td>
<td>Muscle</td>
<td>Muscle tumors (eg, rhabdomyosarcoma)</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>Epithelial cells</td>
<td>Epithelial tumors (eg, squamous cell carcinoma)</td>
</tr>
<tr>
<td>GFAP</td>
<td>NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes)</td>
<td>Astrocytoma, Glioblastoma</td>
</tr>
<tr>
<td>Neurofilament</td>
<td>Neurons</td>
<td>Neuronal tumors (eg, neuroblastoma)</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostatic epithelium</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>TRAP</td>
<td>Tartrate-resistant acid phosphatase</td>
<td>Hairy cell leukemia</td>
</tr>
<tr>
<td>Chromogranin and synaptophysin</td>
<td>Neuroendocrine cells</td>
<td>Small cell carcinoma of the lung, carcinoid tumor</td>
</tr>
</tbody>
</table>

P-glycoprotein

Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenocortical carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of resistance or resistance to chemotherapy over time).

Cachexia

Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF, IFN-γ, IL-1, and IL-6.
Cancer epidemiology

Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

<table>
<thead>
<tr>
<th>Cancer incidence</th>
<th>MEN</th>
<th>WOMEN</th>
<th>CHILDREN (AGE 0–14)</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate</td>
<td>1. Breast</td>
<td>1. Leukemia</td>
<td>Lung cancer incidence has increased in men, but has not changed significantly in women.</td>
<td></td>
</tr>
<tr>
<td>2. Lung</td>
<td>2. Lung</td>
<td>2. CNS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer mortality</th>
<th>MEN</th>
<th>WOMEN</th>
<th>CHILDREN (AGE 0–14)</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lung</td>
<td>1. Lung</td>
<td>1. Leukemia</td>
<td>Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).</td>
<td></td>
</tr>
<tr>
<td>2. Prostate</td>
<td>2. Breast</td>
<td>2. CNS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Common metastases

Most sarcomas spread hematogenously; most carcinomas spread via lymphatics. However, Four Carcinomas Route Hematogenously: Follicular thyroid carcinoma, Choriocarcinoma, Renal cell carcinoma, and Hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>SITE OF METASTASIS</th>
<th>1st TUMOR</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Lung &gt; breast &gt; melanoma, colon, kidney.</td>
<td>50% of brain tumors are from metastases. Commonly seen as multiple well-circumscribed tumors at gray/white matter junction.</td>
</tr>
<tr>
<td>Liver</td>
<td>Colon &gt;&gt; stomach &gt; pancreas.</td>
<td>Liver and lung are the most common sites of metastasis after the regional lymph nodes.</td>
</tr>
<tr>
<td>Bone</td>
<td>Prostate, Breast &gt; Kidney, Thyroid, Lung, Lead (PB) KeT1Le</td>
<td>Bone metastasis &gt;&gt; 1st bone tumors (eg, multiple myeloma, lytic). Common mets to bone: breast (mixed), lung (lytic), thyroid (lytic), kidney (lytic), prostate (blastic). Predilection for axial skeleton.</td>
</tr>
</tbody>
</table>
“Take me, I am the drug; take me, I am hallucinogenic.”
—Salvador Dali

“I was under medication when I made the decision not to burn the tapes.”
—Richard Nixon

“I wonder why ye can always read a doctor’s bill an’ ye niver can read his purscription.”
—Finley Peter Dunne

“Once you get locked into a serious drug collection, the tendency is to push it as far as you can.”
—Hunter S. Thompson

Preparation for pharmacology questions is straightforward. Know all the mechanisms, clinical use, and important adverse effects of key drugs and their major variants. Obscure derivatives are low-yield. Learn their classic and distinguishing toxicities as well as major drug-drug interactions. Reviewing associated biochemistry, physiology, and microbiology concepts can be useful while studying pharmacology. The exam has a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs, which are covered throughout the text. Specific drug dosages or trade names are generally not testable. The exam may use graphs to test various pharmacology content, so make sure you are comfortable interpreting them.
Enzyme kinetics

**Michaelis-Menten kinetics**

$K_m$ is inversely related to the affinity of the enzyme for its substrate.

$V_{max}$ is directly proportional to the enzyme concentration.

Most enzymatic reactions follow a hyperbolic curve (ie, Michaelis-Menten kinetics); however, enzymatic reactions that exhibit a sigmoid curve usually indicate cooperative kinetics (eg, hemoglobin).

$[S] = \text{concentration of substrate; } V = \text{velocity.}$

**Lineweaver-Burk plot**

\[ \frac{1}{V} = \frac{1}{V_{max}} - \frac{K_m}{V_{max} [S]} \]

The further to the right the x-intercept (ie, closer to zero), the greater the $K_m$ and the lower the affinity.

**Competitive inhibitors** cross each other, whereas **noncompetitive inhibitors** do not.

**Competitive inhibitors increase** $K_m$.

<table>
<thead>
<tr>
<th></th>
<th>Competitive inhibitors, reversible</th>
<th>Competitive inhibitors, irreversible</th>
<th>Noncompetitive inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resemble substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Overcome by $[S]$</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bind active site</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Effect on $V_{max}$</td>
<td>Unchanged</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Effect on $K_m$</td>
<td>↑</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>↓ potency</td>
<td>↓ efficacy</td>
<td>↓ efficacy</td>
</tr>
</tbody>
</table>
Pharmacokinetics

**Bioavailability (F)**
Fraction of administered drug reaching systemic circulation unchanged. For an IV dose, F = 100%. Orally: F typically < 100% due to incomplete absorption and first-pass metabolism.

**Volume of distribution (V_d)**
Theoretical volume occupied by the total amount of drug in the body relative to its plasma concentration. Apparent V_d of plasma protein–bound drugs can be altered by liver and kidney disease (↓ protein binding, ↑ V_d). Drugs may distribute in more than one compartment.

\[ V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}} \]

<table>
<thead>
<tr>
<th>Type</th>
<th>Compartment</th>
<th>Drug Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Intravascular</td>
<td>Large/charged molecules; plasma protein bound</td>
</tr>
<tr>
<td>Medium</td>
<td>ECF</td>
<td>Small hydrophilic molecules</td>
</tr>
<tr>
<td>High</td>
<td>All tissues including fat</td>
<td>Small lipophilic molecules, especially if bound to tissue protein</td>
</tr>
</tbody>
</table>

**Clearance (CL)**
The volume of plasma cleared of drug per unit time. Clearance may be impaired with defects in cardiac, hepatic, or renal function.

\[ CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \] (elimination constant)

**Half-life (t_{1/2})**
The time required to change the amount of drug in the body by 1/2 during elimination.
In first-order kinetics, a drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.

\[ t_{1/2} = \frac{0.7 \times V_d}{CL} \text{ in first-order elimination} \]

<table>
<thead>
<tr>
<th># of half-lives</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>% remaining</td>
<td>50%</td>
<td>25%</td>
<td>12.5%</td>
<td>6.25%</td>
</tr>
</tbody>
</table>

**Dosage calculations**

- **Loading dose**
  \[ \frac{C_p \times V_d}{F} \]

- **Maintenance dose**
  \[ \frac{C_p \times CL \times \tau}{F} \]

\( C_p = \) target plasma concentration at steady state \( \tau = \) dosage interval (time between doses), if not administered continuously

In renal or liver disease, maintenance dose \( 4 \) and loading dose is usually unchanged. Time to steady state depends primarily on \( t_{1/2} \) and is independent of dose and dosing frequency.

**Types of drug interactions**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive</td>
<td>Effect of substance A and B together is equal to the sum of their individual effects</td>
<td>Aspirin and acetaminophen</td>
</tr>
<tr>
<td>Permissive</td>
<td>Presence of substance A is required for the full effects of substance B</td>
<td>Cortisol on catecholamine responsiveness</td>
</tr>
<tr>
<td>Synergistic</td>
<td>Effect of substance A and B together is greater than the sum of their individual effects</td>
<td>Clopidogrel with aspirin</td>
</tr>
<tr>
<td>Tachyphylactic</td>
<td>Acute decrease in response to a drug after initial/repeated administration</td>
<td>Nitrates, niacin, phenylephrine, LSD, MDMA</td>
</tr>
</tbody>
</table>
**Receptor binding**

<table>
<thead>
<tr>
<th>Agonist with</th>
<th>Effect</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Competitive antagonist</td>
<td>Shifts curve right (↓ potency), no change in efficacy. Can be overcome by ↑ the concentration of agonist substrate.</td>
<td>Diazepam (agonist) + flumazenil (competitive antagonist) on GABA receptor.</td>
</tr>
<tr>
<td><strong>B</strong> Noncompetitive antagonist</td>
<td>Shifts curve down (↓ efficacy). Cannot be overcome by ↑ agonist substrate concentration.</td>
<td>Norepinephrine (agonist) + phenoxybenzamine (noncompetitive antagonist) on α-receptors.</td>
</tr>
<tr>
<td><strong>C</strong> Partial agonist (alone)</td>
<td>Acts at same site as full agonist, but with lower maximal effect (↓ efficacy). Potency is an independent variable.</td>
<td>Morphine (full agonist) vs buprenorphine (partial agonist) at opioid μ-receptors.</td>
</tr>
</tbody>
</table>

**Elimination of drugs**

**Zero-order elimination**
Rate of elimination is constant regardless of $C_p$ (ie, constant amount of drug eliminated per unit time). $C_p$ ↓ linearly with time. Examples of drugs—Phenytoin, Ethanol, and Aspirin (at high or toxic concentrations).

**First-order elimination**
Rate of First-order elimination is directly proportional to the drug concentration (ie, constant fraction of drug eliminated per unit time). $C_p$ ↓ exponentially with time. Applies to most drugs.

<table>
<thead>
<tr>
<th>Zero-order elimination</th>
<th>First-order elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination rate (=slope)</td>
<td>Elimination rate (=slope)</td>
</tr>
<tr>
<td>2 U/h</td>
<td>4 U/h</td>
</tr>
<tr>
<td>Time of $t_{1/2}$ ↓ as concentration ↓</td>
<td>Time of $t_{1/2}$ as constant concentration ↓</td>
</tr>
<tr>
<td>First $t_{1/2}$ &gt;</td>
<td>First $t_{1/2}$</td>
</tr>
<tr>
<td>Second $t_{1/2}$</td>
<td>Second $t_{1/2}$</td>
</tr>
<tr>
<td>Third $t_{1/2}$</td>
<td>Third $t_{1/2}$</td>
</tr>
</tbody>
</table>
**Pharmacology**

**PHARMACOLOGY—PHARMACOKINETICS AND PHARMACODYNAMICS**

<table>
<thead>
<tr>
<th><strong>Urine pH and drug elimination</strong></th>
<th>Ionized species are trapped in urine and cleared quickly. Neutral forms can be reabsorbed.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weak acids</strong></td>
<td>Examples: phenobarbital, methotrexate, aspirin (salicylates). Trapped in basic environments. Treat overdose with sodium bicarbonate to alkalize urine.</td>
</tr>
<tr>
<td></td>
<td>[ \text{RCOOH} \leftrightarrow \text{RCOO}^- + \text{H}^+ ] \hspace{1cm} (lipid soluble) \hspace{1cm} (trapped)</td>
</tr>
<tr>
<td><strong>Weak bases</strong></td>
<td>Example: TCAs, amphetamines. Trapped in acidic environments. Treat overdose with ammonium chloride to acidify urine.</td>
</tr>
<tr>
<td></td>
<td>[ \text{RNH}_3^+ \leftrightarrow \text{RNH}_2 + \text{H}^+ ] \hspace{1cm} (trapped) \hspace{1cm} (lipid soluble)</td>
</tr>
</tbody>
</table>

**TCA toxicity** is generally treated with sodium bicarbonate to overcome the sodium channel-blocking activity of TCAs, but not for accelerating drug elimination.

<table>
<thead>
<tr>
<th><strong>Drug metabolism</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I</strong></td>
<td><strong>Reduction</strong>, <strong>Oxidation</strong>, <strong>Hydrolysis</strong> with cytochrome P-450 usually yield slightly polar, water-soluble metabolites (often still active).</td>
</tr>
<tr>
<td></td>
<td><strong>Conjugation</strong> (Methylation, Glucuronidation, Acetylation, Sulfation) usually yields very polar, inactive metabolites (renally excreted).</td>
</tr>
</tbody>
</table>
Efficacy vs potency

**Efficacy**

Maximal effect a drug can produce. Represented by the y-value ($V_{max}$). $y-value = V_{max} = \uparrow efficacy$. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.

**Potency**

Amount of drug needed for a given effect. Represented by the x-value ($EC_{50}$). Left shifting $\downarrow EC_{50} = \uparrow potency = \downarrow$ drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).

**Therapeutic index**

Measurement of drug safety. $TD_{50} = \text{median toxic dose}$, $ED_{50} = \text{median effective dose}$

Therapeutic window—dosage range that can safely and effectively treat disease.
Central and peripheral nervous system

Pelvic splanchnic nerves and CNs III, VII, IX and X are part of the parasympathetic nervous system. Adrenal medulla is directly innervated by preganglionic sympathetic fibers. Sweat glands are part of the sympathetic pathway but are innervated by cholinergic fibers.

**Acetylcholine receptors**

Nicotinic ACh receptors are ligand-gated Na⁺/K⁺ channels. Two subtypes: N_N (found in autonomic ganglia, adrenal medulla) and N_M (found in neuromuscular junction of skeletal muscle). Muscarinic ACh receptors are G-protein–coupled receptors that usually act through 2nd messengers. 5 subtypes: M₁–M₅ found in heart, smooth muscle, brain, exocrine glands, and on sweat glands (cholinergic sympathetic).
**G-protein–linked second messengers**

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>G-PROTEIN CLASS</th>
<th>MAJOR FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sympathetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α₁</td>
<td>q</td>
<td>† vascular smooth muscle contraction, † pupillary dilator muscle contraction (mydriasis), † intestinal and bladder sphincter muscle contraction</td>
</tr>
<tr>
<td>α₂</td>
<td>i</td>
<td>† sympathetic (adrenergic) outflow, † insulin release, † lipolysis, † platelet aggregation, † aqueous humor production</td>
</tr>
<tr>
<td>β₁</td>
<td>s</td>
<td>† heart rate, † contractility (one heart), † renin release, † lipolysis, † platelet aggregation</td>
</tr>
<tr>
<td>β₂</td>
<td>s</td>
<td>Vasodilation, bronchodilation (two lungs), † lipolysis, † insulin release, † glycogenolysis, † uterine tone (tocolyis), † aqueous humor production, † cellular K⁺ uptake</td>
</tr>
<tr>
<td>β₃</td>
<td>s</td>
<td>† lipolysis, † thermogenesis in skeletal muscle, † bladder relaxation</td>
</tr>
<tr>
<td><strong>Parasympathetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M₁</td>
<td>q</td>
<td>Mediates higher cognitive functions, stimulates enteric nervous system</td>
</tr>
<tr>
<td>M₂</td>
<td>i</td>
<td>† heart rate and contractility of atria</td>
</tr>
<tr>
<td>M₃</td>
<td>q</td>
<td>† exocrine gland secretions (eg, lacrimal, sweat, salivary, gastric acid), † gut peristalsis, † bladder contraction, bronchoconstriction, † pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation), † insulin release</td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₁</td>
<td>s</td>
<td>Relaxes renal vascular smooth muscle, activates direct pathway of striatum</td>
</tr>
<tr>
<td>D₂</td>
<td>i</td>
<td>Modulates transmitter release, especially in brain, inhibits indirect pathway of striatum</td>
</tr>
<tr>
<td><strong>Histamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₁</td>
<td>q</td>
<td>† nasal and bronchial mucus production, † vascular permeability, bronchoconstriction, pruritus, pain</td>
</tr>
<tr>
<td>H₂</td>
<td>s</td>
<td>† gastric acid secretion</td>
</tr>
<tr>
<td><strong>Vasopressin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V₁</td>
<td>q</td>
<td>† vascular smooth muscle contraction</td>
</tr>
<tr>
<td>V₂</td>
<td>s</td>
<td>† H₂O permeability and reabsorption via upregulating aquaporin-2 in collecting tubules (tubules) of kidney</td>
</tr>
</tbody>
</table>

“After qisses (kisses), you get a qiq (kick) out of siq (sick) sqs (super qinky sex).”

![Diagram showing the interaction between receptors and second messengers](image-url)
**Autonomic drugs**

Release of norepinephrine from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic $\alpha_2$-autoreceptors → negative feedback. Amphetamines use the NE transporter (NET) to enter the presynaptic terminal, where they utilize the vesicular monoamine transporter (VMAT) to enter neurosecretory vesicles. This displaces NE from the vesicles. Once NE reaches a concentration threshold within the presynaptic terminal, the action of NET is reversed, and NE is expelled into the synaptic cleft, contributing to the characteristics and effects of NE observed in patients taking amphetamines.

**CHOLINERGIC**

**NORADRENERGIC**
### Cholinomimetic agents

Watch for exacerbation of COPD, asthma, and peptic ulcers in susceptible patients.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ACTION</th>
<th>APPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bethanechol</strong></td>
<td>Activates bowel and bladder smooth muscle;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>resistant to AChE. No nicotinic activity.</td>
<td>Postoperative ileus, neurogenic ileus, urinary</td>
</tr>
<tr>
<td></td>
<td><strong>“Bethany, call (bethanechol) me to activate</strong></td>
<td>retention</td>
</tr>
<tr>
<td></td>
<td>your bowels and bladder.”</td>
<td></td>
</tr>
<tr>
<td><strong>Carbachol</strong></td>
<td>Carbon copy of acetylcholine (but resistant to</td>
<td>Constricts pupil and relieves intraocular pressure in</td>
</tr>
<tr>
<td></td>
<td>AChE).</td>
<td>open-angle glaucoma</td>
</tr>
<tr>
<td><strong>Methacholine</strong></td>
<td>Stimulates muscarinic receptors in airway when</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inhaled.</td>
<td>Challenge test for diagnosis of asthma</td>
</tr>
<tr>
<td><strong>Pilocarpine</strong></td>
<td>Contracts ciliary muscle of eye (open-angle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>glaucoma), pupillary sphincter (closed-angle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>glaucoma); resistant to AChE, can cross blood-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>brain barrier (tertiary amine). “You cry,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>drool, and sweat on your ‘pilo.’”</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potent stimulator of sweat, tears, and saliva</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open-angle and closed-angle glaucoma, xerostomia (Sjögren syndrome)</td>
</tr>
</tbody>
</table>

| **Indirect agonists (anticholinesterases)** |                                              |                                                        |
| **Donepezil, rivastigmine, galantamine**   | † ACh.                                       | Alzheimer disease (Dona Riva dances at the gala).      |
| **Edrophonium**                            | † ACh.                                       | Historically used to diagnose myasthenia gravis;      |
|                                             |                                              | replaced by anti-AChR Ab (anti-acetylcholine receptor  |
|                                             |                                              | antibody) test.                                        |
| **Neostigmine**                            | † ACh. Neo CNS = No CNS penetration (quaternary amine). | Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative). |
| **Physostigmine**                          | † ACh. Phreely (freely) crosses blood-brain  |
|                                             | barrier → CNS (tertiary amine).              | Antibody for anticholinergic toxicity; physostigmine “phyxes” atropine overdose. |
| **Pyridostigmine**                         | † ACh; † muscle strength. Pyridostigmine gets rid of myasthenia gravis. | Myasthenia gravis (long acting); does not penetrate CNS (quaternary amine). |

| **Cholinesterase inhibitor poisoning**      |                                              |                                                        |
| **Often due to organophosphates, such as** |                                              | DUMBBELSS.                                             |
| **parathion, that irreversibly inhibit AChE.** |                                              | Organophosphates are often components of insecticides; poisoning usually seen in farmers.  |
| **Causes Diarrhea, Urination, Miosis,**     |                                              | Antidote—atropine (competitive inhibitor) + pralidoxime (regenerates AChE if given early). |
| **Bronchospasm, Bradycardia, Emetis,**     |                                              |                                                        |
| **Lacrimation, Sweating, and Salivation.**  |                                              |                                                        |
| **May lead to respiratory failure if untreated.** |                                              |                                                        |
### Muscarinic antagonists

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>ORGAN SYSTEMS</th>
<th>APPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine, homatropine, tropicamide</td>
<td>Eye</td>
<td>Produce mydriasis and cycloplegia.</td>
</tr>
<tr>
<td>Benztropine, trihexyphenidyl</td>
<td>CNS</td>
<td>Parkinson disease (&quot;park my Benz&quot;). Acute dystonia.</td>
</tr>
<tr>
<td>Hyoscyamine, dicyclomine</td>
<td>GI</td>
<td>Antispasmodics for irritable bowel syndrome.</td>
</tr>
<tr>
<td>Ipratropium, tiotropium</td>
<td>Respiratory</td>
<td>COPD, asthma (&quot;I pray I can breathe soon!&quot;).</td>
</tr>
<tr>
<td>Oxybutynin, solifenacin, tolterodine</td>
<td>Genitourinary</td>
<td>Reduce bladder spasms and urge urinary incontinence (overactive bladder).</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>CNS</td>
<td>Motion sickness.</td>
</tr>
</tbody>
</table>

### Atropine

Muscarinic antagonist. Used to treat bradycardia and for ophthalmic applications.

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>ACTION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>↑ pupil dilation, cycloplegia</td>
<td>Blocks DUMBBelSS in cholinesterase inhibitor poisoning. Does not block excitation of skeletal muscle and CNS (mediated by nicotinic receptors).</td>
</tr>
<tr>
<td>Airway</td>
<td>Bronchodilation, ↓ secretions</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>↓ acid secretion</td>
<td></td>
</tr>
<tr>
<td>Gut</td>
<td>↓ motility</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>↓ urgency in cystitis</td>
<td></td>
</tr>
</tbody>
</table>

**ADVERSE EFFECTS**

- ↑ body **temperature** (due to ↓ sweating); rapid pulse; dry mouth; **dry, flushed skin**; cycloplegia; constipation; disorientation
- Can cause acute angle-closure glaucoma in elderly (due to mydriasis), urinary retention in men with prostatic hyperplasia, and hyperthermia in infants.

- Side effects:
  - **Hot** as a hare
  - **Dry** as a bone
  - **Red** as a beet
  - **Blind** as a bat
  - **Mad** as a hatter
  - **Full** as a flask
  - Jimson weed (*Datura*) → gardener’s pupil (mydriasis due to plant alkaloids)
### Sympathomimetics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ACTION</th>
<th>APPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct sympathomimetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol, salmeterol,</td>
<td>$\beta_2 &gt; \beta_1$</td>
<td>Albuterol for acute asthma or COPD. Salmeterol for long-term asthma or COPD management. Terbutaline for acute bronchospasm in asthma and tocolysis.</td>
</tr>
<tr>
<td>terbutaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>$\beta_1 &gt; \beta_2, \alpha$</td>
<td>Heart failure (HF), cardiogenic shock (inotropic &gt; chronotropic), cardiac stress testing.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>$D_1 = D_2 &gt; \beta &gt; \alpha$</td>
<td>Unstable bradycardia, HF, shock; inotropic and chronotropic effects at lower doses due to $\beta$ effects; vasoconstriction at high doses due to $\alpha$ effects.</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>$\beta &gt; \alpha$</td>
<td>Anaphylaxis, asthma, open-angle glaucoma; $\alpha$ effects predominate at high doses. Significantly stronger effect at $\beta_2$-receptor than norepinephrine.</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>$\beta_1 = \beta_2$</td>
<td>Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia. Has negligible $\alpha$ effect.</td>
</tr>
<tr>
<td>Midodrine</td>
<td>$\alpha_1$</td>
<td>Autonomic insufficiency and postural hypotension. May exacerbate supine hypertension.</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>$\beta_3$</td>
<td>Urinary urge incontinence or overactive bladder.</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>$\alpha_1 &gt; \alpha_2 &gt; \beta_1$</td>
<td>Hypotension, septic shock.</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>$\alpha_1 &gt; \alpha_2$</td>
<td>Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant), ischemic priapism.</td>
</tr>
<tr>
<td><strong>Indirect sympathomimetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Indirect general agonist, reuptake inhibitor, also releases stored catecholamines</td>
<td>Narcolepsy, obesity, ADHD.</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Indirect general agonist, reuptake inhibitor</td>
<td>Causes vasoconstriction and local anesthesia. Caution when giving $\beta$-blockers if cocaine intoxication is suspected (can lead to unopposed $\alpha$ activation, activation $\rightarrow$ extreme hypotension, coronary vasospasm).</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Indirect general agonist, releases stored catecholamines</td>
<td>Nasal decongestion (pseudoephedrine), urinary incontinence, hypotension.</td>
</tr>
</tbody>
</table>
Norepinephrine vs isoproterenol

NE ↑ systolic and diastolic pressures as a result of $\alpha_1$-mediated vasoconstriction → ↑ mean arterial pressure → reflex bradycardia. However, isoproterenol (rarely used) has little $\alpha$ effect but causes $\beta_2$-mediated vasodilation, resulting in ↓ mean arterial pressure and ↓ heart rate through $\beta_1$ and reflex activity.

Sympatholytics ($\alpha_2$-agonists)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>APPLICATIONS</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine, guanfacine</td>
<td>Hypertensive urgency (limited situations), ADHD, Tourette syndrome, symptom control in opioid withdrawal</td>
<td>CNS depression, bradycardia, hypotension, respiratory depression, miosis, rebound hypertension with abrupt cessation</td>
</tr>
<tr>
<td>$\alpha$-methyldopa</td>
<td>Hypertension in pregnancy</td>
<td>Direct Coombs $\Theta$ hemolysis, drug-induced lupus</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Relief of spasticity</td>
<td>Hypotension, weakness, xerostomia</td>
</tr>
</tbody>
</table>
### α-blockers

<table>
<thead>
<tr>
<th>DRUG</th>
<th>APPLICATIONS</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonselective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Irreversible. Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis</td>
<td>Orthostatic hypotension, reflex tachycardia</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Reversible. Give to patients on MAO inhibitors who eat tyramine-containing foods and for severe cocaine-induced hypertension (2nd line)</td>
<td></td>
</tr>
<tr>
<td>α₁ selective (-osin ending)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin, terazosin, doxazosin, tamsulosin</td>
<td>Urinary symptoms of BPH, PTSD (prazosin); hypertension (except tamsulosin)</td>
<td>1st-dose orthostatic hypotension, dizziness, headache</td>
</tr>
<tr>
<td>α₂ selective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Depression</td>
<td>Sedation, ↑ serum cholesterol, ↑ appetite</td>
</tr>
</tbody>
</table>

**Effects of α-blocker (eg, phentolamine) on BP responses to epinephrine and phenylephrine**

Epinephrine response exhibits reversal of mean arterial pressure from a net increase (the α response) to a net decrease (the β₂ response).

Phenylephrine response is suppressed but not reversed because it is a “pure” α-agonist (lacks β-agonist properties).
**β-blockers**

<table>
<thead>
<tr>
<th>APPLICATION</th>
<th>ACTIONS</th>
<th>NOTES/EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>↓ heart rate and contractility, resulting in ↓ O₂ consumption</td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>↓ production of aqueous humor</td>
<td>Timolol</td>
</tr>
<tr>
<td>Heart failure</td>
<td>↓ mortality</td>
<td>Bisoprolol, carvedilol, metoprolol</td>
</tr>
<tr>
<td>Hypertension</td>
<td>↓ cardiac output, ↓ renin secretion (due to β₁-receptor blockade on JGA cells)</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Symptom control (↓ heart rate, ↑ tremor), thyroid storm</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>↓ heart rate → ↑ filling time, relieving obstruction</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>↓ mortality</td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>↓ AV conduction velocity (class II antiarrhythmic)</td>
<td>Metoprolol, esmolol</td>
</tr>
<tr>
<td>Varicel bleeding</td>
<td>↓ hepatic venous pressure gradient and portal hypertension (prophylactic use)</td>
<td>Nadolol, propranolol, carvedilol</td>
</tr>
</tbody>
</table>

**ADVERSE EFFECTS**

Erectile dysfunction, cardiovascular (bradycardia, AV block, HF), CNS (seizures, sleep alterations), dyslipidemia (metoprolol), and asthma/COPD exacerbations

Use with caution in cocaine users due to risk of unopposed α-adrenergic receptor agonist activity

**SELECTIVITY**

β₁-selective antagonists (β₁ > β₂)—acebutolol (partial agonist), atenolol, betaxolol, bisoprolol, esmolol, metoprolol

Selective antagonists mostly go from A to M (β₁ with 1st half of alphabet)

Nonselective antagonists (β₁ = β₂)—nadolol, pindolol (partial agonist), propranolol, timolol

Nonselective antagonists mostly go from N to Z (β₂ with 2nd half of alphabet)

Nonselective α- and β-antagonists—carvedilol, labetalol

Nonselective α- and β-antagonists have modified suffixes (instead of “-olol”)

Nebivolol combines cardiac-selective β₁-adrenergic blockade with stimulation of β₁-receptors (activate nitric oxide synthase in the vasculature and ↓ SVR)

Nebivolol increases NO
Ingested seafood toxins

Toxin actions include Histamine release, Total block of Na⁺ channels, or opening of Na⁺ channels to Cause depolarization.

<table>
<thead>
<tr>
<th>TOXIN</th>
<th>SOURCE</th>
<th>ACTION</th>
<th>SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine (scombroid poisoning)</td>
<td>Spoiled dark-meat fish such as tuna, mahi-mahi, mackerel, and bonito.</td>
<td>Bacterial histidine decarboxylase converts histidine to histamine. Frequently misdiagnosed as fish allergy.</td>
<td>Mimics anaphylaxis: acute burning sensation of mouth, flushing of face, erythema, urticaria, itching. May progress to bronchospasm, angioedema, hypotension.</td>
<td>Antihistamines. Albuterol and epinephrine if needed.</td>
</tr>
<tr>
<td>Ciguatoxin</td>
<td>Reef fish such as barracuda, snapper, and moray eel.</td>
<td>Opens Na⁺ channels, causing depolarization.</td>
<td>Nausea, vomiting, diarrhea; perioral numbness; reversal of hot and cold sensations; bradycardia, heart block, hypotension.</td>
<td>Supportive.</td>
</tr>
</tbody>
</table>

Beers criteria

Widely used criteria developed to reduce potentially inappropriate prescribing and harmful polypharmacy in the geriatric population. Includes > 50 medications that should be avoided in elderly patients due to ± efficacy and/or ± risk of adverse events. Examples include:
- α-blockers (± risk of hypotension)
- Anticholinergics, antidepressants, antihistamines, opioids (± risk of delirium, sedation, falls, constipation, urinary retention)
- Benzodiazepines (± risk of delirium, sedation, falls)
- NSAIDs (± risk of GI bleeding, especially with concomitant anticoagulation)
- PPIs (± risk of C difficile infection)
Specific toxicity treatments

<table>
<thead>
<tr>
<th>TOXIN</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine (replenishes glutathione)</td>
</tr>
<tr>
<td>AChE inhibitors, organophosphates</td>
<td>Atropine &gt; pralidoxime</td>
</tr>
<tr>
<td>Antimuscarinic, anticholinergic agents</td>
<td>Physostigmine, control hyperthermia</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Dimercaprol, succimer</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Atropine, glucagon</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>100% O₂, hyperbaric O₂</td>
</tr>
<tr>
<td>Copper</td>
<td>Penicillamine, trientine (Copper penny)</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Nitrite + thiosulfate, hydroxocobalamin</td>
</tr>
<tr>
<td>Digitalis (digoxin)</td>
<td>Anti-dig Fab fragments</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Iron</td>
<td>Deferoxamine, deferasirox, deferiprone</td>
</tr>
<tr>
<td>Lead</td>
<td>EDTA, dimercaprol, succimer, penicillamine</td>
</tr>
<tr>
<td>Mercury</td>
<td>Dimercaprol, succimer</td>
</tr>
<tr>
<td>Methanol, ethylene glycol (antifreeze)</td>
<td>Fomepizole &gt; ethanol, dialysis</td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>Methylene blue, vitamin C (reducing agent)</td>
</tr>
<tr>
<td>Opioids</td>
<td>NaloxOne</td>
</tr>
<tr>
<td>Salicylates</td>
<td>NaHCO₃ (alkalinize urine), dialysis</td>
</tr>
<tr>
<td>TCAs</td>
<td>NaHCO₃ (stabilizes cardiac cell membrane)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K (delayed effect), fresh frozen plasma (immediate)</td>
</tr>
</tbody>
</table>

Drug reactions—cardiovascular

**Coronary vasospasm**
- Cocaine, Amphetamines, Sumatriptan, Ergot alkaloids (CASE)

**Cutaneous flushing**
- Vancomycin, Adenosine, Niacin, Ca²⁺ channel blockers, Echinocandins, Nitrates (flushed from VANCEN [dancing])
- Red man syndrome—rate-dependent infusion reaction to vancomycin causing widespread pruritic erythema. Manage with diphenhydramine, slower infusion rate.

**Dilated cardiomyopathy**
- Anthracyclines (eg, Doxorubicin, Daunorubicin); prevent with Dextrazoxane

**Torsades de pointes**
- Agents that prolong QT interval: antiArrhythmics (class IA, III), antiBiotics (eg, macrolides), antiCytotics (eg, haloperidol), antiDepressants (eg, TCAs), antiEmetics (eg, ondansetron) (ABCDE)
### Drug reactions—endocrine/reproductive

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocortical insufficiency</td>
<td>HPA suppression 2° to glucocorticoid withdrawal</td>
<td></td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Lithium, demeclocycline</td>
<td></td>
</tr>
<tr>
<td>Hot flashes</td>
<td>SERMs (eg, tamoxifen, clomiphene, raloxifene)</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Tacrolimus, Protease inhibitors, Niacin, HCTZ, Corticosteroids</td>
<td>The People Need Hard Candies</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Typical antipsychotics (eg, haloperidol), atypical antipsychotics (eg, quetiapine), metoclopramide, methyl dopa</td>
<td>Presents with hypogonadism (eg, infertility, amenorrhea, erectile dysfunction) and galactorrhea (more common in men)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Lithium, amiodarone</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>AMiodarone, Sulfonamides, Lithium</td>
<td>I AM SUddenly Lethargic</td>
</tr>
<tr>
<td>SIADH</td>
<td>Carbamazepine, Cyclophosphamide, SSRIs</td>
<td>Can’t Concentrate Serum Sodium</td>
</tr>
</tbody>
</table>

### Drug reactions—gastrointestinal

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cholestatic hepatitis, jaundice</td>
<td>Macrolides (eg, erythromycin)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Acamprosate, antidiabetic agents (acarbose, metformin, pramlintide), colchicine, cholinesterase inhibitors, lipid-lowering agents (eg, ezetimibe, orlistat), macrolides (eg, erythromycin), quinidine, SSRIs</td>
<td></td>
</tr>
<tr>
<td>Focal to massive hepatic necrosis</td>
<td>Halothane, Amanita phalloides (death cap mushroom), Valproic acid, Acetaminophen</td>
<td>Liver “HAVAc”</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Rifampin, isoniazid, pyrazinamide, statins, fibrates</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Didanosine, Corticosteroids, Alcohol, Valproic acid, Azathioprine, Diuretics (furosemide, HCTZ)</td>
<td>Drugs Causing A Violent Abdominal Distress</td>
</tr>
<tr>
<td>Pill-induced esophagitis</td>
<td>Bisphosphonates, ferrous sulfate, NSAIDs, potassium chloride, tetracyclines</td>
<td>Caustic effect minimized with upright posture and adequate water ingestion.</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Ampicillin, cephalosporins, clindamycin, fluoroquinolones</td>
<td>Antibiotics predispose to superinfection by resistant C difficile</td>
</tr>
</tbody>
</table>
### Drug reactions—hematologic

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agranulocytosis</td>
<td>Clozapine, Carbamazepine, Propylthiouracil, Methimazole, Colchicine, Ganciclovir</td>
<td>Can Cause Pretty Major Collapse of Granulocytes</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Carbamazepine, Methimazole, NSAIDs, Benzene, Chloramphenicol, Propylthiouracil</td>
<td>Can’t Make New Blood Cells Properly</td>
</tr>
<tr>
<td>Direct Coombs-positive hemolytic anemia</td>
<td>Penicillin, methylDopa, Cephalosporins</td>
<td>P Diddy Coombs</td>
</tr>
<tr>
<td>Drug reaction with eosinophilia and systemic symptoms</td>
<td>Allopurinol, anticonvulsants, antibiotics, sulfa drugs</td>
<td>DRESS is a potentially fatal delayed hypersensitivity reaction. Latency period (2–8 weeks) followed by fever, morbilliform skin rash, and frequent multiorgan involvement. Treatment: withdrawal of offending drug, corticosteroids.</td>
</tr>
<tr>
<td>Gray baby syndrome</td>
<td>Chloramphenicol</td>
<td></td>
</tr>
<tr>
<td>Hemolysis in G6PD deficiency</td>
<td>Isoniazid, Sulfonamides, Dapsone, Primaquine, Aspirin, Ibuprofen, Nitrofuranotin</td>
<td>Hemolysis IS D PAIN</td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>Hydroxyurea, Phenytoin, Methotrexate, Sulfadruugs</td>
<td>You’re having a mega blast with PMS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Heparin, Vancomycin, Linezolid</td>
<td>Help! Very Low platelets</td>
</tr>
<tr>
<td>Thrombotic complications</td>
<td>Combined oral contraceptives, hormone replacement therapy, SERMs (eg, tamoxifen, raloxifene, clomiphene)</td>
<td>Estrogen-mediated side effect</td>
</tr>
</tbody>
</table>

### Drug reactions—musculoskeletal/skin/connective tissue

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-induced lupus</td>
<td>Methyllopa, Sulf drugs, Hydralazine, Isoniazid, Procainamide, Phenytoin, Etanercept</td>
<td>Having lupus is Mega “SHIPP-E”</td>
</tr>
<tr>
<td>Fat redistribution</td>
<td>Protease inhibitors, Glucocorticoids</td>
<td>Fat PiG</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>Cyclosporine, Ca²⁺ channel blockers, Phenytoin</td>
<td>Can Cause Puffy gums</td>
</tr>
<tr>
<td>Hyperuricemia (gout)</td>
<td>Pyrazinamide, Thiazides, Furosemide, Niacin, Cyclosporine</td>
<td>Painful Tophi and Feet Need Care</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Statins, fibrates, niacin, colchicine, daptomycin, hydroxychloroquine, interferon-α, penicillamine, glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Corticosteroids, depot medroxyprogesterone acetate, GnRH agonists, aromatase inhibitors, anticonvulsants, heparin, PPIs</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Sulfonamides, Amiodarone, Tetracyclines, 5-FU</td>
<td>SAT For Photo</td>
</tr>
<tr>
<td>Rash (Stevens-Johnson syndrome)</td>
<td>Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin</td>
<td>Steven Johnson has epileptic allergy to sulfa drugs and penicillin</td>
</tr>
<tr>
<td>Teeth discoloration</td>
<td>Tetracyclines</td>
<td>Teetracyclines</td>
</tr>
<tr>
<td>Tendon and cartilage damage</td>
<td>Fluoroquinolones</td>
<td></td>
</tr>
</tbody>
</table>
### Drug reactions—neurologic

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinchonism</td>
<td>Quinidine, quinine</td>
<td>Can present with tinnitus, hearing/vision loss, psychosis, and cognitive impairment</td>
</tr>
<tr>
<td>Parkinson-like syndrome</td>
<td>Antipsychotics, Reserpine, Metoclopramide</td>
<td>Cogwheel rigidity of ARM</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Phenotoin, vincristine</td>
<td></td>
</tr>
<tr>
<td>Pseudotumor cerebri</td>
<td>Growth hormones, tetracyclines, vitamin A</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>Isoniazid (vitamin B₆ deficiency), Bupropion, Imipenem/cilastatin, Tramadol, Enflurane</td>
<td>With seizures, I BITE my tongue</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Antipsychotics, metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>Topiramate (blurred vision/diplopia, haloes), Digoxin (yellow-tinged vision), Isoniazid (optic neuropathy/color vision changes), Vigabatrin (bilateral visual field defects), PDE-5 inhibitors (blue-tinged vision), Ethambutol (color vision changes)</td>
<td>These Drugs Irritate Very Precious Eyes</td>
</tr>
</tbody>
</table>

### Drug reactions—renal/genitourinary

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi syndrome</td>
<td>Cisplatin, ifosfamide, expired tetracyclines, tenofovir</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>Cyclophosphamide, ifosfamide</td>
<td>Prevent by coadministering with mesna</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Penicillins, furosemide, NSAIDs, proton pump inhibitors, sulfa drugs</td>
<td></td>
</tr>
</tbody>
</table>

### Drug reactions—respiratory

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry cough</td>
<td>ACE inhibitors</td>
<td></td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Methotrexate, Nitrofurantoin, Carmustine, Bleomycin, Busulfan, Amiodarone</td>
<td>My Nose Cannot Breathe Bad Air</td>
</tr>
</tbody>
</table>

### Drug reactions—multiorgan

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimuscarinic</td>
<td>Atropine, TCAs, H₁-blockers, antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Disulfiram-like reaction</td>
<td>1st-generation Sulfonlureas, Procarbazine, certain Cephalosporins, Griseofulvin, Metronidazole</td>
<td>Sorry Pals, Can’t Go Mingle.</td>
</tr>
<tr>
<td>Nephrotoxicity/ototoxicity</td>
<td>Loop diuretics, Aminoglycosides, cisPlatin, Vancocmycin, ampoTERicin B</td>
<td>Listen And Pce Very TERriBly. Cisplatin toxicity may respond to amifostine.</td>
</tr>
</tbody>
</table>
Drugs affecting pupil size

<table>
<thead>
<tr>
<th>↑ pupil size</th>
<th>↓ pupil size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics (atropine, TCA, tropicamide, scopolamine, antihistamines)</td>
<td>Antipsychotics (haloperidol, risperidone, olanzapine)</td>
</tr>
<tr>
<td>Drugs of abuse (amphetamines, cocaine, LSD)</td>
<td>Drugs of abuse (eg, heroin/opioids)</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Parasympathomimetics (pilocarpine), organophosphates</td>
</tr>
</tbody>
</table>

Cytochrome P-450 interactions (selected)

<table>
<thead>
<tr>
<th>Inducers (+)</th>
<th>Substrates</th>
<th>Inhibitors (–)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td>Anti-epileptics</td>
<td>Sodium valproate</td>
</tr>
<tr>
<td>Chronic alcohol use</td>
<td>Theophylline</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Warfarin</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>OCPs</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>Acute alcohol abuse</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td></td>
<td>Erythromycin/clarithromycin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Sulfamides</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Omeprazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grapefruit juice</td>
</tr>
</tbody>
</table>

Most chronic alcoholics
Steal Phen-Phen and Never
Refuse Greasy Carbs
Always Think When Outdoors
SICKFACES.COM (when I Am drinking Grapefruit juice)

Sulfa drugs

Sulfonamide antibiotics, Sulfasalazine, Probencid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonlyureas.
Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, acute interstitial nephritis, and urticaria (hives).
Symptoms range from mild to life threatening.

Scary Sulfa Pharm FACTS
### Drug names

<table>
<thead>
<tr>
<th>ENDING</th>
<th>CATEGORY</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-azole</td>
<td>Ergosterol synthesis inhibitor</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>-bendazole</td>
<td>Antiparasitic/anthelminthic</td>
<td>Mebendazole</td>
</tr>
<tr>
<td>-cillin</td>
<td>Transpeptidase (penicillin-binding protein)</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>-cycline</td>
<td>Protein synthesis inhibitor</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>-ivir</td>
<td>Neuraminidase inhibitor</td>
<td>Oseltamivir</td>
</tr>
<tr>
<td>-navir</td>
<td>Protease inhibitor</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>-ovir</td>
<td>DNA polymerase inhibitor</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>-thromycin</td>
<td>Macrolide antibiotic</td>
<td>Azithromycin</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-ane</td>
<td>Inhalational general anesthetic</td>
<td>Halothane</td>
</tr>
<tr>
<td>-azine</td>
<td>Typical antipsychotic</td>
<td>Thioridazine</td>
</tr>
<tr>
<td>-barbital</td>
<td>Barbiturate</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>-caine</td>
<td>Local anesthetic</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>-ipramine, -triptyline</td>
<td>TCA</td>
<td>Imipramine, amitriptyline</td>
</tr>
<tr>
<td>-triptan</td>
<td>5-HT1B/1D agonist</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>-zepam, -zolam</td>
<td>Benzodiazepine</td>
<td>Diazepam, alprazolam</td>
</tr>
<tr>
<td><strong>Autonomic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-chol</td>
<td>Cholinergic agonist</td>
<td>Bethanechol, carbachol</td>
</tr>
<tr>
<td>-curium, -curonium</td>
<td>Nondepolarizing paralytic</td>
<td>Atracurium, vecuronium</td>
</tr>
<tr>
<td>-olol</td>
<td>β-blocker</td>
<td>Propranolol</td>
</tr>
<tr>
<td>-stigmine</td>
<td>AChE inhibitor</td>
<td>Neostigmine</td>
</tr>
<tr>
<td>-terol</td>
<td>β2-agonist</td>
<td>Albuterol</td>
</tr>
<tr>
<td>-zosin</td>
<td>α1-antagonist</td>
<td>Prazosin</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-afil</td>
<td>PDE-5 inhibitor</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>-dipine</td>
<td>Dihydropyridine Ca2+ channel blocker</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>-pril</td>
<td>ACE inhibitor</td>
<td>Captopril</td>
</tr>
<tr>
<td>-sartan</td>
<td>Angiotensin-II receptor blocker</td>
<td>Losartan</td>
</tr>
<tr>
<td>-xaban</td>
<td>Direct factor Xa inhibitor</td>
<td>Apixaban, edoxaban, rivaroxaban</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-dronate</td>
<td>Bisphosphonate</td>
<td>Alendronate</td>
</tr>
<tr>
<td>-gliptin</td>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>-glitazone</td>
<td>PPAR-γ activator</td>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>-limus</td>
<td>Calcineurin inhibitor</td>
<td>Everolimus, tacrolimus</td>
</tr>
<tr>
<td>-prazole</td>
<td>Proton pump inhibitor</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>-prost</td>
<td>Prostaglandin analog</td>
<td>Latanoprost</td>
</tr>
<tr>
<td>-sentan</td>
<td>Endothelin receptor antagonist</td>
<td>Bosentan</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>
</tbody>
</table>
### Biologic agents

<table>
<thead>
<tr>
<th>ENDING</th>
<th>CATEGORY</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibodies (-mab)—target overexpressed cell surface receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-ximab</td>
<td>Chimeric human-mouse monoclonal Ab</td>
<td>Rituximab</td>
</tr>
<tr>
<td>-zumab</td>
<td>Humanized mouse monoclonal Ab</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>-mumab</td>
<td>Human monoclonal Ab</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td><strong>Small molecule inhibitors (-ib)—target intracellular molecules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-tinib</td>
<td>Tyrosine kinase inhibitor</td>
<td>Imatinib</td>
</tr>
<tr>
<td>-zomib</td>
<td>Proteasome inhibitor</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>-ciclib</td>
<td>Cyclin-dependent kinase inhibitor</td>
<td>Palbociclib</td>
</tr>
<tr>
<td><strong>Receptor fusion proteins (-cept)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-cept</td>
<td>TNF-α antagonist</td>
<td>Etanercept</td>
</tr>
<tr>
<td><strong>Interleukin receptor modulators (-kin)—agonists and antagonists of interleukin receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-leukin</td>
<td>IL-2 agonist/analog</td>
<td>Aldesleukin</td>
</tr>
<tr>
<td>-kinra</td>
<td>Interleukin receptor antagonist</td>
<td>Anakinra</td>
</tr>
</tbody>
</table>
“It is a mathematical fact that fifty percent of all doctors graduate in the bottom half of their class.”
—Unknown

“There are two kinds of statistics: the kind you look up and the kind you make up.”
—Rex Stout

“On a long enough timeline, the survival rate for everyone drops to zero.”
—Chuck Palahniuk

“There are three kinds of lies: lies, damned lies, and statistics.”
—Mark Twain

A heterogenous mix of epidemiology, biostatistics, ethics, law, healthcare delivery, patient safety, quality improvement, and more falls under the heading of public health sciences. Biostatistics and epidemiology are the foundations of evidence-based medicine and are very high yield. Make sure you can quickly apply biostatistical equations such as sensitivity, specificity, and predictive values in a problem-solving format. Also, know how to set up your own 2×2 tables. Quality improvement and patient safety topics were introduced a few years ago on the exam and represent trends in health system science. Medical ethics questions often require application of principles. Typically, you are presented with a patient scenario and then asked how you would respond.
### Observational studies

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>DESIGN</th>
<th>MEASURES/EXAMPLE</th>
</tr>
</thead>
</table>
| Cross-sectional study | Frequency of disease and frequency of risk-related factors are assessed in the present.  
Asks, “What is happening?”                                                                                                                   | Disease prevalence.  
Can show risk factor association with disease, but does not establish causality. |
| Case-control study | Compares a group of people with disease to a group without disease.  
Looks to see if odds of prior exposure or risk factor differs by disease state.  
Patients with COPD had higher odds of a smoking history than those without COPD.       |
| Cohort study     | Compares a group with a given exposure or risk factor to a group without such exposure.  
Looks to see if exposure or risk factor is associated with later development of disease.  
Can be prospective (asks, “Who will develop disease?”) or retrospective (asks, “Who developed the disease [exposed vs nonexposed]?”). | Relative risk (RR).  
Smokers had a higher risk of developing COPD than nonsmokers.                        |
| Twin concordance study | Compares the frequency with which both monozygotic twins vs both dizygotic twins develop the same disease.                                                                                     | Measures heritability and influence of environmental factors (“nature vs nurture”). |
| Adoption study   | Compares siblings raised by biological vs adoptive parents.                                                                                                                                          | Measures heritability and influence of environmental factors.                    |

### Clinical trial

Experimental study involving humans. Compares therapeutic benefits of 2 or more treatments, or of treatment and placebo. Study quality improves when study is randomized, controlled, and double-blinded (ie, neither patient nor doctor knows whether the patient is in the treatment or control group). Triple-blind refers to the additional blinding of the researchers analyzing the data. Four phases (“Does the drug SWIM?”).

<table>
<thead>
<tr>
<th>DRUG TRIALS</th>
<th>TYPICAL STUDY SAMPLE</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Small number of healthy volunteers or patients with disease of interest.</td>
<td>“Is it Safe?” Assesses safety, toxicity, pharmacokinetics, and pharmacodynamics.</td>
</tr>
<tr>
<td>Phase II</td>
<td>Moderate number of patients with disease of interest.</td>
<td>“Does it Work?” Assesses treatment efficacy, optimal dosing, and adverse effects.</td>
</tr>
<tr>
<td>Phase III</td>
<td>Large number of patients randomly assigned either to the treatment under investigation or to the best available treatment (or placebo).</td>
<td>“Is it as good or better?” Compares the new treatment to the current standard of care (any improvement?).</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Postmarketing surveillance of patients after treatment is approved.</td>
<td>“Can it stay?” Detects rare or long-term adverse effects. Can result in treatment being withdrawn from Market.</td>
</tr>
</tbody>
</table>
Evaluation of diagnostic tests

Uses 2 × 2 table comparing test results with the actual presence of disease. Sensitivity and specificity are fixed properties of a test. PPV and NPV vary depending on disease prevalence in population being tested.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>FN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>TN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity (true-positive rate)
Proportion of all people with disease who test positive, or the probability that when the disease is present, the test is positive. Value approaching 100% is desirable for ruling out disease and indicates a low false-negative rate. High sensitivity test used for screening in diseases with low prevalence.

\[
\text{Sensitivity} = \frac{TP}{TP + FN} = 1 - FN \text{ rate}
\]

NPV = 100%, then FN is zero. So, all negatives must be TNs.

Specificity (true-negative rate)
Proportion of all people without disease who test negative, or the probability that when the disease is absent, the test is negative. Value approaching 100% is desirable for ruling in disease and indicates a low false-positive rate. High specificity test used for confirmation after a positive screening test.

\[
\text{Specificity} = \frac{TN}{TN + FP} = 1 - FP \text{ rate}
\]

If specificity is 100%, then FP is zero. So, all positives must be TPs.

Positive predictive value
Probability that a person who has a positive test result actually has the disease.

\[
\text{PPV} = \frac{TP}{TP + FP}
\]

PPV varies directly with pretest probability (baseline risk, such as prevalence of disease): high pretest probability → high PPV

Negative predictive value
Probability that a person with a negative test result actually does not have the disease.

\[
\text{NPV} = \frac{TN}{TN + FN}
\]

NPV varies inversely with prevalence or pretest probability

POSSIBLE CUTTOFF VALUES

\begin{align*}
A &= \text{100% sensitivity cutoff value} \\
B &= \text{practical compromise between specificity and sensitivity} \\
C &= \text{100% specificity cutoff value}
\end{align*}

Likelihood ratio

Likelihood that a given test result would be expected in a patient with the target disorder compared to the likelihood that the same result would be expected in a patient without the target disorder. LR⁺ > 10 and/or LR⁻ < 0.1 indicate a very useful diagnostic test. LRs can be multiplied with pretest odds of disease to estimate posttest odds.

\[
\text{LR⁺} = \frac{\text{sensitivity}}{1 - \text{specificity}} = \frac{TP \text{ rate}}{FP \text{ rate}}
\]

\[
\text{LR⁻} = \frac{1 - \text{sensitivity}}{\text{specificity}} = \frac{FN \text{ rate}}{TN \text{ rate}}
\]
Quantifying risk

Definitions and formulas are based on the classic 2 × 2 or contingency table.

<table>
<thead>
<tr>
<th>Risk Factor or Intervention</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Odds ratio

Typically used in case-control studies. OR depicts the odds of a certain exposure given an event (eg, disease; a/c) vs the odds of exposure in the absence of that event (eg, no disease; b/d).

\[ \text{OR} = \frac{a/c}{b/d} = \frac{ad}{bc} \]

Relative risk

Typically used in cohort studies. Risk of developing disease in the exposed group divided by risk in the unexposed group (eg, if 5/10 people exposed to radiation get cancer, and 1/10 people not exposed to radiation get cancer, the relative risk is 5, indicating a 5 times greater risk of cancer in the exposed than unexposed). For rare diseases (low prevalence), OR approximates RR.

\[ \text{RR} = \frac{a/(a + b)}{c/(c + d)} \]

Attributable risk

The difference in risk between exposed and unexposed groups (eg, if risk of lung cancer in smokers is 21% and risk in nonsmokers is 1%, then the attributable risk is 20%).

\[ \text{AR} = \frac{a}{a + b} - \frac{c}{c + d} \]

Relative risk reduction

The proportion of risk reduction attributable to the intervention as compared to a control (eg, if 2% of patients who receive a flu shot develop the flu, while 8% of unvaccinated patients develop the flu, then RR = 2/8 = 0.25, and RRR = 0.75).

\[ \text{RRR} = 1 - \text{RR} \]

Absolute risk reduction

The difference in risk (not the proportion) attributable to the intervention as compared to a control (eg, if 8% of people who receive a placebo vaccine develop the flu vs 2% of people who receive a flu vaccine, then ARR = 8% - 2% = 6% = .06).

\[ \text{ARR} = \frac{e}{c + d} - \frac{a}{a + b} \]

Number needed to treat

Number of patients who need to be treated for 1 patient to benefit. Lower number = better treatment.

\[ \text{NNT} = 1/\text{ARR} \]

Number needed to harm

Number of patients who need to be exposed to a risk factor for 1 patient to be harmed. Higher number = safer exposure.

\[ \text{NNH} = 1/\text{AR} \]
Incidence vs prevalence

\[
\text{Incidence} = \frac{\text{# of new cases}}{\text{# of people at risk}} \quad \text{(during a specified time period)}
\]

\[
\text{Prevalence} = \frac{\text{# of existing cases}}{\text{Total # of people in a population}} \quad \text{(at a point in time)}
\]

\[
\text{Prevalence} = \frac{\text{Incidence rate} \times \text{average duration of disease}}{1 - \text{prevalence}}
\]

Incidence looks at new cases (incidents).

Prevalence looks at all current cases.

Prevalence = incidence for short duration disease (eg, common cold).

Prevalence > incidence for chronic diseases, due to large # of existing cases (eg, diabetes).

Precision vs accuracy

<table>
<thead>
<tr>
<th>Precision (reliability)</th>
<th>Accuracy (validity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The consistency and reproducibility of a test.</td>
<td>The trueness of test measurements.</td>
</tr>
<tr>
<td>The absence of random variation in a test.</td>
<td>The absence of systematic error or bias in a test.</td>
</tr>
</tbody>
</table>

Random error ↓ precision in a test.

↑ precision → ↓ standard deviation.

↑ precision → ↑ statistical power (1 − β).

Systematic error ↓ accuracy in a test.
### Bias and study errors

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Examples</th>
<th>Strategies to reduce bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recruiting participants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection bias</td>
<td>Nonrandom sampling or treatment allocation of subjects such that study population is not representative of target population. Most commonly a sampling bias.</td>
<td>Berkson bias—study population selected from hospital is less healthy than general population Non-response bias—participating subjects differ from nonrespondents in meaningful ways</td>
<td>Randomization Ensure the choice of the right comparison/reference group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Performing study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall bias</td>
<td>Awareness of disorder alters recall by subjects; common in retrospective studies.</td>
<td>Patients with disease recall exposure after learning of similar cases</td>
<td>Decrease time from exposure to follow-up</td>
</tr>
<tr>
<td>Measurement bias</td>
<td>Information is gathered in a systemically distorted manner.</td>
<td>Association between HTN and MI not observed when using faulty automatic sphygmomanometer Hawthorne effect—participants change behavior upon awareness of being observed</td>
<td>Use objective, standardized, and previously tested methods of data collection that are planned ahead of time Use placebo group</td>
</tr>
<tr>
<td>Procedure bias</td>
<td>Subjects in different groups are not treated the same.</td>
<td>Patients in treatment group spend more time in highly specialized hospital units</td>
<td>Blinding and use of placebo reduce influence of participants and researchers on procedures and interpretation of outcomes as neither are aware of group allocation</td>
</tr>
<tr>
<td>Observer-expectancy bias</td>
<td>Researcher's belief in the efficacy of a treatment changes the outcome of that treatment (aka, Pygmalion effect).</td>
<td>An observer expecting treatment group to show signs of recovery is more likely to document positive outcomes</td>
<td></td>
</tr>
<tr>
<td><strong>Interpreting results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confounding bias</td>
<td>When a factor is related to both the exposure and outcome, but not on the causal pathway, it distorts or confuses effect of exposure on outcome. Contrast with effect modification.</td>
<td>Pulmonary disease is more common in coal workers than the general population; however, people who work in coal mines also smoke more frequently than the general population</td>
<td>Multiple/repeated studies Crossover studies (subjects act as their own controls) Matching (patients with similar characteristics in both treatment and control groups)</td>
</tr>
<tr>
<td>Lead-time bias</td>
<td>Early detection is confused with † survival.</td>
<td>Early detection makes it seem like survival has increased, but the disease's natural history has not changed</td>
<td>Measure “back-end” survival (adjust survival according to the severity of disease at the time of diagnosis)</td>
</tr>
<tr>
<td>Length-time bias</td>
<td>Screening test detects diseases with long latency period, while those with shorter latency period become symptomatic earlier.</td>
<td>A slowly progressive cancer is more likely detected by a screening test than a rapidly progressive cancer</td>
<td>A randomized controlled trial assigning subjects to the screening program or to no screening</td>
</tr>
</tbody>
</table>
### Statistical distribution

**Measures of central tendency**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>( \text{Mean} = \frac{\text{sum of values}}{\text{total number of values}} )</td>
<td>Most affected by outliers (extreme values).</td>
</tr>
<tr>
<td>Median</td>
<td>( \text{Median} = \text{middle value of a list of data sorted from least to greatest} )</td>
<td>If there is an even number of values, the median will be the average of the middle two values.</td>
</tr>
<tr>
<td>Mode</td>
<td>( \text{Mode} = \text{most common value} )</td>
<td>Least affected by outliers.</td>
</tr>
</tbody>
</table>

**Measures of dispersion**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard deviation</td>
<td>( \sigma = \text{SD} )</td>
<td>How much variability exists in a set of values, around the mean of these values.</td>
</tr>
<tr>
<td>Standard error</td>
<td>( \text{SE} = \frac{\sigma}{\sqrt{n}} )</td>
<td>An estimate of how much variability exists in a (theoretical) set of sample means around the true population mean.</td>
</tr>
<tr>
<td>Variance</td>
<td>( \text{Variance} = (\text{SD})^2 )</td>
<td></td>
</tr>
</tbody>
</table>

### Normal distribution

Gaussian, also called bell-shaped.
\[ \text{Mean} = \text{median} = \text{mode} \]

### Nonnormal distributions

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimodal</td>
<td>Suggests two different populations (e.g., metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).</td>
</tr>
<tr>
<td>Positive skew</td>
<td>Typically, mean &gt; median &gt; mode. Asymmetry with longer tail on right.</td>
</tr>
<tr>
<td>Negative skew</td>
<td>Typically, mean &lt; median &lt; mode. Asymmetry with longer tail on left.</td>
</tr>
</tbody>
</table>

### Statistical hypotheses

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null (( H_0 ))</td>
<td>Hypothesis of no difference or relationship (e.g., there is no association between the disease and the risk factor in the population).</td>
</tr>
<tr>
<td>Alternative (( H_1 ))</td>
<td>Hypothesis of some difference or relationship (e.g., there is some association between the disease and the risk factor in the population).</td>
</tr>
</tbody>
</table>
Outcomes of statistical hypothesis testing

<table>
<thead>
<tr>
<th>Correct result</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stating that there is an effect or difference when one exists (null hypothesis rejected in favor of alternative hypothesis).</td>
<td>Study rejects $H_0$</td>
</tr>
<tr>
<td>Stating that there is no effect or difference when none exists (null hypothesis not rejected).</td>
<td>Study does not reject $H_0$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incorrect result</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I error ($\alpha$)</strong></td>
<td>Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis).</td>
</tr>
<tr>
<td>$\alpha$ is the probability of making a type I error. $\alpha$ is judged against a preset $\alpha$ level of significance (usually 0.05). If $\alpha &lt; 0.05$, then there is less than a 5% chance that the data will show something that is not really there.</td>
<td>Also known as false-positive error. $\alpha = \text{you accused an innocent man.}$</td>
</tr>
<tr>
<td><strong>Type II error ($\beta$)</strong></td>
<td>Stating that there is not an effect or difference when one exists (null hypothesis is not rejected when it is in fact false).</td>
</tr>
<tr>
<td>$\beta$ is the probability of making a type II error. $\beta$ is related to statistical power $(1 - \beta)$, which is the probability of rejecting the null hypothesis when it is false.</td>
<td>Also known as false-negative error. $\beta = \text{you blindly let the guilty man go free.}$</td>
</tr>
<tr>
<td>$\uparrow$ power and $\uparrow \beta$ by:</td>
<td>If you $\uparrow$ sample size, you $\uparrow$ power. There is power in numbers.</td>
</tr>
<tr>
<td>* $\uparrow$ sample size</td>
<td></td>
</tr>
<tr>
<td>* $\uparrow$ expected effect size</td>
<td></td>
</tr>
<tr>
<td>* $\uparrow$ precision of measurement</td>
<td></td>
</tr>
</tbody>
</table>

**Confidence interval**

Range of values within which the true mean of the population is expected to fall, with a specified probability.

CI for sample mean $= \bar{x} \pm Z(\text{SE})$
The 95% CI (corresponding to $\alpha = 0.05$) is often used.
For the 95% CI, $Z = 1.96$.
For the 99% CI, $Z = 2.58$.

If the 95% CI for a mean difference between 2 variables includes 0, then there is no significant difference and $H_0$ is not rejected.
If the 95% CI for odds ratio or relative risk includes 1, $H_0$ is not rejected.
If the CIs between 2 groups do not overlap $\rightarrow$ statistically significant difference exists.
If the CIs between 2 groups overlap $\rightarrow$ usually no significant difference exists.
**Meta-analysis**

A method of statistical analysis that pools summary data (e.g., means, RRs) from multiple studies for a more precise estimate of the size of an effect. Also estimates heterogeneity of effect sizes between studies. Improves strength of evidence and generalizability of study findings. Limited by quality of individual studies and bias in study selection.

---

**Common statistical tests**

- **t-test**
  Checks differences between means of 2 groups. Example: comparing the mean blood pressure between men and women.

- **ANOVA**
  Checks differences between means of 3 or more groups. 3 words: ANalysis Of VAriance. Example: comparing the mean blood pressure between members of 3 different ethnic groups.

- **Chi-square ($\chi^2$)**
  Checks differences between 2 or more percentages or proportions of categorical outcomes (not mean values). Pronounce Chi-tetrical. Example: comparing the percentage of members of 3 different ethnic groups who have essential hypertension.

---

**Pearson correlation coefficient**

$r$ is always between $-1$ and $+1$. The closer the absolute value of $r$ is to $1$, the stronger the linear correlation between the 2 variables.

- Positive $r$ value → positive correlation (as one variable ↑, the other variable ↑).
- Negative $r$ value → negative correlation (as one variable ↑, the other variable ↓).

Coefficient of determination = $r^2$ (amount of variance in one variable that can be explained by variance in another variable).
Core ethical principles

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomy</td>
<td>Obligation to respect patients as individuals (truth-telling, confidentiality), to create conditions necessary for autonomous choice (informed consent), and to honor their preference in accepting or not accepting medical care.</td>
</tr>
<tr>
<td>Beneficence</td>
<td>Physicians have a special ethical (fiduciary) duty to act in the patient’s best interest. May conflict with autonomy (an informed patient has the right to decide) or what is best for society (e.g., mandatory TB treatment). Traditionally, patient interest supersedes.</td>
</tr>
<tr>
<td>Nonmaleficence</td>
<td>“Do no harm.” Must be balanced against beneficence; if the benefits outweigh the risks, a patient may make an informed decision to proceed (most surgeries and medications fall into this category).</td>
</tr>
<tr>
<td>Justice</td>
<td>To treat persons fairly and equitably. This does not always imply equally (e.g., triage).</td>
</tr>
</tbody>
</table>

Informed consent

A process (not just a document/signature) that requires:

- Disclosure: discussion of pertinent information
- Understanding: ability to comprehend
- Capacity: ability to reason and make one’s own decisions (distinct from competence, a legal determination)
- Voluntariness: freedom from coercion and manipulation

Patients must have an intelligent understanding of their diagnosis and the risks/benefits of proposed treatment and alternative options, including no treatment. Patient must be informed that he or she can revoke written consent at any time, even orally.

Exceptions to informed consent (WIPE it away):

- Waiver—patient explicitly waives the right of informed consent
- Legally Incompetent—patient lacks decision-making capacity (obtain consent from legal surrogate)
- Therapeutic Privilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity
- Emergency situation—implied consent may apply

Consent for minors

A minor is generally any person < 18 years old. Parental consent laws in relation to healthcare vary by state. In general, parental consent should be obtained, but exceptions exist for emergency treatment (e.g., blood transfusions) or if minor is legally emancipated (e.g., married, self supporting, or in the military).

Situations in which parental consent is usually not required:

- Sex (contraception, STIs, pregnancy)
- Drugs (substance abuse)
- Rock and roll (emergency/trauma)

Physicians should always encourage healthy minor-guardian communication. Physician should seek a minor’s assent even if their consent is not required.
Decision-making capacity

Physician must determine whether the patient is psychologically and legally capable of making a particular healthcare decision. Note that decisions made with capacity cannot be revoked simply if the patient later loses capacity. Capacity is determined by a physician for a specific healthcare-related decision (e.g., to refuse medical care). Competency is determined by a judge and usually refers to more global categories of decision making (e.g., legally unable to make any healthcare-related decision).

Components (think GIEMSA):
- Decision is consistent with patient’s values and Goals
- Patient is Informed (knows and understands)
- Patient Expresses a choice
- Decision is not a result of altered Mental status (e.g., delirium, psychosis, intoxication), Mood disorder
- Decision remains Stable over time
- Patient is ≥ 18 years of Age or otherwise legally emancipated

Advance directives

Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law.

Oral advance directive

Incapacitated patient’s prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive was specific, patient made a choice, and decision was repeated over time to multiple people, then the oral directive is more valid.

Written advance directive

Specifies specific healthcare interventions that a patient anticipates he or she would accept or reject during treatment for a critical or life-threatening illness. A living will is an example.

Medical power of attorney

Patient designates an agent to make medical decisions in the event that he/she loses decision-making capacity. Patient may also specify decisions in clinical situations. Can be revoked by patient if decision-making capacity is intact. More flexible than a living will.

Do not resuscitate order

DNR order prohibits cardiopulmonary resuscitation (CPR). Other resuscitative measures that may follow (e.g., intubation) are also typically avoided.

Surrogate decision-maker

If a patient loses decision-making capacity and has not prepared an advance directive, individuals (surrogates) who know the patient must determine what the patient would have done. Priority of surrogates: spouse → adult Children → Parents → Siblings → other relatives (the spouse ChiPS in).
<table>
<thead>
<tr>
<th>Ethical situations</th>
<th>APPROPRIATE RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is not adherent.</td>
<td>Attempt to identify the reason for nonadherence and determine his/her willingness to change; do not coerce the patient into adhering and do not refer him/her to another physician.</td>
</tr>
<tr>
<td>Patient desires an unnecessary procedure.</td>
<td>Attempt to understand why the patient wants the procedure and address underlying concerns. Do not refuse to see the patient and do not refer him/her to another physician. Avoid performing unnecessary procedures.</td>
</tr>
<tr>
<td>Patient has difficulty taking medications.</td>
<td>Provide written instructions; attempt to simplify treatment regimens; use teach-back method (ask patient to repeat regimen back to physician) to ensure comprehension.</td>
</tr>
<tr>
<td>Family members ask for information about patient’s prognosis.</td>
<td>Avoid discussing issues with relatives without the patient’s permission.</td>
</tr>
<tr>
<td>A patient’s family member asks you not to disclose the results of a test if the prognosis is poor because the patient will be “unable to handle it.”</td>
<td>Attempt to identify why the family member believes such information would be detrimental to the patient’s condition. Explain that as long as the patient has decision-making capacity and does not indicate otherwise, communication of information concerning his/her care will not be withheld. However, if you believe the patient might seriously harm himself or others if informed, then you may invoke therapeutic privilege and withhold the information.</td>
</tr>
<tr>
<td>A 17-year-old girl is pregnant and requests an abortion.</td>
<td>Many states require parental notification or consent for minors for an abortion. Unless there are specific medical risks associated with pregnancy, a physician should not sway the patient’s decision for, or against, an elective abortion (regardless of maternal age or fetal condition).</td>
</tr>
<tr>
<td>A 15-year-old girl is pregnant and wants to keep the child. Her parents want you to tell her to give the child up for adoption.</td>
<td>The patient retains the right to make decisions regarding her child, even if her parents disagree. Provide information to the teenager about the practical issues of caring for a baby. Discuss the options, if requested. Encourage discussion between the teenager and her parents to reach the best decision.</td>
</tr>
<tr>
<td>A terminally ill patient requests physician assistance in ending his/her own life.</td>
<td>In the overwhelming majority of states, refuse involvement in any form of physician-assisted suicide. Physicians may, however, prescribe medically appropriate analgesics that coincidentally shorten the patient’s life.</td>
</tr>
<tr>
<td>Patient is suicidal.</td>
<td>Assess the seriousness of the threat. If it is serious, suggest that the patient remain in the hospital voluntarily; patient can be hospitalized involuntarily if he/she refuses.</td>
</tr>
<tr>
<td>Patient states that he/she finds you attractive.</td>
<td>Ask direct, closed-ended questions and use a chaperone if necessary. Romantic relationships with patients are never appropriate. It may be necessary to transition care to another physician.</td>
</tr>
<tr>
<td>A woman who had a mastectomy says she now feels “ugly.”</td>
<td>Find out why the patient feels this way. Do not offer falsely reassuring statements (eg, “You still look good”).</td>
</tr>
<tr>
<td>Patient is angry about the long time he/she spent in the waiting room.</td>
<td>Acknowledge the patient’s anger, but do not take a patient’s anger personally. Apologize for any inconvenience. Stay away from efforts to explain the delay.</td>
</tr>
<tr>
<td>Patient is upset with the way he/she was treated by another doctor.</td>
<td>Suggest that the patient speak directly to that physician regarding his/her concerns. If the problem is with a member of the office staff, tell the patient you will speak to that person.</td>
</tr>
<tr>
<td>An invasive test is performed on the wrong patient.</td>
<td>Regardless of the outcome, a physician is ethically obligated to inform a patient that a mistake has been made.</td>
</tr>
<tr>
<td>A patient requires a treatment not covered by his/her insurance.</td>
<td>Never limit or deny care because of the expense in time or money. Discuss all treatment options with patients, even if some are not covered by their insurance companies.</td>
</tr>
</tbody>
</table>
### Ethical situations (continued)

<table>
<thead>
<tr>
<th>SITUATION</th>
<th>APPROPRIATE RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 7-year-old boy loses a sister to cancer and now feels responsible.</td>
<td>At ages 5–7, children begin to understand that death is permanent, that all life functions end completely at death, and that everything that is alive eventually dies. Provide a direct, concrete description of his sister’s death. Avoid clichés and euphemisms. Reassure the boy that he is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).</td>
</tr>
<tr>
<td>Patient is victim of intimate partner violence.</td>
<td>Ask if patient is safe and has an emergency plan. Do not necessarily pressure patient to leave his or her partner, or disclose the incident to the authorities (unless required by state law).</td>
</tr>
<tr>
<td>Patient wants to try alternative or holistic medicine.</td>
<td>Find out why and allow patient to do so as long as there are no contraindications, medication interactions, or adverse effects to the new treatment.</td>
</tr>
<tr>
<td>Physician colleague presents to work impaired.</td>
<td>If impaired or incompetent, colleague is a threat to patient safety. Report the situation to local supervisory personnel. Should the organization fail to take action, alert the state licensing board.</td>
</tr>
<tr>
<td>Patient is officially determined to suffer brain death. Patient’s family insists on maintaining life support indefinitely because patient is still moving when touched.</td>
<td>Gently explain to family that there is no chance of recovery, and that brain death is equivalent to death. Movement is due to spinal arc reflex and is not voluntary. Bring case to appropriate ethics board regarding futility of care and withdrawal of life support.</td>
</tr>
<tr>
<td>A pharmaceutical company offers you a sponsorship in exchange for advertising its new drug.</td>
<td>Reject this offer. Generally, decline gifts and sponsorships to avoid any appearance of conflict of interest. The AMA Code of Ethics does make exceptions for gifts directly benefitting patients; gifts of minimal value; special funding for medical education of students, residents, fellows; grants whose recipients are chosen by independent institutional criteria; and funds that are distributed without attribution to sponsors.</td>
</tr>
<tr>
<td>An adult refuses care because it is against his/her religious beliefs.</td>
<td>Work with the patient by either explaining the treatment or pursuing alternative treatments. However, a physician should never force a competent adult to receive care if it is contrary to the patient’s religious beliefs.</td>
</tr>
<tr>
<td>Mother and 15-year-old daughter are unresponsive following a car accident and are bleeding internally. Father says do not transfuse because they are Jehovah’s Witnesses.</td>
<td>Transfuse daughter, but do not transfuse mother. Emergent care can be refused by the healthcare proxy for an adult, particularly when patient preferences are known or reasonably inferred, but not for a minor based solely on faith.</td>
</tr>
<tr>
<td>A 2-year-old girl presents with injuries inconsistent with parental story.</td>
<td>Contact child protective services and ensure child is in a safe location. Physicians are required by law to report any reasonable suspicion of child abuse or endangerment.</td>
</tr>
</tbody>
</table>
Confidentiality

Confidentiality respects patient privacy and autonomy. If the patient is incapacitated or the situation is emergent, disclosing information to family and friends should be guided by professional judgment of patient’s best interest. The patient may voluntarily waive the right to confidentiality (eg, insurance company request).

General principles for exceptions to confidentiality:
- Potential physical harm to others is serious and imminent
- Likelihood of harm to self is great
- No alternative means exist to warn or to protect those at risk
- Physicians can take steps to prevent harm

Examples of exceptions to patient confidentiality (many are state-specific) include the following (“The physician’s good judgment saved the day”):
- Suicidal/homicidal patients
- Abuse (children, elderly, and/or prisoners)
- Duty to protect—State-specific laws that sometimes allow physician to inform or somehow protect potential victim from harm.
- Epileptic patients and other impaired automobile drivers.
- Reportable Diseases (eg, STIs, hepatitis, food poisoning); physicians may have a duty to warn public officials, who will then notify people at risk. Dangerous communicable diseases, such as TB or Ebola, may require involuntary treatment.

PUBLIC HEALTH SCIENCES—THE WELL PATIENT

Car seats for children

Children should ride in rear-facing car seats until they are 2 years old and in car seats with a harness until they are 4 years. Older children should use a booster seat until they are 8 years old or until the seat belt fits properly. Children < 12 years old should not ride in a seat with a front-facing airbag.

Changes in the elderly

Sexual changes:
- Men—slower erection/ejaculation, longer refractory period.
- Women—vaginal shortening, thinning, and dryness.

Sleep patterns: ↓ REM and slow-wave sleep; ↑ sleep onset latency; ↑ early awakenings.
- ↓ suicide rate.
- ↓ vision and hearing.
- ↓ immune response.
- ↓ renal, pulmonary, and GI function.
- ↓ muscle mass, ↑ fat.

Intelligence does not decrease.
## Disease prevention

<table>
<thead>
<tr>
<th>Disease prevention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary disease prevention</strong></td>
<td>Prevent disease before it occurs (eg, HPV vaccination)</td>
</tr>
<tr>
<td><strong>Secondary disease prevention</strong></td>
<td>Screen early for and manage existing but asymptomatic disease (eg, Pap smear for cervical cancer)</td>
</tr>
<tr>
<td><strong>Tertiary disease prevention</strong></td>
<td>Treatment to reduce complications from disease that is ongoing or has long-term effects (eg, chemotherapy)</td>
</tr>
<tr>
<td><strong>Quaternary disease prevention</strong></td>
<td>Identifying patients at risk of unnecessary treatment, protecting from the harm of new interventions (eg, electronic sharing of patient records to avoid duplicating recent imaging studies)</td>
</tr>
</tbody>
</table>

## Major medical insurance plans

<table>
<thead>
<tr>
<th>Plan</th>
<th>Providers</th>
<th>Payments</th>
<th>Specialist care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusive provider organization</td>
<td>Restricted to limited panel (except emergencies)</td>
<td>Denied for any service that does not meet established, evidence-based guidelines</td>
<td>No referral required</td>
</tr>
<tr>
<td>Health maintenance organization</td>
<td>Restricted to limited panel (except emergencies)</td>
<td>Requires referral from primary care provider</td>
<td></td>
</tr>
<tr>
<td>Point of service</td>
<td>Patient can see providers outside network</td>
<td>Requires referral from primary care provider</td>
<td></td>
</tr>
<tr>
<td>Preferred provider organization</td>
<td>Patient can see providers outside network</td>
<td>Higher copays and deductibles for all services</td>
<td>No referral required</td>
</tr>
</tbody>
</table>

## Healthcare payment models

<table>
<thead>
<tr>
<th>Payment model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bundled payment</td>
<td>Healthcare organization receives a set amount per service, regardless of ultimate cost, to be divided among all providers and facilities involved.</td>
</tr>
<tr>
<td>Capitation</td>
<td>Physicians receive a set amount per patient assigned to them per period of time, regardless of how much the patient uses the healthcare system. Used by some HMOs.</td>
</tr>
<tr>
<td>Discounted fee-for-service</td>
<td>Patient pays for each individual service at a discounted rate predetermined by providers and payers (eg, PPOs).</td>
</tr>
<tr>
<td>Fee-for-service</td>
<td>Patient pays for each individual service.</td>
</tr>
<tr>
<td>Global payment</td>
<td>Patient pays for all expenses associated with a single incident of care with a single payment. Most commonly used during elective surgeries, as it covers the cost of surgery as well as the necessary pre- and postoperative visits.</td>
</tr>
</tbody>
</table>
Medicare and Medicaid

Medicare and Medicaid—federal social healthcare programs that originated from amendments to the Social Security Act.

Medicare is available to patients ≥ 65 years old, < 65 with certain disabilities, and those with end-stage renal disease.

Medicaid is joint federal and state health assistance for people with limited income and/or resources.

Medicare is for Elderly.

Medicaid is for Destitute.

The 4 parts of Medicare:

- Part A: Hospice insurance, home hospice care
- Part B: Basic medical bills (eg, doctor’s fees, diagnostic testing)
- Part C: (parts A + B = Combo) delivered by approved private companies
- Part D: Prescription Drugs

Hospice care

Medical care focused on providing comfort and palliation instead of definitive cure. Available to patients on Medicare or Medicaid and in most private insurance plans whose life expectancy is < 6 months.

During end-of-life care, priority is given to improving the patient’s comfort and relieving pain (often includes opioid, sedative, or anxiolytic medications). Facilitating comfort is prioritized over potential side effects (eg, respiratory depression). This prioritization of positive effects over negative effects is known as the principle of double effect.

Common causes of death (US) by age

<table>
<thead>
<tr>
<th></th>
<th>&lt; 1YR</th>
<th>1-14YR</th>
<th>15-34YR</th>
<th>35-44YR</th>
<th>45-64YR</th>
<th>65+ YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Congenital malformations</td>
<td>Unintentional injury</td>
<td>Unintentional injury</td>
<td>Unintentional injury</td>
<td>Cancer</td>
<td>Heart disease</td>
</tr>
<tr>
<td>#2</td>
<td>Preterm birth</td>
<td>Cancer</td>
<td>Suicide</td>
<td>Cancer</td>
<td>Heart disease</td>
<td>Cancer</td>
</tr>
<tr>
<td>#3</td>
<td>SIDS</td>
<td>Congenital malformations</td>
<td>Homicide</td>
<td>Heart disease</td>
<td>Unintentional injury</td>
<td>Chronic respiratory disease</td>
</tr>
</tbody>
</table>

Hospitalized conditions with frequent readmissions

Defined as readmission for any reason within 30 days of discharge from original admission. Readmissions may be reduced by discharge planning and outpatient follow-up appointments.

<table>
<thead>
<tr>
<th></th>
<th>Medicare</th>
<th>Medicaid</th>
<th>Private Insurance</th>
<th>Uninsured</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Congestive HF</td>
<td>Mood disorders</td>
<td>Maintenance of chemotherapy or radiotherapy</td>
<td>Mood disorders</td>
</tr>
<tr>
<td>#2</td>
<td>Septicemia</td>
<td>Schizophrenia/psychotic disorders</td>
<td>Mood disorders</td>
<td>Alcohol-related disorders</td>
</tr>
<tr>
<td>#3</td>
<td>Pneumonia</td>
<td>Diabetes mellitus with complications</td>
<td>Complications of surgical procedures or medical care</td>
<td>Diabetes mellitus with complications</td>
</tr>
</tbody>
</table>
Safety culture
Organizational environment in which everyone can freely bring up safety concerns without fear of censure. Facilitates error identification.

Event reporting systems collect data on errors for internal and external monitoring.

Human factors design
Forcing functions (those that prevent undesirable actions [eg, connecting feeding syringe to IV tubing]) are the most effective. Standardization improves process reliability (eg, clinical pathways, guidelines, checklists). Simplification reduces wasteful activities (eg, consolidating electronic medical records).

Deficient designs hinder workflow and lead to staff workarounds that bypass safety features (eg, patient ID barcodes affixed to computers due to unreadable wristbands).

PDSA cycle
Process improvement model to test changes in real clinical setting. Impact on patients:
- Plan—define problem and solution
- Do—test new process
- Study—measure and analyze data
- Act—integrate new process into regular workflow

Quality measurements

<table>
<thead>
<tr>
<th>Measure</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural</td>
<td>Physical equipment, resources, facilities</td>
</tr>
<tr>
<td>Process</td>
<td>Performance of system as planned</td>
</tr>
<tr>
<td>Outcome</td>
<td>Impact on patients</td>
</tr>
<tr>
<td>Balancing</td>
<td>Impact on other systems/outcomes</td>
</tr>
</tbody>
</table>

Swiss cheese model
Focuses on systems and conditions rather than an individual’s error. The risk of a threat becoming a reality is mitigated by differing layers and types of defenses. Patient harm can occur despite multiple safeguards when “the holes in the cheese line up.”
### Types of medical errors

<table>
<thead>
<tr>
<th>Error Type</th>
<th>Description</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active error</td>
<td>Occurs at level of frontline operator (eg, wrong IV pump dose programmed).</td>
<td>Immediate impact.</td>
</tr>
<tr>
<td>Latent error</td>
<td>Occurs in processes indirect from operator but impacts patient care (eg, different types of IV pumps used within same hospital).</td>
<td>Accident waiting to happen.</td>
</tr>
</tbody>
</table>

### Medical error analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>Design</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root cause analysis</td>
<td>Retrospective approach. Applied after failure event to prevent recurrence.</td>
<td>Uses records and participant interviews to identify all the underlying problems (eg, process, people, environment, equipment, materials, management) that led to an error.</td>
</tr>
<tr>
<td>Failure mode and effects analysis</td>
<td>Forward-looking approach. Applied before process implementation to prevent failure occurrence.</td>
<td>Uses inductive reasoning to identify all the ways a process might fail and prioritizes them by their probability of occurrence and impact on patients.</td>
</tr>
</tbody>
</table>
“Symptoms, then, are in reality nothing but the cry from suffering organs.”
—Jean-Martin Charcot

“Man is an intelligence in servitude to his organs.”
—Aldous Huxley

“When every part of the machine is correctly adjusted and in perfect harmony, health will hold dominion over the human organism by laws as natural and immutable as the laws of gravity.”
—Andrew T. Still
APPROACHING THE ORGAN SYSTEMS

In this section, we have divided the High-Yield Facts into the major Organ Systems. Within each Organ System are several subsections, including Embryology, Anatomy, Physiology, Pathology, and Pharmacology. As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a “vertically integrated” framework for learning. Below is some general advice for studying the organ systems by these subsections.

Embryology

Relevant embryology is included in each organ system subsection. Embryology tends to correspond well with the relevant anatomy, especially with regard to congenital malformations.

Anatomy

Several topics fall under this heading, including gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two or more steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

When studying, stress clinically important material. For example, be familiar with gross anatomy and radiologic anatomy related to specific diseases (eg, Pancoast tumor, Horner syndrome), traumatic injuries (eg, fractures, sensory and motor nerve deficits), procedures (eg, lumbar puncture), and common surgeries (eg, cholecystectomy). There are also many questions on the exam involving x-rays, CT scans, and neuro MRI scans. Many students suggest browsing through a general radiology atlas, pathology atlas, and histology atlas. Focus on learning basic anatomy at key levels in the body (eg, sagittal brain MRI; axial CT of the mid thorax, abdomen, and pelvis). Basic neuroanatomy (especially pathways, blood supply, and functional anatomy), associated neuropathology, and neurophysiology have good yield. Please note that many of the photographic images in this book are for illustrative purposes and are not necessarily reflective of Step 1 emphasis.

Physiology

The portion of the examination dealing with physiology is broad and concept oriented and thus does not lend itself as well to fact-based review. Diagrams are often the best study aids, especially given the increasing number of questions requiring the interpretation of diagrams. Learn to apply basic physiologic relationships in a variety of ways (eg, the Fick equation, clearance equations). You are seldom asked to perform complex
calculations. Hormones are the focus of many questions, so learn their sites of production and action as well as their regulatory mechanisms.

A large portion of the physiology tested on the USMLE Step 1 is clinically relevant and involves understanding physiologic changes associated with pathologic processes (eg, changes in pulmonary function with COPD). Thus, it is worthwhile to review the physiologic changes that are found with common pathologies of the major organ systems (eg, heart, lungs, kidneys, GI tract) and endocrine glands.

**Pathology**

Questions dealing with this discipline are difficult to prepare for because of the sheer volume of material involved. Review the basic principles and hallmark characteristics of the key diseases. Given the clinical orientation of Step 1, it is no longer sufficient to know only the “buzzword” associations of certain diseases (eg, café-au-lait macules and neurofibromatosis); you must also know the clinical descriptions of these findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of major diseases that have a high prevalence in the United States (eg, alcoholism, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

**Pharmacology**

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (eg, mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.
“As for me, except for an occasional heart attack, I feel as young as I ever did.”

—Robert Benchley

“Hearts will never be practical until they are made unbreakable.”

—The Wizard of Oz

“As the arteries grow hard, the heart grows soft.”

—H. L. Mencken

“Nobody has ever measured, not even poets, how much the heart can hold.”

—Zelda Fitzgerald

“Only from the heart can you touch the sky.”

—Rumi

“It is not the size of the man but the size of his heart that matters.”

—Evander Holyfield

The cardiovascular system is one of the highest yield areas for the boards and, for some students, may be the most challenging. Focusing on understanding the mechanisms instead of memorizing the details can make a big difference, especially for this topic. Pathophysiology of atherosclerosis and heart failure, MOA of drugs (particular physiology interactions) and their adverse effects, ECGs of heart blocks, the cardiac cycle, and the Starling curve are some of the more high-yield topics. Differentiating between systolic and diastolic dysfunction is also very important. Heart murmurs and maneuvers that affect these murmurs have also been high yield.
Heart embryology

<table>
<thead>
<tr>
<th>DEVELOPMENTAL STRUCTURE</th>
<th>GIVES RISE TO</th>
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<tbody>
<tr>
<td>Truncus arteriosus</td>
<td>Ascending aorta and pulmonary trunk</td>
</tr>
<tr>
<td>Bulbus cordis</td>
<td>Smooth parts (outflow tract) of left and right ventricles</td>
</tr>
<tr>
<td>Endocardial cushion</td>
<td>Atrial septum, membranous interventricular septum; AV and semilunar valves</td>
</tr>
<tr>
<td>Primitive atrium</td>
<td>Trabeculated part of left and right atria</td>
</tr>
<tr>
<td>Primitive ventricle</td>
<td>Trabeculated part of left and right ventricles</td>
</tr>
<tr>
<td>Primitive pulmonary vein</td>
<td>Smooth part of left atrium</td>
</tr>
<tr>
<td>Left horn of sinus venosus</td>
<td>Coronary sinus</td>
</tr>
<tr>
<td>Right horn of sinus venosus</td>
<td>Smooth part of right atrium (sinus venarum)</td>
</tr>
<tr>
<td>Right common cardinal vein and right anterior cardinal vein</td>
<td>Superior vena cava (SVC)</td>
</tr>
</tbody>
</table>

Heart morphogenesis

First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.

Cardiac looping

Primary heart tube loops to establish left-right polarity; begins in week 4 of gestation.

Defect in left-right Dynein (involved in L/R asymmetry) can lead to Dextrocardia, as seen in Kartagener syndrome (1° ciliary Dyskinesia).

Septation of the chambers

Atria

1. Septum primum grows toward endocardial cushions, narrowing foramen primum.
2. Foramen secundum forms in septum primum (foramen primum disappears).
3. Septum secundum develops as foramen secundum maintains right-to-left shunt.
4. Septum secundum expands and covers most of the foramen secundum. The residual foramen is the foramen ovale.
5. Remaining portion of septum primum forms valve of foramen ovale.
6. (Not shown) Septum secundum and septum primum fuse to form the atrial septum.
7. (Not shown) Foramen ovale usually closes soon after birth because of ↑ LA pressure.

Patent foramen ovale—caused by failure of septum primum and septum secundum to fuse after birth, most are left untreated. Can lead to paradoxical emboli (venous thromboemboli that enter systemic arterial circulation), similar to those resulting from an ASD.
Heart morphogenesis (continued)

Ventricles

1. Muscular interventricular septum forms. Opening is called interventricular foramen.
2. Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen.
3. Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.

Ventricular septal defect—most common congenital cardiac anomaly, usually occurs in membranous septum.

Outflow tract formation

Neural crest and endocardial cell migrations → truncal and bulbar ridges that spiral and fuse to form aorticopulmonary septum → ascending aorta and pulmonary trunk.

Conotruncal abnormalities associated with failure of neural crest cells to migrate:
- Transposition of great vessels.
- Tetralogy of Fallot.
- Persistent truncus arteriosus.

Valve development

Aortic/pulmonary: derived from endocardial cushions of outflow tract.
Mitral/tricuspid: derived from fused endocardial cushions of the AV canal.

Valvular anomalies may be stenotic, regurgitant, atretic (eg, tricuspid atresia), or displaced (eg, Ebstein anomaly).
Blood in umbilical vein has a $P_O_2$ of $\approx 30$ mm Hg and is $\approx 80\%$ saturated with $O_2$. Umbilical arteries have low $O_2$ saturation.

3 important shunts:

1. Blood entering fetus through the umbilical vein is conducted via the ductus venosus into the IVC, bypassing hepatic circulation.
2. Most of the highly oxygenated blood reaching the heart via the IVC is directed through the foramen ovale and pumped into the aorta to supply the head and body.
3. Deoxygenated blood from the SVC passes through the RA $\rightarrow$ RV $\rightarrow$ main pulmonary artery $\rightarrow$ Ductus arteriosus $\rightarrow$ Descending aorta; shunt is due to high fetal pulmonary artery resistance (due partly to low $O_2$ tension).

At birth, infant takes a breath $\rightarrow$ resistance in pulmonary vasculature $\rightarrow$ left atrial pressure vs right atrial pressure $\rightarrow$ foramen ovale closes (now called fossa ovalis); $\uparrow$ in $O_2$ (from respiration) and $\downarrow$ in prostaglandins (from placental separation) $\rightarrow$ closure of ductus arteriosus.

Indomethacin helps close PDA $\rightarrow$ ligamentum arteriosum (remnant of ductus arteriosus). Prostaglandins $E_1$ and $E_2$ $\rightarrow$ PDA open.

### Fetal-postnatal derivatives

<table>
<thead>
<tr>
<th>FETAL STRUCTURE</th>
<th>POSTNATAL DERIVATIVE</th>
<th>NOTES</th>
</tr>
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<tbody>
<tr>
<td>Allantoid $\rightarrow$ urachus</td>
<td>MediaN umbilical ligament</td>
<td>Urachus is part of allantoic duct between bladder and umbilicus.</td>
</tr>
<tr>
<td>Ductus arteriosus</td>
<td>Ligamentum arteriosum</td>
<td></td>
</tr>
<tr>
<td>Ductus venosus</td>
<td>Ligamentum venosum</td>
<td></td>
</tr>
<tr>
<td>Foramen ovale</td>
<td>Fossa ovalis</td>
<td></td>
</tr>
<tr>
<td>Notochord</td>
<td>Nucleus pulposus</td>
<td></td>
</tr>
<tr>
<td>Umbilical arteries</td>
<td>MediaL umbilical ligaments</td>
<td></td>
</tr>
<tr>
<td>Umbilical vein</td>
<td>Ligamentum teres hepatis (round ligament)</td>
<td>Contained in falciform ligament.</td>
</tr>
</tbody>
</table>
Anatomy of the heart

Right coronary artery (RCA) supplies lateral and posterior walls of left ventricle, anterolateral papillary muscle.

Left circumflex coronary artery (LCX) supplies lateral and posterior walls of left ventricle, anterolateral papillary muscle.

Left anterior descending artery (LAD) supplies anterior of interventricular septum, anterolateral papillary muscle, and anterior surface of left ventricle.

Left (obtuse) marginal artery supplies right ventricle.

Posterior descending/interventricular artery (PDA) supplies AV node, posterior 1/2/3 of interventricular septum, posterior 2/3 walls of ventricles, and posteromedial papillary muscle.

SA node commonly supplied by RCA (blood supply independent of dominance); AV node supplied by PDA. Infarct may cause nodal dysfunction (bradycardia or heart block).

Right-dominant circulation (85%) = PDA arises from RCA.

Left-dominant circulation (8%) = PDA arises from LCX.

Codominant circulation (7%) = PDA arises from both LCX and RCA.

Coronary artery occlusion most commonly occurs in the LAD.

Coronary blood flow peaks in early diastole.

The most posterior part of the heart is the left atrium. Enlargement can cause dysphagia (due to compression of the esophagus) or hoarseness (due to compression of the left recurrent laryngeal nerve, a branch of the vagus nerve).

Pericardium consists of 3 layers (from outer to inner):

- Fibrous pericardium
- Parietal layer of serous pericardium
- Visceral layer of serous pericardium

Pericardial cavity lies between parietal and visceral layers. Pericardium innervated by phrenic nerve. Pericarditis can cause referred pain to the shoulder.
Cardiac output

CO = stroke volume (SV) × heart rate (HR)

Fick principle:

\[
CO = \frac{\text{rate of O}_2 \text{ consumption}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}}
\]

Mean arterial pressure (MAP) = CO × total peripheral resistance (TPR)

MAP (at resting HR) = \(\frac{1}{3}\) diastolic pressure + \(\frac{2}{3}\) systolic pressure

Pulse pressure = systolic pressure – diastolic pressure

Pulse pressure is proportional to SV, inversely proportional to arterial compliance.

SV = end-diastolic volume (EDV) – end-systolic volume (ESV)

During the early stages of exercise, CO is maintained by ↑ HR and ↑ SV. During the late stages of exercise, CO is maintained by ↑ HR only (SV plateaus).

Diastole is preferentially shortened with ↑ HR; less filling time → ↓ CO (eg, ventricular tachycardia).

↑ pulse pressure in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea (↑ sympathetic tone), anemia, exercise (transient).

↓ pulse pressure in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced heart failure (HF).
### Cardiac output variables

#### Stroke volume

Stroke Volume affected by **Contractility**, **Afterload**, and **Preload**.

- **↑ SV** with:
  - ↑ Contractility (eg, anxiety, exercise)
  - ↑ Preload (eg, early pregnancy)
  - ↓ Afterload

#### Contractility

Contractility (and SV) **↑** with:

- Catecholamine stimulation via β₁ receptor:
  - Ca²⁺ channels phosphorylated → ↑ Ca²⁺ entry → ↑ Ca²⁺-induced Ca²⁺ release and ↑ Ca²⁺ storage in sarcoplasmic reticulum
  - Phospholamban phosphorylation → active Ca²⁺ ATPase → ↑ Ca²⁺ storage in sarcoplasmic reticulum
- ↑ intracellular Ca²⁺
- ↓ extracellular Na⁺ (↓ activity of Na⁺/Ca²⁺ exchanger)
- Digitalis (blocks Na⁺/K⁺ pump → ↑ intracellular Na⁺ → ↓ Na⁺/Ca²⁺ exchanger activity → ↑ intracellular Ca²⁺)

#### Preload

Preload approximated by ventricular EDV; depends on venous tone and circulating blood volume.

VENous vasodilators (eg, nitroglycerin) ↓ **preload**.

#### Afterload

Afterload approximated by MAP.

- ↑ afterload → ↑ pressure → ↑ wall tension per Laplace's law.

LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall tension.

Arterial vasodilators (eg, hydrAlAzione) ↓ **afterload**.

ACE inhibitors and ARBs ↓ both preload and afterload.

Chronic hypertension (↑ MAP) → LV hypertrophy.

#### Myocardial oxygen demand

Myocardial O₂ demand is ↑ by:

- ↑ Contractility
- ↑ Afterload (proportional to arterial pressure)
- ↑ heart Rate
- ↑ Diameter of ventricle (↑ wall tension)

Wall tension follows Laplace's law:

- Wall tension = pressure × radius
- Wall stress = pressure × radius × wall thickness

#### Ejection fraction

\[
EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}
\]

Left ventricular EF is an index of ventricular contractility.

EF ↓ in systolic HF.

EF normal in HF with preserved ejection fraction.
Starling curve

Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

*↑* contractility with catecholamines, positive inotropes (eg, digoxin).

*↓* contractility with loss of myocardium (eg, MI), β-blockers (acutely), non-dihydropyridine Ca²⁺ channel blockers, dilated cardiomyopathy.

Resistance, pressure, flow

\[ \Delta P = Q \times R \]

Similar to Ohm's law: \( \Delta V = IR \)

Volumetric flow rate \( (Q) = \) flow velocity \( (v) \times \) cross-sectional area \( (A) \)

Resistance

\[ R = \frac{\text{driving pressure (}\Delta P\text{)}}{\text{flow (}\dot{Q}\text{)}} = \frac{8\eta}{\pi r^4} \]

Total resistance of vessels in series:

\[ R_T = R_1 + R_2 + R_3 \ldots \]

Total resistance of vessels in parallel:

\[ \frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \ldots \]

Capillaries have highest total cross-sectional area and lowest flow velocity.

Pressure gradient drives flow from high pressure to low pressure.

Arterioles account for most of TPR. Veins provide most of blood storage capacity.

Viscosity depends mostly on hematocrit.

Viscosity ↑ in hyperproteinemic states (eg, multiple myeloma), polycythemia.

Viscosity ↓ in anemia.

Compliance = \( \Delta V/\Delta P \).
Intersection of curves = operating point of heart (ie, venous return and CO are equal).

<table>
<thead>
<tr>
<th>GRAPH</th>
<th>EFFECT</th>
<th>EXAMPLES</th>
</tr>
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<tbody>
<tr>
<td>A Inotropy</td>
<td>Changes in contractility (\rightarrow) altered CO for a given RA pressure (preload).</td>
<td>1 Catecholamines, digoxin (\oplus), exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 HF with reduced EF, narcotic overdose, sympathetic inhibition (\ominus)</td>
</tr>
<tr>
<td>B Venous return</td>
<td>Changes in circulating volume or venous tone (\rightarrow) altered RA pressure for a given CO. Mean systemic pressure (x-intercept) changes with volume/venous tone.</td>
<td>3 Fluid infusion, sympathetic activity (\oplus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 Acute hemorrhage, spinal anesthesia (\ominus)</td>
</tr>
<tr>
<td>C Total peripheral resistance</td>
<td>At a given mean systemic pressure (x-intercept) and RA pressure, changes in TPR (\rightarrow) altered CO.</td>
<td>5 Vasopressors (\oplus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 Exercise, AV shunt (\ominus)</td>
</tr>
</tbody>
</table>

Changes often occur in tandem, and may be reinforcing (eg, exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (eg, HF ↓ inotropy \(\rightarrow\) fluid retention to ↑ preload to maintain CO).
Pressure-volume loops and cardiac cycle

The black loop represents normal cardiac physiology.

Phases—left ventricle:
1. **Isovolumetric contraction**—period between mitral valve closing and aortic valve opening; period of highest O₂ consumption
2. **Systolic ejection**—period between aortic valve opening and closing
3. **Isovolumetric relaxation**—period between aortic valve closing and mitral valve opening
4. **Rapid filling**—period just after mitral valve opening
5. **Reduced filling**—period just before mitral valve closing

Heart sounds:
- S₁—mitral and tricuspid valve closure. Loudest at mitral area.
- S₂—aortic and pulmonary valve closure. Loudest at left upper sternal border.
- S₃—in early diastole during rapid ventricular filling phase. Associated with ↑ filling pressures (eg, mitral regurgitation, HF) and more common in dilated ventricles (but can be normal in children, young adults, and pregnant women).

Jugular venous pulse (JVP):
- **a wave**—atrial contraction. Absent in atrial fibrillation (AF).
- **c wave**—RV contraction (closed tricuspid valve bulging into atrium).
- **x descent**—downward displacement of closed tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.
- **v wave**—↑ right atrial pressure due to filling (“villing”) against closed tricuspid valve.
- **y descent**—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.
### Splitting

**Normal splitting**
- Inspiration → drop in intrathoracic pressure
- ↑ venous return → ↑ RV filling → ↑ RV stroke volume → ↑ RV ejection time
- delayed closure of pulmonic valve.
- ↑ pulmonary impedance (↑ capacity of the pulmonary circulation) also occurs during inspiration, which contributes to delayed closure of pulmonic valve.

**Wide splitting**
- Seen in conditions that delay RV emptying (eg, pulmonic stenosis, right bundle branch block).
- Causes delayed pulmonic sound (especially on inspiration). An exaggeration of normal splitting.

**Fixed splitting**
- Heard in ASD. ASD → left-to-right shunt
- ↑ RA and RV volumes → ↑ flow through pulmonic valve such that, regardless of breath, pulmonic closure is greatly delayed.

**Paradoxical splitting**
- Heard in conditions that delay aortic valve closure (eg, aortic stenosis, left bundle branch block). Normal order of valve closure is reversed so that P2 sound occurs before delayed A2 sound. Therefore on inspiration, P2 closes later and moves closer to A2, thereby “paradoxically” eliminating the split (usually heard in expiration).
Auscultation of the heart

Where to listen: APT M

**Aortic area:**
- **Systolic murmur**
  - Aortic stenosis
  - Flow murmur (e.g., physiologic murmur)
  - Aortic valve sclerosis

**Pulmonic area:**
- **Systolic ejection murmur**
  - Pulmonic stenosis
  - Atrial septal defect
  - Flow murmur

**Left sternal border:**
- **Diastolic murmur**
  - Aortic regurgitation
  - Pulmonic regurgitation
  - Hypertrophic cardiomyopathy

**Tricuspid area:**
- **Holosystolic murmur**
  - Tricuspid regurgitation
  - Ventricular septal defect
  - Diastolic murmur
  - Tricuspid stenosis

**Mitral area (apex):**
- **Holosystolic murmur**
  - Mitral regurgitation
  - Systolic murmur
  - Mitral valve prolapse
  - Diastolic murmur
  - Mitral stenosis

<table>
<thead>
<tr>
<th>BEDSIDE MANEUVER</th>
<th>EFFECT</th>
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<tbody>
<tr>
<td>Inspiration (↑ venous return to right atrium)</td>
<td>↑ intensity of right heart sounds</td>
</tr>
<tr>
<td>Hand grip (↑ afterload)</td>
<td>↓ intensity of MR, AR, and VSD murmurs</td>
</tr>
<tr>
<td></td>
<td>↓ intensity of hypertrophic cardiomyopathy and AS murmurs</td>
</tr>
<tr>
<td></td>
<td>MVP: later onset of click/murmur</td>
</tr>
<tr>
<td>Valsalva (phase II), standing up (↓ preload)</td>
<td>↓ intensity of most murmurs (including AS)</td>
</tr>
<tr>
<td></td>
<td>↑ intensity of hypertrophic cardiomyopathy murmur</td>
</tr>
<tr>
<td></td>
<td>MVP: earlier onset of click/murmur</td>
</tr>
<tr>
<td>Rapid squatting (↑ venous return, ↑ preload, ↑ afterload)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ intensity of hypertrophic cardiomyopathy murmur</td>
</tr>
<tr>
<td></td>
<td>↑ intensity of AS, MR, and VSD murmurs</td>
</tr>
<tr>
<td></td>
<td>MVP: later onset of click/murmur</td>
</tr>
</tbody>
</table>

Systolic heart sounds include the murmurs of aortic/pulmonic stenosis, mitral/tricuspid regurgitation, VSD, MVP, hypertrophic cardiomyopathy.

Diastolic heart sounds include the murmurs of aortic/pulmonic regurgitation, mitral/tricuspid stenosis.
## Heart murmurs

### Systolic

**Aortic stenosis**

Crescendo-decrescendo systolic ejection murmur and soft S2 (ejection click may be present). LV >> aortic pressure during systole. Loudest at heart base; radiates to carotids. “Pulsus parvus et tardus”—pulses are weak with a delayed peak. Can lead to Syncope, Angina, and Dyspnea on exertion (SAD). Most commonly due to age-related calcification in older patients (> 60 years old) or in younger patients with early-onset calcification of bicuspid aortic valve.

**Mitral/tricuspid regurgitation**

Holosystolic, high-pitched “blowing murmur.”

Mitral—loudest at apex and radiates toward axilla. MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation.

Tricuspid—loudest at tricuspid area. TR commonly caused by RV dilatation.

Rheumatic fever and infective endocarditis can cause either MR or TR.

**Mitral valve prolapse**

Late systolic crescendo murmur with midsystolic click (MC; due to sudden tensing of chordae tendineae). Most frequent valvular lesion. Best heard over apex. Loudest just before S2. Usually benign. Can predispose to infective endocarditis. Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever, chordae rupture.

**Ventricular septal defect**

Holosystolic, harsh-sounding murmur. Loudest at tricuspid area.

### Diastolic

**Aortic regurgitation**

High-pitched “blowing” early diastolic decrescendo murmur. Long diastolic murmur, hyperdynamic pulse, and head bobbing when severe and chronic. Wide pulse pressure. Often due to aortic root dilatation, bicuspid aortic valve, endocarditis, rheumatic fever. Progresses to left HF.

**Mitral stenosis**

Follows opening snap (OS; due to abrupt halt in leaflet motion in diastole, after rapid opening due to fusion at leaflet tips). Delayed rumbling mid-to-late diastolic murmur (interval between S2 and OS correlates with severity). LA >> LV pressure during diastole.

Often a late (and highly specific) sequela of rheumatic fever. Chronic MS can result in LA dilatation → dysphagia/hoarseness via compression of esophagus/left recurrent laryngeal nerve, respectively.

### Continuous

**Patent ductus arteriosus**

Continuous machine-like murmur. Best heard at left infraclavicular area. Loudest at S2. Often due to congenital rubella or prematurity.

“PDA's (Public Displays of Affection) are continuously annoying.”
Myocardial action potential

Also occurs in bundle of His and Purkinje fibers.

**Phase 0** = rapid upstroke and depolarization—voltage-gated Na⁺ channels open.

**Phase 1** = initial repolarization—inactivation of voltage-gated Na⁺ channels. Voltage-gated K⁺ channels begin to open.

**Phase 2** = plateau—Ca²⁺ influx through voltage-gated Ca²⁺ channels balances K⁺ efflux. Ca²⁺ influx triggers Ca²⁺ release from sarcoplasmic reticulum and myocyte contraction.

**Phase 3** = rapid repolarization—massive K⁺ efflux due to opening of voltage-gated slow K⁺ channels and closure of voltage-gated Ca²⁺ channels.

**Phase 4** = resting potential—high K⁺ permeability through K⁺ channels.

In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau, which is due to Ca²⁺ influx and K⁺ efflux.
- Cardiac muscle contraction requires Ca²⁺ influx from ECF to induce Ca²⁺ release from sarcoplasmic reticulum (Ca²⁺-induced Ca²⁺ release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.
Pacemaker action potential

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

**Phase 0** = upstroke—opening of voltage-gated Ca\(^{2+}\) channels. Fast voltage-gated Na\(^{+}\) channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles. Phases 1 and 2 are absent.

**Phase 3** = repolarization—inactivation of the Ca\(^{2+}\) channels and ↑ activation of K\(^{+}\) channels → ↑ K\(^{+}\) efflux.

**Phase 4** = slow spontaneous diastolic depolarization due to I\(_{f}\) (“funny current”). I\(_{f}\) channels responsible for a slow, mixed Na\(^{+}\)/K\(^{+}\) inward current; different from I\(_{N_{a}}\) in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACh/adenosine ↓ the rate of diastolic depolarization and ↓ HR, while catecholamines ↑ depolarization and ↑ HR. Sympathetic stimulation ↑ the chance that I\(_{f}\) channels are open and thus ↑ HR.
Electrocardiogram

Conduction pathway: SA node → atria
→ AV node → bundle of His → right and left bundle branches → Purkinje fibers
→ ventricles; left bundle branch divides into left anterior and posterior fascicles.
SA node “pacemaker” inherent dominance with slow phase of upstroke.
AV node—located in posteroinferior part of interatrial septum. Blood supply usually from RCA. 100-msec delay allows time for ventricular filling.
Pacemaker rates—SA > AV > bundle of His/Purkinje/ventricles.
Speed of conduction—Purkinje > atria > ventricles > AV node.

P wave—atrial depolarization. Atrial repolarization is masked by QRS complex.
PR interval—time from start of atrial depolarization to start of ventricular depolarization (normally < 200 msec).
QRS complex—ventricular depolarization (normally < 120 msec).
QT interval—ventricular depolarization, mechanical contraction of the ventricles, ventricular repolarization.
T wave—ventricular repolarization. T-wave inversion may indicate ischemia or recent MI.
J point—junction between end of QRS complex and start of ST segment.
ST segment—isolectric, ventricles depolarized.
U wave—prominent in hypokalemia (think hyp“U”kalemia), bradycardia.
Torsades de pointes
Polymorphic ventricular tachycardia, characterized by shifting sinusoidal waveforms on ECG; can progress to ventricular fibrillation (VF). Long QT interval predisposes to torsades de pointes. Caused by drugs, ↓K⁺, ↓Mg²⁺, congenital abnormalities. Treatment includes magnesium sulfate.

Congenital long QT syndrome
Inherited disorder of myocardial repolarization, typically due to ion channel defects; ↑ risk of sudden cardiac death (SCD) due to torsades de pointes. Includes:
- Romano-Ward syndrome—autosomal dominant, pure cardiac phenotype (no deafness).
- Jervell and Lange-Nielsen syndrome—autosomal recessive, sensorineural deafness.

Brugada syndrome
Autosomal dominant disorder most common in Asian males. ECG pattern of pseudo-right bundle branch block and ST elevations in V₁-V₃. ↑ risk of ventricular tachyarrhythmias and SCD. Prevent SCD with implantable cardioverter-defibrillator (ICD).

Wolff-Parkinson-White syndrome
Most common type of ventricular pre-excitation syndrome. Abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) bypasses the rate-slowing AV node → ventricles begin to partially depolarize earlier → characteristic delta wave with widened QRS complex and shortened PR interval on ECG. May result in reentry circuit → supraventricular tachycardia.

Drug-induced long QT (ABCDE):
- AntiArrhythmics (class IA, III)
- AntiBiotics (eg, macrolides)
- AntiC”ychotics (eg, haloperidol)
- AntiDepressants (eg, TCAs)
- AntiEmetics (eg, ondansetron)

Torsades de pointes = twisting of the points
### ECG Tracings

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td>Chaotic and erratic baseline with no discrete P waves in between irregularly spaced QRS complexes. Irregularly irregular heartbeat. Most common risk factors include hypertension and coronary artery disease (CAD). Can lead to thromboembolic events, particularly stroke. Treatment includes anticoagulation, rate control, rhythm control, and/or cardioversion.</td>
<td><img src="https://example.com" alt="Irregular baseline (absent P waves)" /></td>
</tr>
<tr>
<td><strong>Atrial Flutter</strong></td>
<td>A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the “sawtooth” appearance of the flutter waves. Treat like atrial fibrillation. Definitive treatment is catheter ablation.</td>
<td><img src="https://example.com" alt="4:1 sawtooth pattern" /></td>
</tr>
<tr>
<td><strong>Ventricular Fibrillation</strong></td>
<td>A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.</td>
<td><img src="https://example.com" alt="No discernible rhythm" /></td>
</tr>
</tbody>
</table>

### AV Block

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Degree AV Block</strong></td>
<td>The PR interval is prolonged (&gt; 200 msec). Benign and asymptomatic. No treatment required.</td>
<td><img src="https://example.com" alt="PR interval prolonged" /></td>
</tr>
<tr>
<td><strong>Second-Degree AV Block</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mobitz Type I</strong></td>
<td>Progressive lengthening of PR interval until a beat is “dropped” (a P wave not followed by a QRS complex). Usually asymptomatic. Variable RR interval with a pattern (regularly irregular).</td>
<td><img src="https://example.com" alt="P wave, absent QRS" /></td>
</tr>
<tr>
<td><strong>Mobitz Type II</strong></td>
<td>Dropped beats that are not preceded by a change in the length of the PR interval (as in type I). May progress to 3rd-degree block. Often treated with pacemaker.</td>
<td><img src="https://example.com" alt="P wave, absent QRS" /></td>
</tr>
<tr>
<td><strong>Third-Degree AV Block</strong></td>
<td>The atria and ventricles beat independently of each other. P waves and QRS complexes not rhythmically associated. Atrial rate &gt; ventricular rate. Usually treated with pacemaker. Can be caused by Lyme disease.</td>
<td><img src="https://example.com" alt="P wave on QRS complex" />  <img src="https://example.com" alt="P wave on T wave" />  <img src="https://example.com" alt="P wave on T wave" /></td>
</tr>
</tbody>
</table>
**Atrial natriuretic peptide**

Released from atrial myocytes in response to ↑ blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and ↓ Na⁺ reabsorption at the renal collecting tubule. Dilates afferent renal arterioles and constricts efferent arterioles, promoting diuresis and contributing to “aldosterone escape” mechanism.

---

**B-type (brain) natriuretic peptide**

Released from ventricular myocytes in response to ↑ tension. Similar physiologic action to ANP, with longer half-life. BNP blood test used for diagnosing HF (very good negative predictive value). Available in recombinant form (nesiritide) for treatment of HF.

---

**Baroreceptors and chemoreceptors**

![Diagram of baroreceptors and chemoreceptors](image)

**Receptors:**
- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).

**Baroreceptors:**
- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasconstriction, ↑ HR, ↑ contractility, ↓ BP. Important in the response to severe hemorrhage.
- Carotid massage—↓ pressure on carotid sinus → ↓ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
- Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ pCO₂ and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor-induced bradycardia.

**Chemoreceptors:**
- Peripheral—carotid and aortic bodies are stimulated by ↓ PO₂ (< 60 mm Hg), ↑ PCO₂, and ↓ pH of blood.
- Central—are stimulated by changes in pH and Pco₂ of brain interstitial fluid, which in turn are influenced by arterial CO₂. Do not directly respond to PO₂.
Normal cardiac pressures

Pulmonary capillary wedge pressure (PCWP; in mm Hg) is a good approximation of left atrial pressure. In mitral stenosis, PCWP > LV end diastolic pressure. PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).

Autoregulation

How blood flow to an organ remains constant over a wide range of perfusion pressures.

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>FACTORS DETERMINING AUTOREGULATION</th>
<th>The pulmonary vasculature is unique in that alveolar hypoxia causes vasoconstriction so that only well-ventilated areas are perfused. In other organs, hypoxia causes vasodilation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Local metabolites (vasodilatory): adenosine, NO, CO₂, ↓ O₂</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>Local metabolites (vasodilatory): CO₂ (pH)</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>Myogenic and tubuloglomerular feedback</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>Hypoxia causes vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Local metabolites during exercise: CO₂, H⁺, Adenosine, Lactate, K⁺</td>
<td>CHALK.</td>
</tr>
<tr>
<td></td>
<td>At rest: sympathetic tone</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Sympathetic stimulation most important mechanism for temperature control</td>
<td></td>
</tr>
</tbody>
</table>
Capillary fluid exchange

Starling forces determine fluid movement through capillary membranes:
- $P_c$ = capillary pressure—pushes fluid out of capillary
- $P_i$ = interstitial fluid pressure—pushes fluid into capillary
- $\pi_c$ = plasma colloid osmotic (oncotic) pressure—pulls fluid into capillary
- $\pi_i$ = interstitial fluid colloid osmotic pressure—pulls fluid out of capillary

$J_v = \text{net fluid flow} = K_f \left[ (P_c - P_i) - \sigma (\pi_c - \pi_i) \right]$

- $K_f$ = capillary permeability to fluid
- $\sigma$ = reflection coefficient (measure of capillary permeability to protein)

Edema—excess fluid outflow into interstitium commonly caused by:
- ↑ capillary pressure (↑ $P_c$; eg, HF)
- ↓ plasma proteins (↓ $\pi_c$; eg, nephrotic syndrome, liver failure, protein malnutrition)
- ↑ capillary permeability (↑ $K_f$; eg, toxins, infections, burns)
- ↑ interstitial fluid colloid osmotic pressure (↑ $\pi_i$; eg, lymphatic blockage)
Congenital heart diseases

**RIGHT-TO-LEFT SHUNTS**

Early cyanosis—“blue babies.” Often diagnosed prenatally or become evident immediately after birth. Usually require urgent surgical treatment and/or maintenance of a PDA.

The 5 Ts:
1. Truncus arteriosus (1 vessel)
2. Transposition (2 switched vessels)
3. Tricuspid atresia (3 = Tri)
4. Tetralogy of Fallot (4 = Tetra)
5. TAPVR (5 letters in the name)

**Persistent truncus arteriosus**

Truncus arteriosus fails to divide into pulmonary trunk and aorta due to lack of aorticopulmonary septum formation; most patients have accompanying VSD.

**D-transposition of great vessels**

Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow mixing of blood (eg, VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral.

Without surgical intervention, most infants die within the first few months of life.

**Tricuspid atresia**

Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.

**Tetralogy of Fallot**

Caused by anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis.

1. Pulmonary infundibular stenosis (most important determinant for prognosis)
2. Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR
3. Overriding aorta
4. VSD

Pulmonary stenosis forces right-to-left flow across VSD → RVH, “tet spells” (often caused by crying, fever, and exercise due to exacerbation of RV outflow obstruction).

**Total anomalous pulmonary venous return**

Pulmonary veins drain into right heart circulation (SVC, coronary sinus, etc); associated with ASD and sometimes PDA to allow for right-to-left shunting to maintain CO.

**Ebstein anomaly**

Characterized by displacement of tricuspid valve leaflets downward into RV, artificially “atrializing” the ventricle. Associated with tricuspid regurgitation, accessory conduction pathways, and right-sided HF. Can be caused by lithium exposure in utero.

**PROVe.**

Squatting: ↑ SVR, ↓ right-to-left shunt, improves cyanosis.

Treatment: early surgical correction.
Congenital heart diseases (continued)

**LEFT-TO-RIGHT SHUNTS**

Acyanotic at presentation; cyanosis may occur years later.

**Right-to-Left shunts:**

- **csrLy cyanosis.**
- **Left-to-Right shunts:**
  - **LateR** cyanosis.

**Ventricular septal defect**

Most common congenital cardiac defect.

Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life.

Most self resolve; larger lesions may lead to LV overload and HF.

**O₂ saturation ↑ in RV and pulmonary artery.**

Frequency: VSD > ASD > PDA.

**Atrial septal defect**

Defect in interatrial septum, wide, fixed split S2. Ostium secundum defects most common and usually an isolated finding; ostium primum defects rarer and usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale in that septa are missing tissue rather than unfused.

**O₂ saturation ↑ in RA, RV, and pulmonary artery.**

May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli).

**Patent ductus arteriosus**

In fetal period, shunt is right to left (normal). In neonatal period, pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF. Associated with a continuous, “machine-like” murmur. Patency is maintained by PGE synthesis and low O₂ tension. Uncorrected PDA can eventually result in late cyanosis in the lower extremities (differential cyanosis).

“Endomethacin” (indomethacin) ends patency of PDA; PGE keeps ductus going (may be necessary to sustain life in conditions such as transposition of the great vessels).

PDA is normal in utero and normally closes only after birth.

**Eisenmenger syndrome**

Uncorrected left-to-right shunt (VSD, ASD, PDA) → ↑ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension. RVH occurs to compensate → shunt becomes right to left. Causes late cyanosis, clubbing, and polycythemia. Age of onset varies.

**OTHER ANOMALIES**

**Coarctation of the aorta**

Aortic narrowing near insertion of ductus arteriosus (“juxtaductal”). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities and weak, delayed pulse in lower extremities (brachial-femoral delay). With age, intercostal arteries enlarge due to collateral circulation; arteries erode ribs → notched appearance on CXR. Complications include HF, ↑ risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and possible endocarditis.
### Congenital cardiac defect associations

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol exposure in utero (fetal alcohol syndrome)</td>
<td>VSD, PDA, ASD, tetralogy of Fallot</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>PDA, pulmonary artery stenosis, septal defects</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>AV septal defect (endocardial cushion defect), VSD, ASD</td>
</tr>
<tr>
<td>Infant of diabetic mother</td>
<td>Transposition of great vessels, VSD</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>MVP, thoracic aortic aneurysm and dissection, aortic regurgitation</td>
</tr>
<tr>
<td>Prenatal lithium exposure</td>
<td>Ebstein anomaly</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Bicuspid aortic valve, coarctation of aorta</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>Supravalvular aortic stenosis</td>
</tr>
<tr>
<td>22q11 syndromes</td>
<td>Truncus arteriosus, tetralogy of Fallot</td>
</tr>
</tbody>
</table>

### Hypertension

**Defined as persistent systolic BP \( \geq 140 \) mm Hg and/or diastolic BP \( \geq 90 \) mm Hg**

**Risk factors**
- Age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, cigarette smoking, family history; African American > Caucasian > Asian.

**Features**
- 90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR. Remaining 10% mostly 2° to renal/renovascular diseases such as fibromuscular dysplasia (characteristic “string of beads” appearance of renal artery A) and atherosclerotic renal artery stenosis or to 1° hyperaldosteronism.

**Hypertensive urgency**—severe (≥ 180/≥ 120 mm Hg) hypertension without acute end-organ damage.

**Hypertensive emergency**—severe hypertension with evidence of acute end-organ damage (e.g., encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF, aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

**Predisposes to**
- CAD, LVH, HF, atrial fibrillation; aortic dissection, aortic aneurysm; stroke; chronic kidney disease (hypertensive nephropathy); retinopathy.
Hyperlipidemia signs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthomas</td>
<td>Plaques or nodules composed of lipid-laden histiocytes in skin A, especially the eyelids (xanthelasma D).</td>
</tr>
<tr>
<td>Tendinous xanthoma</td>
<td>Lipid deposit in tendon C, especially Achilles.</td>
</tr>
<tr>
<td>Corneal arcus</td>
<td>Lipid deposit in cornea. Common in elderly (arcus senilis D), but appears earlier in life with hypercholesterolemia.</td>
</tr>
</tbody>
</table>

Arteriosclerosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriosclerosis</td>
<td>Hardening of arteries, with arterial wall thickening and loss of elasticity.</td>
</tr>
<tr>
<td>Arteriolosclerosis</td>
<td>Common. Affects small arteries and arterioles. Two types: hyaline (thickening of vessel walls in essential hypertension or diabetes mellitus A) and hyperplastic (“onion skinning” in severe hypertension B with proliferation of smooth muscle cells).</td>
</tr>
</tbody>
</table>
Atherosclerosis

Very common. Disease of elastic arteries and large- and medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques.

**LOCATION**

Abdominal aorta > coronary artery > popliteal artery > carotid artery

“A After I workout my abs, I grab a Corona and pop my collar up to my carotid.”

**RISK FACTORS**

Modifiable: smoking, hypertension, dyslipidemia (↑ LDL, ↓ HDL), diabetes. Non-modifiable: age, sex (↑ in men and postmenopausal women), family history.

**SYMPTOMS**

Angina, claudication, but can be asymptomatic.

**PROGRESSION**

Inflammation important in pathogenesis: endothelial cell dysfunction → macrophage and LDL accumulation → foam cell formation → fatty streaks → smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition → fibrous plaque → complex atheromas

**COMPlications**

Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.

---

**Aortic aneurysm**

Localized pathologic dilatation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.

**Abdominal aortic aneurysm**

Associated with atherosclerosis. Risk factors include history of tobacco use, ↑ age, male sex, family history. May present as palpable pulsatile abdominal mass (arrows in point to outer dilated calcified aortic wall, with partial crescent-shaped non-opacification of aorta due to flap/clot). Most often infrarenal (distal to origin of renal arteries).

**Thoracic aortic aneurysm**

 Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also associated with 3° syphilis (obliterative endarteritis of the vasa vasorum). Aortic root dilatation may lead to aortic valve regurgitation.

**Traumatic aortic rupture**

Due to trauma and/or deceleration injury, most commonly at aortic isthmus (proximal descending aorta just distal to origin of left subclavian artery).
Aortic dissection

Longitudinal intimal tear forming a false lumen. Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing, sudden-onset chest pain radiating to the back ± markedly unequal BP in arms. CXR shows mediastinal widening. Can result in organ ischemia, aortic rupture, death. Two types:

* Stanford type A (proximal): involves ascending aorta. May extend to aortic arch or descending aorta. May result in acute aortic regurgitation or cardiac tamponade. Treatment: surgery.
* Stanford type B (distal): involves only descending aorta (below ligamentum arteriosum). Treat medically with β-blockers, then vasodilators.

Ischemic heart disease manifestations

Angina

Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no myocyte necrosis.

* Stable—usually 2° to atherosclerosis (≥ 70% occlusion); exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin.
* Vasospastic (also known as Prinzmetal or Variant)—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Smoking is a risk factor; hypertension and hypercholesterolemia are not. Triggers include cocaine, alcohol, and triptans. Treat with Ca²⁺ channel blockers, nitrates, and smoking cessation (if applicable).
* Unstable—thrombosis with incomplete coronary artery occlusion; +/− ST depression and/or T-wave inversion on ECG but no cardiac biomarker elevation (unlike NSTEMI); ↑ in frequency or intensity of chest pain or any chest pain at rest.

Coronary steal syndrome

Distal to coronary stenosis, vessels are maximally dilated at baseline. Administration of vasodilators (eg, dipyridamole, regadenoson) dilates normal vessels → blood is shunted toward well-perfused areas → ischemia in myocardium perfused by stenosed vessels. Principle behind pharmacologic stress tests with coronary vasodilators.

Sudden cardiac death

Death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia (eg, VF). Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (eg, long QT syndrome, Brugada syndrome). Prevent with ICD.

Chronic ischemic heart disease

Progressive onset of HF over many years due to chronic ischemic myocardial damage.

Myocardial infarction

Most often due to rupture of coronary artery atherosclerotic plaque → acute thrombosis. ↑ cardiac biomarkers (CK-MB, troponins) are diagnostic.

**ST-segment elevation MI (STEMI)**

Transmural infarcts

Full thickness of myocardial wall involved

ST elevation on ECG, Q waves

**Non–ST-segment elevation MI (NSTEMI)**

Subendocardial infarcts

Subendocardium (inner ⅓) especially vulnerable to ischemia

ST depression on ECG
### Evolution of myocardial infarction

Commonly occluded coronary arteries: LAD > RCA > circumflex.
Symptoms: diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue.

<table>
<thead>
<tr>
<th>TIME</th>
<th>GROSS</th>
<th>LIGHT MICROSCOPE</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–24 hr</td>
<td>None</td>
<td>Early coagulative necrosis, release of necrotic cell contents into blood; edema, hemorrhage, wavy fibers. Neutrophils appear. Reperfusion injury, associated with generation of free radicals, leads to hypercontraction of myofibrils through $^{+}$ free calcium influx.</td>
<td>Ventricular arrhythmia, HF, cardiogenic shock.</td>
</tr>
<tr>
<td>1–3 days</td>
<td>Hyperemia</td>
<td>Extensive coagulative necrosis. Tissue surrounding infarct shows acute inflammation with neutrophils.</td>
<td>Postinfarction fibrinous pericarditis.</td>
</tr>
<tr>
<td>3–14 days</td>
<td>Hyperemic border; central yellow-brown softening—maximally yellow and soft by 10 days</td>
<td>Macrophages, then granulation tissue at margins.</td>
<td>Free wall rupture $\rightarrow$ tamponade; papillary muscle rupture $\rightarrow$ mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation. LV pseudoaneurysm (risk of rupture).</td>
</tr>
<tr>
<td>2 weeks to several months</td>
<td>Recanalized artery; Gray-white</td>
<td>Contracted scar complete.</td>
<td>Dressler syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus).</td>
</tr>
</tbody>
</table>
Diagnosis of myocardial infarction

In the first 6 hours, ECG is the gold standard. Cardiac troponin I rises after 4 hours (peaks at 24 hr) and is ↑ for 7–10 days; more specific than other protein markers. CK-MB rises after 6–12 hours (peaks at 16–24 hr) and is predominantly found in myocardium but can also be released from skeletal muscle. Useful in diagnosing reinfarction following acute MI because levels return to normal after 48 hours. Large MIs lead to greater elevations in troponin I and CK-MB. Exact curves vary with testing procedure.

ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, new left bundle branch block, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).

### ECG localization of STEMI

<table>
<thead>
<tr>
<th>INFARCT LOCATION</th>
<th>LEADS WITH ST ELEVATIONS OR Q WAVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteroseptal (LAD)</td>
<td>V1–V2</td>
</tr>
<tr>
<td>Anteroapical (distal LAD)</td>
<td>V3–V4</td>
</tr>
<tr>
<td>Anterolateral (LAD or LCX)</td>
<td>V5–V6</td>
</tr>
<tr>
<td>Lateral (LCX)</td>
<td>I, aVL</td>
</tr>
<tr>
<td>Inferior (RCA)</td>
<td>II, III, aVF</td>
</tr>
<tr>
<td>Posterior (PDA)</td>
<td>V7–V9, ST depression in V1–V3 with tall R waves</td>
</tr>
</tbody>
</table>
### Myocardial infarction complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac arrhythmia</strong></td>
<td>Occurs within the first few days after MI. Important cause of death before reaching the hospital and within the first 24 hours post-MI.</td>
</tr>
<tr>
<td><strong>Postinfarction fibrinous pericarditis</strong></td>
<td>Occurs 1–3 days after MI. Friction rub.</td>
</tr>
<tr>
<td><strong>Papillary muscle rupture</strong></td>
<td>Occurs 2–7 days after MI. Posteromedial papillary muscle rupture <strong>↑</strong> risk due to single blood supply from posterior descending artery. Can result in severe mitral regurgitation.</td>
</tr>
<tr>
<td><strong>Interventricular septal rupture</strong></td>
<td>Occurs 3–5 days after MI. Macrophage-mediated degradation <strong>→</strong> VSD <strong>→</strong> ↓ O₂ saturation and pressure in RV.</td>
</tr>
<tr>
<td><strong>Ventricular pseudoaneurysm formation</strong></td>
<td>Occurs 3–14 days after MI. Contained free wall rupture <strong>↑</strong>; ↓ CO₂, risk of arrhythmia, embolus from mural thrombus.</td>
</tr>
<tr>
<td><strong>Ventricular free wall rupture</strong></td>
<td>Occurs 5–14 days after MI. Free wall rupture <strong>↑</strong> cardiac tamponade. LV hypertrophy and previous MI protect against free wall rupture. Acute form usually leads to sudden death.</td>
</tr>
<tr>
<td><strong>True ventricular aneurysm</strong></td>
<td>Occurs 2 weeks to several months after MI. Outward bulge with contraction (“dyskinesia”), associated with fibrosis.</td>
</tr>
<tr>
<td><strong>Dressler syndrome</strong></td>
<td>Occurs several weeks after MI. Autoimmune phenomenon resulting in fibrinous pericarditis.</td>
</tr>
<tr>
<td><strong>LV failure and pulmonary edema</strong></td>
<td>Can occur 2° to LV infarction, VSD, free wall rupture, papillary muscle rupture with mitral regurgitation.</td>
</tr>
</tbody>
</table>

### Acute coronary syndrome treatments

**Unstable angina/NSTEMI**—Anticoagulation (eg, heparin), antiplatelet therapy (eg, aspirin) + ADP receptor inhibitors (eg, clopidogrel), β-blockers, ACE inhibitors, statins. Symptom control with nitroglycerin and morphine.

**STEMI**—In addition to above, reperfusion therapy most important (percutaneous coronary intervention preferred over fibrinolysis).
### Cardiomyopathies

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dilated cardiomyopathy</strong></td>
<td>Most common cardiomyopathy (90% of cases). Often idiopathic or familial. Other etiologies</td>
<td>Leads to systolic dysfunction. Dilated cardiomyopathy displays eccentric hypertrophy (sarcomeres added in series). <strong>ABCCCD</strong>.</td>
</tr>
<tr>
<td></td>
<td>include chronic Alcohol abuse, wet Beriberi, Coxsackie B viral myocarditis, chronic Cocaine use,</td>
<td><strong>Takotsubo cardiomyopathy</strong>: broken heart syndrome—ventricular apical ballooning likely due to increased sympathetic stimulation (eg, stressful situations).</td>
</tr>
<tr>
<td></td>
<td>Chagas disease, Doxorubicin toxicity, hemochromatosis, sarcoidosis, thyrotoxicosis, peripartum cardiomyopathy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment: Na+ restriction, ACE inhibitors, β-blockers, diuretics, digoxin, ICD, heart transplant.</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertrophic obstructive cardiomyopathy</strong></td>
<td>60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β-myosin heavy chain). Causes synecope during exercise and may lead to sudden death (eg, in young athletes) due to ventricular arrhythmia. Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure. Treatment: cessation of high-intensity athletics, use of β-blocker or non-dihydropyridine Ca2+ channel blockers (eg, verapamil). ICD if patient is high risk.</td>
<td>Diastolic dysfunction ensues. Marked ventricular concentric hypertrophy (sarcomeres added in parallel) <strong>B</strong>, often septal predominance. Myofibrillar disarray and fibrosis. <strong>Physiology of HOCM</strong>—asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope. Other causes of concentric LV hypertrophy: chronic HTN, Friedreich ataxia.</td>
</tr>
<tr>
<td><strong>Restrictive/infiltrative cardiomyopathy</strong></td>
<td>Postradiation fibrosis, Löffler endocarditis, Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Amyloidosis, Sarcoidosis, Hemochromatosis (although dilated cardiomyopathy is more common) (Puppy LEASH).</td>
<td>Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially in amyloidosis). <strong>Löffler endocarditis</strong>—associated with hypereosinophilic syndrome; histology shows eosinophilic infiltrates in myocardium.</td>
</tr>
</tbody>
</table>

---
Heart failure

Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema.

Systolic dysfunction—reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.

Diastolic dysfunction—preserved EF, normal EDV; ↓ compliance (↑ EDP) often 2° to myocardial hypertrophy.

Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

ACE inhibitors or angiotensin II receptor blockers, β-blockers (except in acute decompensated HF), and spironolactone ↓ mortality. Thiazide or loop diuretics are used mainly for symptomatic relief. Hydralazine with nitrate therapy improves both symptoms and mortality in select patients.

Left heart failure

Orthopnea

Shortness of breath when supine: ↑ venous return from redistribution of blood (immediate gravity effect) exacerbates pulmonary vascular congestion.

Paroxysmal nocturnal dyspnea

Breathless awakening from sleep: ↑ venous return from redistribution of blood, reabsorption of peripheral edema, etc.

Pulmonary edema

↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages (“HF” cells) in lungs.

Right heart failure

Hepatomegaly (nutmeg liver)

↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to “cardiac cirrhosis.”

Jugular venous distention

↑ venous pressure.

Peripheral edema

↑ venous pressure → fluid transudation.
Shock

Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function. Initially may be reversible but life threatening if not treated promptly.

<table>
<thead>
<tr>
<th>Shock Type</th>
<th>Cause/Event</th>
<th>Skin</th>
<th>PCWP (preload)</th>
<th>CO</th>
<th>SVR (afterload)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic shock</td>
<td>Hemorrhage, dehydration, burns</td>
<td>Cold, clammy</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>IV fluids</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>Acute MI, HF, valvular dysfunction, arrhythmia</td>
<td>Cold, clammy</td>
<td>↑ or ↓</td>
<td>↓</td>
<td>↑</td>
<td>Inotropes, diuresis</td>
</tr>
<tr>
<td>Obstructive shock</td>
<td>Cardiac tamponade, pulmonary embolism, tension pneumothorax</td>
<td>Cold, clammy</td>
<td>↑ or ↓</td>
<td>↓</td>
<td>↑</td>
<td>Relieve obstruction</td>
</tr>
<tr>
<td>Distributive shock</td>
<td>Sepsis, anaphylaxis, CNS injury</td>
<td>Warm, dry</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>IV fluids, pressors, epinephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(anaphylaxis)</td>
</tr>
</tbody>
</table>

Bacterial endocarditis

**Acute**—*S. aureus* (high virulence). Large vegetations on previously normal valves. Rapid onset.

**Subacute**—*viridans streptococci* (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. Gradual onset.

Symptoms: fever (most common), new murmur, Roth spots (round white spots on retina surrounded by hemorrhage), Osler nodes (tender raised lesions on finger or toe pads due to immune complex deposition), Janeway lesions (small, painless, erythematous lesions on palm or sole), splinter hemorrhages on nail bed.

Associated with glomerulonephritis, septic arterial or pulmonary emboli.

May be nonbacterial (marantic/thrombotic) to malignancy, hypercoagulable state, or lupus.

- **Bacteria FROM JANE:**
  - Fever
  - Roth spots
  - Osler nodes
  - Murmur
  - Janeway lesions
  - Anemia
  - Nail-bed hemorrhage
  - Emboli

Requires multiple blood cultures for diagnosis. If culture positive, most likely *Coxiella burnetti*, *Bartonella* spp, HACEK (*Haemophilus*, *Aggregatibacter* [formerly *Actinobacillus*], *Cardiobacterium*, *Eikenella*, *Kingella*). Mitral valve is most frequently involved.

**Tricuspid valve endocarditis** is associated with IV drug abuse (don’t “tri” drugs). Associated with *S. aureus*, *Pseudomonas*, and *Candida*. *S. bovis* (*galloyticus*) is present in colon cancer, *S. epidermidis* on prosthetic valves.
Rheumatic fever

A consequence of pharyngeal infection with group A β-hemolytic streptococci. Late sequelae include rheumatic heart disease, which affects heart valves—mitral > aortic >> tricuspid (high-pressure valves affected most). Early lesion is mitral valve regurgitation; late lesion is mitral stenosis.

Associated with Aschoff bodies (granuloma with giant cells [blue arrows in A], Anitschkow cells [enlarged macrophages with ovoid, wavy, rod-like nucleus [red arrow in A]], † anti-streptolysin O (ASO) titers.

Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to M protein cross-react with self antigens (molecular mimicry).

Treatment/prophylaxis: penicillin.

J♥NES (major criteria):
Joint (migratory polyarthritis)
♥ (carditis)
Nodules in skin (subcutaneous)
Erythema marginatum (evanescent rash with ring margin)
Sydenham chorea

Acute pericarditis

Inflammation of the pericardium [A, red arrows]. Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [between yellow arrows in A]. Presents with friction rub. ECG changes include widespread ST-segment elevation and/or PR depression.

Causes include idiopathic (most common; presumed viral), confirmed infection (eg, coxsackievirus B), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.
Myocarditis
Inflammation of myocardium → global enlargement of heart and dilation of all chambers. Major cause of SCD in adults < 40 years old. Presentation highly variable, can include dyspnea, chest pain, fever, arrhythmias (persistent tachycardia out of proportion to fever is characteristic). Multiple causes:
* Viral (eg, adenovirus, coxsackie B, parvovirus B19, HIV, HHV-6); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis.
* Parasitic (eg, *Trypanosoma cruzi, Toxoplasma gondii*).
* Bacterial (eg, *Borrelia burgdorferi, Mycoplasma pneumoniae*).
* Toxins (eg, carbon monoxide, black widow venom).
* Rheumatic fever.
* Drugs (eg, doxorubicin, cocaine).
* Autoimmune (eg, Kawasaki disease, sarcoidosis, SLE, polymyositis/dermatomyositis).
Complications include sudden death, arrhythmias, heart block, dilated cardiomyopathy, HF, mural thrombus with systemic emboli.

Cardiac tamponade
Compression of the heart by fluid (eg, blood, effusions [arrows in A in pericardial space] → ↓ CO. Equilibration of diastolic pressures in all 4 chambers. Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), ↑ HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans (due to “swinging” movement of heart in large effusion).

Pulsus paradoxus — ↓ in amplitude of systolic BP by > 10 mm Hg during inspiration. Seen in cardiac tamponade, asthma, obstructive sleep apnea, pericarditis, croup.

Syphilitic heart disease
3° syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilatation of aorta and valve ring. May see calcification of aortic root, ascending aortic arch, and thoracic aorta. Leads to “tree bark” appearance of aorta. Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.
### Vasculitides

<table>
<thead>
<tr>
<th>Type</th>
<th>Epidemiology/Presentation</th>
<th>Pathology/Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large-vessel vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell (temporal) arteritis</td>
<td>Usually elderly females. Unilateral headache (temporal artery), jaw claudication. May lead to irreversible blindness due to ophthalmic artery occlusion. Associated with polymyalgia rheumatica.</td>
<td>Most commonly affects branches of carotid artery. Focal granulomatous inflammation. ESR. Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness.</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>Usually Asian females &lt; 40 years old. &quot;Pulseless disease&quot; (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances.</td>
<td>Granulomatous thickening and narrowing of aortic arch and proximal great vessels. ESR. Treat with corticosteroids.</td>
</tr>
<tr>
<td><strong>Medium-vessel vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawasaki disease (mucocutaneous lymph node syndrome)</td>
<td>Asian children &lt; 4 years old. Conjunctival injection, Rash (polymorphous desquamating), Adenopathy (cervical), Strawberry tongue (oral mucositis), Hand-foot changes (edema, erythema), fever.</td>
<td><strong>CRASH and burn.</strong> May develop coronary artery aneurysms; thrombosis or rupture can cause death. Treat with IV immunoglobulin and aspirin.</td>
</tr>
<tr>
<td>Buerger disease (thromboangiitis obliterans)</td>
<td>Heavy smokers, males &lt; 40 years old. Intermittent claudication may lead to gangrene, autoamputation of digits, superficial nodular phlebitis. Raynaud phenomenon is often present.</td>
<td>Segmental thrombosing vasculitis with vein and nerve involvement. Treat with smoking cessation.</td>
</tr>
<tr>
<td><strong>Small-vessel vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura. Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement.</td>
<td>No granulomas. MPO-ANCA/p-ANCA (anti-myeloperoxidase). Treat with cyclophosphamide, corticosteroids.</td>
</tr>
</tbody>
</table>
### Vasculitides (continued)

#### Small-vessel vasculitis (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology/Presentation</th>
<th>Pathology/Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behçet syndrome</strong></td>
<td>High incidence in Turkish and eastern Mediterranean descent.</td>
<td>Immune complex vasculitis. Associated with HLA-B51.</td>
</tr>
<tr>
<td></td>
<td>Recurrent aphthous ulcers, genital ulcerations, uveitis, erythema nodosum. Can be precipitated by HSV or parvovirus. Flares last 1–4 weeks.</td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)</strong></td>
<td>Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (eg, wrist/foot drop). Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis).</td>
<td>Granulomatous, necrotizing vasculitis with eosinophilia. MPO-ANCA/p-ANCA, ↑ IgE level.</td>
</tr>
</tbody>
</table>
| **Immunoglobulin A vasculitis**          | Also known as Henoch-Schönlein purpura. Most common childhood systemic vasculitis. Often follows URI. Classic triad:  
Skin: palpable purpura on buttocks/legs  
Arthralgias  
GI: abdominal pain (associated with intussusception) | Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease). |

#### Cardiac tumors

**Myxomas**

Most common 1° cardiac tumor in adults (arrows in A). 90% occur in the atria (mostly left atrium). Myxomas are usually described as a “ball valve” obstruction in the left atrium (associated with multiple syncopal episodes). May auscultate early diastolic “tumor plop” sound. Histology: gelatinous material, myxoma cells immersed in glycosaminoglycans.

**Rhabdomyomas**

**Kussmaul sign**

+ in JVP on inspiration instead of a normal ↓.

Inspiration → negative intrathoracic pressure not transmitted to heart → impaired filling of right ventricle → blood backs up into vena cava → JVD. May be seen with constrictive pericarditis, restrictive cardiomyopathies, right atrial or ventricular tumors.

**Hereditary hemorrhagic telangiectasia**

Also known as Osler-Weber-Rendu syndrome. Inherited disorder of blood vessels. Findings:

- blanching lesions (telangiectasias) on skin and mucous membranes, recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria.

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**CARDIOVASCULAR—PHARMACOLOGY**

### Hypertension treatment

<table>
<thead>
<tr>
<th>Classification</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary (essential) hypertension</strong></td>
<td>Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca²⁺ channel blockers.</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension with heart failure</strong></td>
<td>Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists.</td>
<td>β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock. In HF, ARBs may be combined with the neprilysin inhibitor sacubitril.</td>
</tr>
<tr>
<td><strong>Hypertension with diabetes mellitus</strong></td>
<td>ACE inhibitors/ARBs, Ca²⁺ channel blockers, thiazide diuretics, β-blockers.</td>
<td>ACE inhibitors/ARBs are protective against diabetic nephropathy.</td>
</tr>
<tr>
<td><strong>Hypertension in asthma</strong></td>
<td>ARBs, Ca²⁺ channel blockers, thiazide diuretics, selective β-blockers.</td>
<td>Avoid nonselective β-blockers to prevent β₂-receptor–induced bronchoconstriction. Avoid ACE inhibitors to prevent confusion between drug or asthma-related cough.</td>
</tr>
<tr>
<td><strong>Hypertension in pregnancy</strong></td>
<td>Hydralazine, labetalol, methyldopa, nifedipine.</td>
<td>“He likes my neonate.”</td>
</tr>
</tbody>
</table>
### Calcium channel blockers

**Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).**

**MECHANISM**
Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility.

Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil.
Heart—verapamil = diltiazem > amlodipine = nifedipine (verapamil = ventricle).

**CLINICAL USE**
Dihydropyridines (except nimodipine): hypertension, angina (including Prinzmetal), Raynaud phenomenon.
Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).
Nicardipine, clevidipine: hypertensive urgency or emergency.
Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.

**ADVERSE EFFECTS**
Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia, constipation, gingival hyperplasia.
Dihydropyridine: peripheral edema, flushing, dizziness.

### Hydralazine

**MECHANISM**
† cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.

**CLINICAL USE**
Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy.
Frequently coadministered with a β-blocker to prevent reflex tachycardia.

**ADVERSE EFFECTS**
Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina.
SLE-like syndrome.

### Hypertensive emergency

Treat with clevidipine, fenoldopam, labetalol, nicardipine, or nitroprusside.

### Nitroprusside

Short acting; † cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide).

### Fenoldopam

Dopamine D₁ receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. † BP, † natriuresis. Also used postoperatively as an antihypertensive. Can cause hypotension and tachycardia.

### Nitrates

Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate.

**MECHANISM**
Vasodilate by † NO in vascular smooth muscle → † in cGMP and smooth muscle relaxation.
Dilate veins >> arteries. ↓ preload.

**CLINICAL USE**
Angina, acute coronary syndrome, pulmonary edema.

**ADVERSE EFFECTS**
Reflex tachycardia (treat with β-blockers), hypotension, flushing, headache, “Monday disease” in industrial exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure.
Contraindicated in right ventricular infarction.
**Antianginal therapy**

Goal is reduction of myocardial \( \text{O}_2 \) consumption (MVO\(_2\)) by 1 or more of the determinants of MVO\(_2\): end-diastolic volume, BP, HR, contractility.

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>NITRATES</th>
<th>β-BLOCKERS</th>
<th>NITRATES + β-BLOCKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume</td>
<td>↓</td>
<td>No effect or ↑</td>
<td>No effect or ↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Contractility</td>
<td>No effect</td>
<td>↓</td>
<td>Little/no effect</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑ (reflex response)</td>
<td>↓</td>
<td>No effect or ↓</td>
</tr>
<tr>
<td>Ejection time</td>
<td>↓</td>
<td>↑</td>
<td>Little/no effect</td>
</tr>
<tr>
<td>MVO(_2)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Verapamil is similar to β-blockers in effect.
Pindolol and acebutolol are partial β-agonists that should be used with caution in angina.

**Ranolazine**

**MECHANISM**

Inhibits the late phase of sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or contractility.

**CLINICAL USE**

Angina refractory to other medical therapies.

**ADVERSE EFFECTS**

Constipation, dizziness, headache, nausea, QT prolongation.

**Milrinone**

**MECHANISM**


**CLINICAL USE**

Short-term use in acute decompensated HF.

**ADVERSE EFFECTS**

Arrhythmias, hypotension.
### Lipid-lowering agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LDL</th>
<th>HDL</th>
<th>TRIGLYCERIDES</th>
<th>MECHANISMS OF ACTION</th>
<th>ADVERSE EFFECTS/PROBLEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG-CoA reductase inhibitors</strong> (eg, lovastatin, pravastatin)</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
<td>Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor; ↑ mortality in CAD patients</td>
<td>Hepatotoxicity (↑ LFTs), myopathy (esp. when used with fibrates or niacin)</td>
</tr>
<tr>
<td><strong>Bile acid resins</strong> Cholestyramine, colestipol, colesevelam</td>
<td>↓↓</td>
<td>Slightly ↑</td>
<td>Slightly ↑</td>
<td>Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more</td>
<td>GI upset, ↓ absorption of other drugs and fat-soluble vitamins</td>
</tr>
<tr>
<td><strong>Ezetimibe</strong></td>
<td>↓↓</td>
<td>↓/—</td>
<td>↓/—</td>
<td>Prevent cholesterol absorption at small intestine brush border</td>
<td>Rare ↑ LFTs, diarrhea</td>
</tr>
<tr>
<td><strong>Fibrates</strong> Gemfibrozil, bezafibrate, fenofibrate</td>
<td>↓</td>
<td>↑</td>
<td>↓↓↓</td>
<td>Upregulate LPL → ↑ TG clearance Activates PPAR-α to induce HDL synthesis</td>
<td>Myopathy (↑ risk with statins), cholesterol gallstones (via inhibition of cholesterol 7α-hydroxylase)</td>
</tr>
<tr>
<td><strong>Niacin (vitamin B3)</strong></td>
<td>↓↓</td>
<td>↑±</td>
<td>↓</td>
<td>Inhibits lipolysis (hormone-sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis</td>
<td>Red, flushed face, which is ↑ by NSAIDs or long-term use Hyperglycemia Hyperuricemia</td>
</tr>
<tr>
<td><strong>PCSK9 inhibitors</strong> Alirocumab, evolocumab</td>
<td>↓↓↓</td>
<td>↑</td>
<td>↓</td>
<td>Inactivation of LDL-receptor degradation, increasing amount of LDL removed from bloodstream</td>
<td>Myalgias, delirium, dementia, other neurocognitive effects</td>
</tr>
</tbody>
</table>
### Cardiac glycosides

**Digoxin.**

#### Mechanism
- Direct inhibition of Na\(^+\)/K\(^+\) ATPase
- Indirect inhibition of Na\(^+\)/Ca\(^{2+}\) exchanger.
- \(\uparrow [Ca^{2+}]_i\) → positive inotropy. Stimulates vagus nerve → ↓ HR.

![Diagram](image)

#### Clinical Use
- HF (↑ contractility); atrial fibrillation (↓ conduction at AV node and depression of SA node).

#### Adverse Effects
- Cholinergic—nausea, vomiting, diarrhea, blurry yellow vision (think van Gogh), arrhythmias, AV block.
- Can lead to hyperkalemia, which indicates poor prognosis.
- Factors predisposing to toxicity: renal failure (↓ excretion), hypokalemia (permissive for digoxin binding at K\(^+\)-binding site on Na\(^+\)/K\(^+\) ATPase), drugs that displace digoxin from tissue-binding sites, and ↓ clearance (eg, verapamil, amiodarone, quinidine).

#### Antidote
- Slowly normalize K\(^+\), cardiac pacer, anti-digoxin Fab fragments, Mg\(^{2+}\).
**Antiarrhythmics—sodium channel blockers (class I)**

Slow or block (↓) conduction (especially in depolarized cells). ↓ slope of phase 0 depolarization. Are state dependent (selectively depress tissue that is frequently depolarized [eg, tachycardia]).

**Class IA**
- **Quinidine, Procainamide, Disopyramide.**
  - "The Queen Proclaims Diso’s pyramid."
  - ↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval, some potassium channel blocking effects.

**CLINICAL USE**
- Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.

**ADVERSE EFFECTS**
- Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), HF (disopyramide), thrombocytopenia, torsades de pointes due to ↑ QT interval.

**Class IB**
- **Lidocaine, Mexiletine.**
  - “I’d Buy Liddy’s Mexican Tacos.”
  - ↓ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue. Phenytoin can also fall into the IB category.

**CLINICAL USE**
- Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias.

**ADVERSE EFFECTS**
- CNS stimulation/depression, cardiovascular depression.

**Class IC**
- **Flecainide, Propafenone.**
  - “Can I have Fries, Please.”
  - Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.

**CLINICAL USE**
- SVTs, including atrial fibrillation. Only as a last resort in refractory VT.

**ADVERSE EFFECTS**
- Proarrhythmic, especially post-MI (contraindicated). IC is Contraindicated in structural and ischemic heart disease.
Antiarrhythmics—
\textbf{β}-blockers (class II)

**MECHANISM**
Decrease SA and AV nodal activity by ↓ cAMP, ↓ Ca^{2+} currents. Suppress abnormal pacemakers by ↓ slope of phase 4.
AV node particularly sensitive—↑ PR interval. Esmolol very short acting.

**CLINICAL USE**
SVT, ventricular rate control for atrial fibrillation and atrial flutter.

**ADVERSE EFFECTS**
Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia.
Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in Prinzmetal angina.
β-blockers (except the nonselective α- and β-antagonists carvedilol and labetalol) cause unopposed α₁-agonism if given alone for pheochromocytoma or cocaine toxicity. Treat β-blocker overdose with saline, atropine, glucagon.

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**Antiarrhythmics—potassium channel blockers (class III)**

**MECHANISM**
↑ AP duration, ↑ ERP, ↑ QT interval.

**CLINICAL USE**
Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol).

**ADVERSE EFFECTS**
Sotalol—torsades de pointes, excessive β-blockade.
Ibutilide—torsades de pointes.
Amiodarone—pulmonary fibrosis, hepatotoxicity, hypothyroidism or hyperthyroidism (amiodarone is 40% iodine by weight), acts as hapten (corneal deposits, blue/gray skin deposits resulting in photodermatitis), neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, HF).

Remember to check PFTs, LFTs, and TFTs when using amiodarone. Amiodarone is lipophilic and has class I, II, III, and IV effects.
### Antiarrhythmics—calcium channel blockers (class IV)

Verapamil, diltiazem.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↓ conduction velocity, ↑ ERP, ↑ PR interval.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical use</td>
<td>Prevention of nodal arrhythmias (eg, SVT), rate control in atrial fibrillation.</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).</td>
</tr>
</tbody>
</table>

#### Other antiarrhythmics

**Adenosine**

↑ K⁺ out of cells → hyperpolarizing the cell and ↓ I_Ca, decreasing AV node conduction. Drug of choice in diagnosing/terminating certain forms of SVT. Very short acting (~ 15 sec). Effects blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects include flushing, hypotension, chest pain, sense of impending doom, bronchospasm.

**Mg²⁺**

Effective in torsades de pointes and digoxin toxicity.

### Ivabradine

**Mechanism**

Selective inhibition of funny sodium channels (I_f), prolonging slow depolarization phase (phase 4). ↓ SA node firing; negative chronotropic effect without inotropy. Reduces cardiac O₂ requirement.

**Clinical use**

Chronic stable angina in patients who cannot take β-blockers. Chronic HF with reduced ejection fraction.

**Adverse effects**

Luminous phenomena/visual brightness, hypertension, bradycardia.
HIGH-YIELD SYSTEMS

Endocrine

“If you skew the endocrine system, you lose the pathways to self.”
—Hilary Mantel

“We have learned that there is an endocrinology of elation and despair, a chemistry of mystical insight, and, in relation to the autonomic nervous system, a meteorology and even . . . an astro-physics of changing moods.”
—Aldous (Leonard) Huxley

“Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy.”
—Elaine Sherman, Book of Divine Indulgences

The endocrine system comprises widely distributed organs that work in a highly integrated manner to orchestrate a state of hormonal equilibrium within the body. Generally speaking, endocrine diseases can be classified either as diseases of underproduction or overproduction, or as conditions involving the development of mass lesions—which themselves may be associated with underproduction or overproduction of hormones. Therefore, study the endocrine system first by learning the glands, their hormones, and their regulation, and then by integrating disease manifestations with diagnosis and management. Take time to learn the multisystem connections.
**Thyroid development**

Thyroid diverticulum arises from floor of primitive pharynx and descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as cysts or the pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct. Most common ectopic thyroid tissue site is the tongue (lingual thyroid). Removal may result in hypothyroidism if it is the only thyroid tissue present. Thyroglossal duct cyst presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs persistent cervical sinus leading to branchial cleft cyst in lateral neck). Thyroid follicular cells are derived from endoderm; parafollicular cells (aka, C cells, produce Calcitonin) are derived from neural crest.

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**Adrenal cortex and medulla**

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

GFR corresponds with Salt (mineralocorticoids), Sugar (glucocorticoids), and Sex (androgens). “The deeper you go, the sweeter it gets.”
### Pituitary gland

**Anterior pituitary (adenohypophysis)**
- Secretes FSH, LH, ACTH, TSH, prolactin, GH, and β-endorphin. Melanotropin (MSH) secreted from intermediate lobe of pituitary.
- Derived from oral ectoderm (Rathke pouch).
- **α** subunit—hormone subunit common to TSH, LH, FSH, and hCG.
- **β** subunit—determines hormone specificity.
- ACTH, MSH, and β-endorphin are derivatives of proopiomelanocortin.
- **FLAT** FSH, LH, ACTH, TSH, PRL, GH.
- **B-FLAT** Basophils—FSH, LH, ACTH, TSH.
- Acidophils: GH, PRL.

**Posterior pituitary (neurohypophysis)**
- Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins).
- Derived from neuroectoderm.

### Endocrine pancreas cell types
- Islets of Langerhans are collections of α, β, and δ endocrine cells. Islets arise from pancreatic buds.
  - **α** = glucagon (peripheral)
  - **β** = insulin (central)
  - **δ** = somatostatin (interspersed)

---

**Insulin (β cells) inside.**
Insulin

**SYNTHESIS**
Preproinsulin (synthesized in RER) → cleavage of "presignal" → proinsulin (stored in secretory granules) → cleavage of proinsulin → exocytosis of insulin and C-peptide equally. Insulin and C-peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.

**FUNCTION**
Released from pancreatic β cells. Binds insulin receptors (tyrosine kinase activity 1), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue 2 and gene transcription.

Anabolic effects of insulin:
- ↑ glucose transport in skeletal muscle and adipose tissue
- ↑ glycogen synthesis and storage
- ↑ triglyceride synthesis
- ↑ Na⁺ retention (kidneys)
- ↑ protein synthesis (muscles)
- ↑ cellular uptake of K⁺ and amino acids
- ↑ glucagon release
- ↓ lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

**REGULATION**
Glucose is the major regulator of insulin release. ↑ insulin response with oral vs IV glucose due to incretins (eg, glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and ↑ β cell sensitivity to glucose. Release ↓ by α₂, ↑ by β₂ (2 = regulates insulin)

Glucose enters β cells 3 → ↑ ATP generated from glucose metabolism 4 closes K⁺ channels (target of sulfonylureas) 5 and depolarizes β cell membrane 6. Voltage-gated Ca²⁺ channels open 6 → Ca²⁺ influx 7 and stimulation of insulin exocytosis 8.

Insulin-dependent glucose uptake

Insulin secretion by pancreatic β cells
### Glucagon

**SOURCE**
Made by \( \alpha \) cells of pancreas.

**FUNCTION**
Promotes glycogenolysis, gluconeogenesis, lipolysis, and ketone production. Elevates blood sugar levels to maintain homeostasis when concentration of bloodstream glucose falls too low (ie, fasting state).

**REGULATION**
Secreted in response to hypoglycemia. Inhibited by insulin, hyperglycemia, and somatostatin.

### Hypothalamic-pituitary hormones

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>FUNCTION</th>
<th>CLINICAL NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption</td>
<td>Stimulus for secretion is ↑ plasma osmolality, except in cases of SIADH, where ADH is inappropriately elevated despite ↓ plasma osmolality.</td>
</tr>
<tr>
<td>CRH</td>
<td>↑ ACTH, MSH, ( \beta )-endorphin</td>
<td>↓ in chronic exogenous steroid use.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↓ prolactin, TSH</td>
<td>Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia.</td>
</tr>
<tr>
<td>GHRH</td>
<td>↑ GH</td>
<td>Analog (tesamorelin) used to treat HIV-associated lipodystrophy.</td>
</tr>
<tr>
<td>MSH</td>
<td>↑ melanogenesis by melanocytes</td>
<td>Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin.</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Causes uterine contractions during labor. Responsible for milk letdown reflex in response to suckling.</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>↓ GnRH</td>
<td>Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea.</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>↓ GH, TSH</td>
<td>Analogs used to treat acromegaly.</td>
</tr>
<tr>
<td>TRH</td>
<td>↑ TSH, prolactin</td>
<td>↑ TRH (eg, in 1(^{1/2}) hypothyroidism) may increase prolactin secretion → galactorrhea.</td>
</tr>
</tbody>
</table>
**Prolactin**

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th>Secreted mainly by anterior pituitary.</th>
<th>Structurally homologous to growth hormone.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNCTION</strong></td>
<td>Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release.</td>
<td>Excessive amounts of prolactin associated with ↓ libido.</td>
</tr>
<tr>
<td><strong>REGULATION</strong></td>
<td>Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from tuberoinfundibular pathway of hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (e.g., in 1° or 2° hypothyroidism).</td>
<td>Dopamine agonists (e.g., bromocriptine) inhibit prolactin secretion and can be used in treatment of prolactinoma. Dopamine antagonists (e.g., most antipsychotics) and estrogens (e.g., OCPs, pregnancy) stimulate prolactin secretion.</td>
</tr>
</tbody>
</table>

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![Image of prolactin regulation](image_url)
Growth hormone (somatotropin)

**SOURCE**
Secreted by anterior pituitary.

**FUNCTION**
Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).

**REGULATION**
Released in pulses in response to growth hormone–releasing hormone (GHRH). Secretion ↑ during exercise, deep sleep, puberty, hypoglycemia. Secretion inhibited by glucose and somatostatin release via negative feedback by somatomedin.

Somatostatin keeps your growth **static**. Somatomedin mediates your growth.

Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treat with somatostatin analogs (eg, octreotide) or surgery.

Appetite regulation

**Ghrelin**
Stimulates hunger (orexigenic effect) and GH release (via GH secretagogue receptor). Produced by stomach. Sleep deprivation or Prader-Willi syndrome → ↑ ghrelin production.

Ghrelin makes you hung**hre** and ghre**ow** (grow). Acts via lateral area of hypothalamus to ↑ appetite (hunger center).

**Leptin**
Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → congenital obesity. Sleep deprivation or starvation → ↓ leptin production.

Leptin keeps you thin. Acts via ventromedial area of hypothalamus to ↓ appetite (satiety center).

**Endocannabinoids**
Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.

Exogenous cannabinoids cause “the munchies.”

Antidiuretic hormone (vasopressin)

**SOURCE**
Synthesized in hypothalamus (supraoptic and paraventricular nuclei), stored and secreted by posterior pituitary.

**FUNCTION**
Regulates serum osmolality (V2-receptors) and blood pressure (V1-receptors). Primary function is serum osmolality regulation (ADH ↓ serum osmolality, ↑ urine osmolality) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.

ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI. Nephrogenic DI can be caused by mutation in V2-receptor. Desmopressin (ADH analog) is a treatment for central DI and nocturnal enuresis.

**REGULATION**
Osmoreceptors in hypothalamus (1°), hypovolemia.
### Adrenal steroids and congenital adrenal hyperplasias

<table>
<thead>
<tr>
<th>Enzyme Deficiency</th>
<th>Mineralocorticoids</th>
<th>Cortisol</th>
<th>Sex Hormones</th>
<th>BP</th>
<th>K+</th>
<th>Labs</th>
<th>Presentation</th>
</tr>
</thead>
</table>
| **A 17α-hydroxylase**<sup>a</sup> | ↑ | ↓ | ↓ | ↑ | ↓ | ↓ androstenedione | XY: ambiguous genitalia, undescended testes  
XX: lacks 2° sexual development |
| **B 21-hydroxylase**<sup>a</sup> | ↓ | ↓ | ↑ | ↓ | ↑ | ↑ renin activity  
↑ 17-hydroxyprogesterone | Most common  
Presents in infancy (salt wasting) or childhood (precocious puberty)  
XX: virilization |
| **C 11β-hydroxylase**<sup>a</sup> | ↓ aldosterone  
↑ 11-deoxycorticosterone (results in ↑ BP) | ↓ | ↑ | ↑ | ↓ | ↓ renin activity | XX: virilization |

<sup>a</sup>All congenital adrenal enzyme deficiencies are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to ↑ ACTH stimulation). If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

---

**ACHT**  
**Ketoconazole** (blocks several steps in steroidogenesis)

**3β-hydroxysteroid dehydrogenase**

**21-hydroxylase**

**11β-hydroxylase**

**Aldosterone synthase**

**Angiotensin II**

**ACTH**  
**Ketoconazole** (blocks several steps in steroidogenesis)

**ZONA GLOMERULOSA**  
Mineralocorticoids

**ZONA FASCICULATA**  
Glucocorticoids

**ZONA RETICULARIS**  
Androgens

**Adrenal cortex**

**Peripheral tissue**

**Anastrozole, exemestane**

**Estrone**

**Estradiol**

**Testosterone**

**Aromatase**

**Dihydrotestosterone (DHT)**

**Finasteride**

**Estrogens, DHT**

**Glycyrrhetinic acid**

**Metyrapone**

---

<sup>a</sup>Rate-limiting step.
**Cortisol**

**SOURCE**
Adrenal zona fasciculata.

**FUNCTION**
- Appetite
- Blood pressure:
  - Upregulates α₁-receptors on arterioles
  - ↑ sensitivity to norepinephrine and epinephrine (permissive action)
- At high concentrations, can bind to mineralocorticoid (aldosterone) receptors
- Insulin resistance (diabetogenic)
- Gluconeogenesis, lipolysis, and proteolysis
  - ↓ glucose utilization
- Fibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae)
- Inflammatory and Immune responses:
  - Inhibits production of leukotrienes and prostaglandins
  - Inhibits WBC adhesion → neutrophilia
  - Blocks histamine release from mast cells
  - Eosinopenia, lymphopenia
  - Blocks IL-2 production
- Bone formation (↓ osteoblast activity)

**REGULATION**
CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.

**Calcium homeostasis**
Plasma Ca²⁺ exists in three forms:
- Ionized/free (~ 45%, active form)
- Bound to albumin (~ 40%)
- Bound to anions (~ 15%)

↑ in pH → ↑ affinity of albumin (↑ negative charge) to bind Ca²⁺ → hypocalcemia (eg, cramps, pain, paresthesias, carpopedal spasm). Ionized/free Ca²⁺ is ↓ regulator of PTH; changes in pH alter PTH secretion, whereas changes in albumin do not.

Cortisol is a **A BIG FIB**. Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-2 production).
Parathyroid hormone

**SOURCE**
Chief cells of parathyroid.

**FUNCTION**
- ↑ bone resorption of Ca\(^{2+}\) and PO\(_4\)\(^{3−}\).
- ↑ kidney reabsorption of Ca\(^{2+}\) in distal convoluted tubule.
- ↓ reabsorption of PO\(_4\)\(^{3−}\) in proximal convoluted tubule.
- ↑ 1,25-(OH)\(_2\)D\(_3\) (calcitriol) production by stimulating kidney 1α-hydroxylase in proximal convoluted tubule.
- PTH ↑ serum Ca\(^{2+}\), ↓ serum (PO\(_4\)\(^{3−}\)), ↑ urine (PO\(_4\)\(^{3−}\)), ↑ urine cAMP.
- ↑ RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes. Binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ Ca\(^{2+}\) → bone resorption. Intermittent PTH release can also stimulate bone formation.
- PTH = Phosphate-Trashing Hormone.
- PTH-related peptide (PTHrP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma).

**REGULATION**
- ↓ serum Ca\(^{2+}\) → ↑ PTH secretion.
- ↓ serum PO\(_4\)\(^{3−}\) → ↑ PTH secretion.
- ↓ serum Mg\(^{2+}\) → ↑ PTH secretion.
- ↓↓ serum Mg\(^{2+}\) → ↓ PTH secretion.
- Common causes of ↓ Mg\(^{2+}\) include diarrhea, aminoglycosides, diuretics, alcohol abuse.
Calcitonin

**SOURCE**
Parafollicular cells (C cells) of thyroid.

**FUNCTION**
↓ bone resorption of Ca^{2+}.

**REGULATION**
↑ serum Ca^{2+} → calcitonin secretion.

Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis. Calcitonin tones down serum Ca^{2+} levels and keeps it in bones.

---

**Thyroid hormones (T_{3}/T_{4})**

Iodine-containing hormones that control the body’s metabolic rate.

**SOURCE**
Follicles of thyroid. 5'-deiodinase converts T_{4} (the major thyroid product) to T_{3} in peripheral tissue (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids, β-blockers and propylthiouracil (PTU).

Functions of thyroid peroxidase include oxidation, organification of iodide and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole. DIT + DIT = T_{4} DIT + MIT = T_{3}. Wolff-Chaikoff effect—excess iodine temporarily ⊖ thyroid peroxidase → ↓ T_{3}/T_{4} production.

**FUNCTION**
Only free hormone is active. T_{3} binds nuclear receptor with greater affinity than T_{4}. T_{3} functions—6 B’s:
- Brain maturation
- Bone growth (synergy with GH)
- β-adrenergic effects. ↑ β_{1} receptors in heart → ↑ CO, HR, SV, contractility; β-blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate ↑ (via Na^{+}/K^{+}-ATPase activity → ↑ O_{2} consumption, RR, body temperature)
- Blood sugar (↑ glycogenolysis, gluconeogenesis)
- Break down lipids (↑ lipolysis)

**REGULATION**
TRH ⊕ TSH release → ⊕ follicular cells. Thyroid-stimulating immunoglobulin (TSI) may ⊕ follicular cells in Graves disease.

Negative feedback primarily by free T_{3}/T_{4}:
- Anterior pituitary → ↓ sensitivity to TRH
- Hypothalamus → ↓ TRH secretion

Thyroxine-binding globulin (TBG) binds most T_{3}/T_{4} in blood. Bound T_{3}/T_{4} is inactive.
- ↑ TBG in pregnancy, OCP use (estrogen → ↑ TBG) → ↑ total T_{3}/T_{4}
- ↓ TBG in hepatic failure, steroids, nephrotic syndrome
Signaling pathways of endocrine hormones

<table>
<thead>
<tr>
<th>cAMP</th>
<th>FSH, LH, ACTH, TSH, CRH, hCG, ADH (V₁-receptor), MSH, PTH, calcitonin, GHRH, glucagon, histamine (H₁-receptor)</th>
<th>FLAT ChAMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGMP</td>
<td>BNP, ANP, EDRF (NO)</td>
<td>BAD GraMPa</td>
</tr>
<tr>
<td>IP₃</td>
<td>GnRH, Oxytocin, ADH (V₁-receptor), TRH, Histamine (H₁-receptor), Angiotensin II, Gastrin</td>
<td>GOAT HAG</td>
</tr>
<tr>
<td>Intracellular receptor</td>
<td>Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T₃/T₄, Vitamin D</td>
<td>PET CAT on TV</td>
</tr>
<tr>
<td>Receptor tyrosine kinase</td>
<td>Insulin, IGF-1, FGF, PDGF, EGF</td>
<td>MAP kinase pathway</td>
</tr>
<tr>
<td>Nonreceptor tyrosine kinase</td>
<td>Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin</td>
<td>JAK/STAT pathway</td>
</tr>
</tbody>
</table>

Signaling pathways of steroid hormones

Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility. In men, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone → gynecomastia. In women, ↓ SHBG raises free testosterone → hirsutism. OCPs, pregnancy → ↑ SHBG.
Cushing syndrome

**Etiology**

- hypercortisol due to a variety of causes:
  - Exogenous corticosteroids—result in ↓ ACTH, bilateral adrenal atrophy. Most common cause.
  - Primary adrenal adenoma, hyperplasia, or carcinoma—result in ↓ ACTH, atrophy of uninvolved adrenal gland.
  - ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids)—result in ↑ ACTH, bilateral adrenal hyperplasia.
  - Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

**Findings**

- Hypertension, weight gain, moon facies, abdominal striae and truncal obesity, buffalo hump, skin changes (eg, thinning, striae), hirsutism, osteoporosis, hyperglycemia (insulin resistance), amenorrhea, immunosuppression. Can also present with pseudohyperaldosteronism.

**Diagnosis**

- Screening tests include:
  - ↑ free cortisol on 24-hr urinalysis, ↑ midnight salivary cortisol, and no suppression with overnight low-dose dexamethasone test. Measure serum ACTH. If ↓, suspect adrenal tumor or exogenous glucocorticoids. If ↑, distinguish between Cushing disease and ectopic ACTH secretion (eg, from small cell lung cancer).
## Adrenal insufficiency

Inability of adrenal glands to generate enough glucocorticoids +/- mineralocorticoids for the body’s needs. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings. Treatment: glucocorticoid/mineralocorticoid replacement.

Diagnosis involves measurement of serum electrolytes, morning/random serum cortisol and ACTH (low cortisol, high ACTH in 1° adrenal insufficiency; low cortisol, low ACTH in 2°/3° adrenal insufficiency due to pituitary/hypothalamic disease), and response to ACTH stimulation test. Alternatively, can use metyrapone stimulation test: metyrapone blocks last step of cortisol synthesis (11-deoxycortisol → cortisol). Normal response is ↓ cortisol and compensatory ↑ ACTH and 11-deoxycortisol. In 1° adrenal insufficiency, ACTH is ↑ but 11-deoxycortisol remains ↓ after test. In 2°/3° adrenal insufficiency, both ACTH and 11-deoxycortisol remain ↓ after test.

### Primary adrenal insufficiency

Deficiency of aldosterone and cortisol production due to loss of gland function → hypotension (hypotensive volume contraction), hyperkalemia, metabolic acidosis, skin and mucosal hyperpigmentation (due to ↑ MSH, a byproduct of ACTH production from proopiomelanocortin).

- **Acute**—sudden onset (eg, due to massive hemorrhage). May present with shock in acute adrenal crisis.
- **Chronic**—Addison disease. Due to adrenal atrophy or destruction by disease (autoimmune destruction most common in the Western world; TB most common in the developing world).

### Secondary adrenal insufficiency

Seen with ↓ pituitary ACTH production. No skin/mucosal hyperpigmentation, no hyperkalemia (aldosterone synthesis preserved due to intact renin-angiotensin-aldosterone axis).

### Tertiary adrenal insufficiency

Seen in patients with chronic exogenous steroid use, precipitated by abrupt withdrawal. Aldosterone synthesis unaffected.

### Hyperaldosteronism

Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ normal K⁺, metabolic alkalosis. 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

### Primary hyperaldosteronism

Seen with adrenal adenoma (Conn syndrome) or bilateral adrenal hyperplasia. ↑ aldosterone, ↓ renin. Causes resistant hypertension.

### Secondary hyperaldosteronism

Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome).
Neuroendocrine tumors

Heterogeneous group of neoplasms that begin in specialized cells called neuroendocrine cells (have traits similar to nerve cells and hormone-producing cells). Characteristics vary considerably depending on anatomical site, neuroendocrine cell(s) of origin (eg, enterochromaffin cells, enterochromaffin-like cells, insulin-producing β cells), and secretory products. Cells contain amine precursor uptake decarboxylase (APUD) and secrete different hormones (eg, serotonin, histamine, calcitonin, neuron-specific enolase [NSE], chromogranin A). Most tumors arise in the GI system (eg, carcinoid, gastrinoma), pancreas (eg, insulinoma, glucagonoma), and lungs (eg, small cell carcinoma). Other organs include thyroid (eg, medullary carcinoma) and adrenals (eg, pheochromocytoma).

Neuroblastoma

Most common tumor of the adrenal medulla in children, usually < 4 years old. Originates from Neural crest cells. Occurs anywhere along the sympathetic chain. Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with pheochromocytoma (Neuroblastoma is normotensive). Can also present with opsoclonus-myoclonus syndrome (“dancing eyes-dancing feet”). HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes characteristic of neuroblastoma and medulloblastoma. Bombesin and NSE. Associated with overexpression of N-myc oncogene. Classified as an APUD tumor.
# Pheochromocytoma

**Etiology**

Most common tumor of the adrenal medulla in **adults**. Derived from chromaffin cells (arise from neural crest).

May be associated with germline mutations (eg, *NF-1, VHL, RET* [MEN 2A, 2B]).

**Rule of 10’s:**

- 10% malignant
- 10% bilateral
- 10% extra-adrenal (eg, bladder wall, organ of Zuckerkandl)
- 10% calcify
- 10% kids

**Symptoms**

Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. May also secrete EPO → polycythemia.

Symptoms occur in “spells”—relapse and remit.

Episodic hyperadrenergic symptoms (**5 P’s**):

- Pressure († BP)
- Pain (headache)
- Perspiration
- Palpitations (tachycardia)
- Pallor

**Findings**

† catecholamines and catecholamine metabolites (eg, metanephrines) in urine and plasma.

**Treatment**

Irreversible α-antagonists (eg, phenoxybenzamine) followed by β-blockers prior to tumor resection. α-blockade must be achieved before giving β-blockers to avoid a hypertensive crisis. **A before B.**

Phenoxybenzamine (16 letters) is given for pheochromocytoma (also 16 letters).

---

# VIPoma

Rare neuroendocrine tumor that secretes vasoactive intestinal peptide (VIP). Most commonly arises in pancreas. Associated with MEN-1. Primary symptom is secretory diarrhea. Associated with *WDHA* (Watery Diarrhea, Hypokalemia, Achlorhydria) syndrome.
### Hypothyroidism vs hyperthyroidism

<table>
<thead>
<tr>
<th>METABOLIC FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic changes</td>
<td>Cold intolerance, ↓ sweating, weight gain (↑ basal metabolic rate → ↓ calorigenesis), hyponatremia (↑ free water clearance)</td>
<td>Heat intolerance, ↑ sweating, weight loss (↑ synthesis of Na⁺-K⁺ ATPase → ↑ basal metabolic rate → ↑ calorigenesis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SKIN/HAIR FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and hair</td>
<td>Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema) due to ↑ GAGs in interstitial spaces → ↑ osmotic pressure → water retention</td>
<td>Warm, moist skin (due to vasodilation); fine hair; onycholysis (¶); pretibial myxedema in Graves disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OCULAR FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td>Periorbital edema</td>
<td>Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/retraction (↑ sympathetic stimulation of levator palpebrae superioris)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GASTROINTESTINAL FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Constipation (↓ GI motility), ↓ appetite</td>
<td>Hyperdefecation/diarrhea (↑ GI motility), ↑ appetite</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MUSCULOSKELETAL FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Hypothyroid myopathy (proximal weakness, ↑ CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer)</td>
<td>Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/↑ fracture rate (T₃ directly stimulates bone resorption)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REPRODUCTIVE FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive</td>
<td>Menorrhagia and/or oligomenorrhoe; ↓ libido, infertility</td>
<td>Oligomenorrhoe or amenorrhoe, gynecomastia, ↓ libido, infertility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NEUROPSYCHIATRIC FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing)</td>
<td>Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to ↑ β-adrenergic activity), ↑ reflexes (brisk)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIOVASCULAR FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Bradycardia, dyspnea on exertion (↑ cardiac output)</td>
<td>Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β-adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LAB FINDINGS</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>↑ TSH (if 1°)</td>
<td>↓ TSH (if 1°)</td>
</tr>
<tr>
<td>Free T₃ and T₄</td>
<td>↓ free T₃ and T₄</td>
<td>↑ free T₃ and T₄</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>(due to ↓ LDL receptor expression)</td>
<td>↓ LDL, HDL, and total cholesterol</td>
</tr>
</tbody>
</table>
### Hypothyroidism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hashimoto thyroiditis</strong></td>
<td>Most common cause of hypothyroidism in iodine-sufficient regions; an autoimmune disorder with antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies. Associated with HLA-DR3, ↑ risk of non-Hodgkin lymphoma (typically of B-cell origin). May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture. Histology: Hürthle cells, lymphoid aggregates with germinal centers. Findings: moderately enlarged, nontender thyroid.</td>
</tr>
<tr>
<td><strong>Postpartum thyroiditis</strong></td>
<td>Self-limited thyroiditis arising up to 1 year after delivery. Presents as transient hyperthyroidism, hypothyroidism, or hyperthyroidism followed by hypothyroidism. Majority of women are euthyroid following resolution. Thyroid usually painless and normal in size. Histology: lymphocytic infiltrate with occasional germinal center formation.</td>
</tr>
<tr>
<td><strong>Congenital hypothyroidism (cretinism)</strong></td>
<td>Severe fetal hypothyroidism due to antibody-mediated maternal hypothyroidism, thyroid agenesis, thyroid dysgenesis (most common cause in US), iodine deficiency, dyshormonogenetic goiter. Findings: Pot-bellied, Pale, Puffy-faced child with Protruding umbilicus, Protruberant tongue, and Poor brain development: the 6 P’s.</td>
</tr>
<tr>
<td><strong>Subacute granulomatous thyroiditis (de Quervain)</strong></td>
<td>Self-limited disease often following a flu-like illness (eg, viral infection). May be hyperthyroid early in course, followed by hypothyroidism (permanent in ~15% of cases). Histology: granulomatous inflammation. Findings: ↑ ESR, jaw pain, very tender thyroid. (de Quervain is associated with pain.)</td>
</tr>
<tr>
<td><strong>Riedel thyroiditis</strong></td>
<td>Thyroid replaced by fibrous tissue with inflammatory infiltrate. Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma. ¼ are hypothyroid. Considered a manifestation of IgG4-related systemic disease (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis). Findings: fixed, hard (rock-like), painless goiter.</td>
</tr>
</tbody>
</table>

### Other causes

- Iodine deficiency, goitrogens (eg, amiodarone, lithium), Wolff-Chaikoff effect (thyroid gland downregulation in response to ↑ iodide).
Hyperthyroidism

**Graves disease**
Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter) and dermal fibroblasts (pretibial myxedema). Infiltration of retroorbital space by activated T-cells → ↑ cytokines (eg, TNF-α, IFN-γ) → ↑ fibroblast secretion of hydrophilic GAGs → ↑ osmotic muscle swelling, muscle inflammation, and adipocyte count → exophthalmos. Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8. Histology: tall, crowded follicular epithelial cells; scalloped colloid.

**Toxic multinodular goiter**
Focal patches of hyperfunctioning follicular cells distended with colloid working independently of TSH (due to TSH receptor mutations in 60% of cases). ↑ release of T₃ and T₄. Hot nodules are rarely malignant.

**Thyroid storm**
Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see ↑ LFTs. Treat with the 4 P’s: β-blockers (eg, Propranolol), Propylthiouracil, corticosteroids (eg, Prednisolone), Potassium iodide (Lugol iodine).

**Jod-Basedow phenomenon**
Thyrotoxicosis if a patient with iodine deficiency and partially autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Can happen after iodine IV contrast. Opposite to Wolff-Chaikoff effect.

Causes of goiter

<table>
<thead>
<tr>
<th>Smooth/diffuse</th>
<th>Nodular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>Toxic multinodular goiter</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>Thyroid adenoma</td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>TSH-secreting pituitary</td>
<td>Thyroid cyst</td>
</tr>
</tbody>
</table>

### Causes of goiter

- Smooth/diffuse:
  - Graves disease
  - Hashimoto thyroiditis
  - Iodine deficiency
  - TSH-secreting pituitary adenoma

- Nodular:
  - Toxic multinodular goiter
  - Thyroid adenoma
  - Thyroid cancer
  - Thyroid cyst
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid adenoma</strong></td>
<td>Benign solitary growth of the thyroid. Most are nonfunctional (“cold”), can rarely cause hyperthyroidism via autonomous thyroid hormone production (“hot” or “toxic”). Most common histology is follicular; absence of capsular or vascular invasion (unlike follicular carcinoma).</td>
</tr>
<tr>
<td><strong>Thyroid cancer</strong></td>
<td>Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hoarseness (due to recurrent laryngeal nerve damage), hypocalcemia (due to removal of parathyroid glands), and transection of recurrent and superior laryngeal nerves (during ligation of inferior thyroid artery and superior laryngeal artery, leading to dysphagia, dysphonia).</td>
</tr>
<tr>
<td><strong>Papillary carcinoma</strong></td>
<td>Most common, excellent prognosis. Empty-appearing nuclei with central clearing (“Orphan Annie” eyes), psamMoma bodies, nuclear grooves (Papi and Moma adopted Orphan Annie). Risk with RET/PTC rearrangements and BRAF mutations, childhood irradiation.</td>
</tr>
<tr>
<td><strong>Follicular carcinoma</strong></td>
<td>Good prognosis. Invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with RAS mutation and PAX8-PPAR-γ translocations.</td>
</tr>
<tr>
<td><strong>Medullary carcinoma</strong></td>
<td>From parafollicular “C cells”; produces calcitonin, sheets of cells in an amyloid stroma (stains with Congo red). Associated with MEN 2A and 2B (RET mutations).</td>
</tr>
<tr>
<td>**Undifferentiated/</td>
<td>Older patients; invades local structures, very poor prognosis.</td>
</tr>
<tr>
<td>anaplastic carcinoma**</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
<td>Associated with Hashimoto thyroiditis.</td>
</tr>
</tbody>
</table>
Diagnosing parathyroid disease

Hyoparathyroidism

Due to accidental surgical excision of parathyroid glands, autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia.

Chvostek sign—tapping of facial nerve (tap the Cheek) → contraction of facial muscles.

Trousseau sign—occlusion of brachial artery with BP cuff (cuff the Triceps) → carpal spasm.

Pseudohyoparathyroidism type 1A—unresponsiveness of kidney to PTH → hypocalcemia despite ↑ PTH levels. Presents as a constellation of physical findings known as Albright hereditary osteodystrophy: shortened 4th/5th digits, short stature, obesity, developmental delay. Autosomal dominant. Due to defective Gα protein α-subunit causing end-organ resistance to PTH. Defect must be inherited from mother due to imprinting.

Pseudopseudohyoparathyroidism—physical exam features of Albright hereditary osteodystrophy but without end-organ PTH resistance (PTH level normal). Occurs when defective Gα protein α-subunit is inherited from father.
Hyperparathyroidism

**Primary hyperparathyroidism**

Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal stones), polyuria (thrones), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ cAMP in urine. Most often asymptomatic. May present with weakness and constipation (“groans”), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances (“psychiatric overtones”).

**Osteitis fibrosa cystica** — cystic bone spaces filled with brown fibrous tissue ("brown tumor” consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to ↑ PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism. “Stones, thrones, bones, groans, and psychiatric overtones.”

**Secondary hyperparathyroidism**

2° hyperplasia due to ↓ Ca\(^{2+}\) absorption and/or ↓ PO\(_4^{3-}\), most often in chronic renal disease (causes hypovitaminosis D and hyperphosphatemia → ↓ Ca\(^{2+}\)). **Hypocalcemia**, hyperphosphatemia in chronic renal failure (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.

**Renal osteodystrophy** — renal disease → 2° and 3° hyperparathyroidism → bone lesions.

**Tertiary hyperparathyroidism**

Refractory (autonomous) hyperparathyroidism resulting from chronic renal disease. ↑↑ PTH, ↑ Ca\(^{2+}\).

**Familial hypocalciuric hypercalcemia**

Defective G-coupled Ca\(^{2+}\)-sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca\(^{2+}\) levels required to suppress PTH. Excessive renal Ca\(^{2+}\) reuptake → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.

**Nelson syndrome**

Enlargement of existing ACTH-secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease (due to removal of cortisol feedback mechanism). Presents with hyperpigmentation, headaches and bitemporal hemianopia. Treatment: pituitary irradiation or surgical resection.
### Acromegaly

**FINDINGS**
Large tongue with deep furrows, deep voice, large hands and feet, coarsening of facial features with aging, frontal bossing, diaphoresis (excessive sweating), impaired glucose tolerance (insulin resistance), hypertension. ↑ risk of colorectal polyps and cancer.

**DIAGNOSIS**
↑ serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.

**TREATMENT**
Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog) or pegvisomant (growth hormone receptor antagonist), dopamine agonists (eg, cabergoline).

### Laron syndrome (dwarfism)
Defective growth hormone receptors → ↓ linear growth. ↑ GH, ↓ IGF-1. Clinical features: short height, small head circumference, characteristic facies with saddle nose and prominent forehead, delayed skeletal maturation, small genitalia.
**Diabetes insipidus**

Characterized by intense thirst and polyuria with inability to concentrate urine due to lack of ADH (central) or failure of response to circulating ADH (nephrogenic).

<table>
<thead>
<tr>
<th>Central DI</th>
<th>Nephrogenic DI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETIOLOGY</strong></td>
<td>Pituitary tumor, autoimmune, trauma, surgery, ischemic encephalopathy, idiopathic</td>
</tr>
<tr>
<td><strong>FINDINGS</strong></td>
<td>$ADH$</td>
</tr>
<tr>
<td></td>
<td>Urine specific gravity $&lt;$ 1.006</td>
</tr>
<tr>
<td></td>
<td>Serum osmolality $&gt;$ 290 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>Hyperosmotic volume contraction</td>
</tr>
<tr>
<td><strong>WATER DEPRIVATION TEST$^a$</strong></td>
<td>$&gt;$ 50% $ADH$ level increase only after administration of $ADH$ analog</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Desmopressin, Hydration</td>
</tr>
</tbody>
</table>

$^a$No water intake for 2–3 hr followed by hourly measurements of urine volume and osmolality and plasma Na$^+$ concentration and osmolality. ADH analog (desmopressin) is administered if serum osmolality $>$ 295–300 mOsm/kg, plasma Na$^+$ $\geq$ 145 mEq/L, or urine osmolality does not rise despite a rising plasma osmolality.

---

**Syndrome of inappropriate antidiuretic hormone secretion**

Characterized by:
- Excessive free water retention
- Euvolemic hyponatremia with continued urinary Na$^+$ excretion
- Urine osmolality $>$ serum osmolality

Body responds to water retention with:
- $\downarrow$ aldosterone and $\uparrow$ ANP and BNP
- $\rightarrow$ $\downarrow$ urinary Na$^+$ secretion $\rightarrow$ normalization of extracellular fluid volume $\rightarrow$ euvolemic hyponatremia.

Very low serum Na$^+$ levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly known as central pontine myelinolysis).

**SIADH causes include:**
- Ectopic ADH (eg, small cell lung cancer)
- CNS disorders/head trauma
- Pulmonary disease
- Drugs (eg, cyclophosphamide)

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, conivaptan, tolvaptan, demeclocycline.

Increased urine osmolality during water deprivation test indicates psychogenic polydipsia.
Hypopituitarism

Undersecretion of pituitary hormones due to:

- Nonsecreting pituitary adenoma, craniopharyngioma
- Sheehan syndrome—ischemic infarct of pituitary following postpartum bleeding; pregnancy-induced pituitary growth → ↑ susceptibility to hypoperfusion. Usually presents with failure to lactate, absent menstruation, cold intolerance
- Empty sella syndrome—atrophy or compression of pituitary (which lies in the sella turcica), often idiopathic, common in obese women; associated with idiopathic intracranial hypertension
- Pituitary apoplexy—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism.
- Brain injury
- Radiation

Treatment: hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone).
Diabetes mellitus

**ACUTE MANIFESTATIONS**
Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar hyperglycemic state (type 2). Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).

**CHRONIC COMPLICATIONS**
Nonenzymatic glycation:
- Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, neuropathy, nephropathy (nodular glomerulosclerosis, aka Kimmelstiel-Wilson nodules → progressive proteinuria [initially microalbuminuria; ACE inhibitors are renoprotective] and arteriosclerosis → hypertension; both lead to chronic renal failure).
- Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene → limb loss, cerebrovascular disease. MI most common cause of death.
Osmotic damage (sorbitol accumulation in organs with aldose reductase and Ⅳ or absent sorbitol dehydrogenase):
- Neuropathy (motor, sensory [glove and stocking distribution], and autonomic degeneration)
- Cataracts

**DIAGNOSIS**

<table>
<thead>
<tr>
<th>TEST</th>
<th>DIAGNOSTIC CUTOFF</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>≥ 6.5%</td>
<td>Reflects average blood glucose over prior 3 months</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>≥ 126 mg/dL</td>
<td>Fasting for &gt; 8 hours</td>
</tr>
<tr>
<td>2-hour oral glucose tolerance test</td>
<td>≥ 200 mg/dL</td>
<td>2 hours after consumption of 75 g of glucose in water</td>
</tr>
</tbody>
</table>

**Insulin deficiency or severe insulin insensitivity**

- ↓ tissue glucose uptake
- ↑ glycogenolysis
- ↑ gluconeogenesis
- ↑ proteolysis
- ↑ lipolysis

- ↑ plasma osmolality
- ↑ thirst
- ↓ protein, weight loss
- ↑ plasma free fatty acids

- Osmotic diuresis
- Loss of water, Na⁺, and K⁺
- Hypovolemia
- Circulation failure, ↓ tissue perfusion
- Coma/death

- Hypoglycemia, glycosuria
- ↓ protein, weight loss
- ↑ plasma free fatty acids

- Vomiting
- ↑ ketogenesis, ketonemia, ketonuria
- ↑ serum lactate

- Hyperglycemia, glucosuria
- ↓ protein, weight loss
- ↑ plasma free fatty acids

- Hyperventilation/Kussmaul respiration
- ↑ serum lactate
- Anion gap metabolic acidosis
### Type 1 vs Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1° Defect</strong></td>
<td>Autoimmune destruction of β cells (e.g., due to glutamic acid decarboxylase antibodies)</td>
<td>↑ resistance to insulin, progressive pancreatic β-cell failure</td>
</tr>
<tr>
<td><strong>Insulin Necessary in Treatment</strong></td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td><strong>Age (exceptions commonly occur)</strong></td>
<td>&lt; 30 yr</td>
<td>&gt; 40 yr</td>
</tr>
<tr>
<td><strong>Association with obesity</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Genetic predisposition</strong></td>
<td>Relatively weak (50% concordance in identical twins), polygenic</td>
<td>Relatively strong (90% concordance in identical twins), polygenic</td>
</tr>
<tr>
<td><strong>Association with HLA system</strong></td>
<td>Yes, HLA-DR4 and -DR3 (4–3 = type 1)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Glucose intolerance</strong></td>
<td>Severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td><strong>Insulin sensitivity</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Ketoacidosis</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>β-cell numbers in the islets</strong></td>
<td>↓</td>
<td>Variable (with amyloid deposits)</td>
</tr>
<tr>
<td><strong>Serum insulin level</strong></td>
<td>↓</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Classic symptoms of polyuria, polydipsia, polyphagia, weight loss</strong></td>
<td>Common</td>
<td>Sometimes</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Islet leukocytic infiltrate</td>
<td>Islet amyloid polypeptide (IAPP) deposits</td>
</tr>
</tbody>
</table>

### Diabetic Ketoacidosis

One of the most feared complications of diabetes. Usually due to insulin noncompliance or ↑ insulin requirements from ↑ stress (e.g., infection). Excess fat breakdown and ↑ ketogenesis from ↑ free fatty acids, which are then made into ketone bodies (β-hydroxybutyrate > acetoacetate). Usually occurs in type 1 diabetes, as endogenous insulin in type 2 diabetes usually prevents lipolysis.

#### Signs/Symptoms

**DKA** is **Deadly**: Delirium/psychosis, Kussmaul respirations (rapid, deep breathing), Abdominal pain/nausea/vomiting, Dehydration. Fruity breath odor (due to exhaled acetone).

#### Labs

Hyperglycemia, ↑ H⁺, ↑ HCO₃⁻ (↑ anion gap metabolic acidosis), ↑ blood ketone levels, leukocytosis. Hyperkalemia, but depleted intracellular K⁺ due to transcellular shift from ↓ insulin and acidosis. Osmotic diuresis → ↓ K⁺ loss in urine → total body K⁺ depletion.

#### Complications

Life-threatening mucormycosis (usually caused by *Rhizopus* infection), cerebral edema, cardiac arrhythmias, heart failure.

#### Treatment

IV fluids, IV insulin, and K⁺ (to replete intracellular stores); glucose if necessary to prevent hypoglycemia.
Hyperosmolar hyperglycemic state
State of profound hyperglycemia-induced dehydration and ↑ serum osmolality, classically seen in elderly type 2 diabetics with limited ability to drink. Hyperglycemia → excessive osmotic diuresis → dehydration → eventual onset of HHS. Symptoms: thirst, polyuria, lethargy, focal neurological deficits (eg, seizures), can progress to coma and death if left untreated. Labs: hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), no acidosis (pH > 7.35, ketone production inhibited by presence of insulin). Treatment: aggressive IV fluids, insulin therapy.

Glucagonoma
Tumor of pancreatic α cells → overproduction of glucagon. Presents with dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression. Treatment: octreotide, surgery.

Insulinoma
Tumor of pancreatic β cells → overproduction of insulin → hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of glucose levels. Symptomatic patients have ↓ blood glucose and ↑ C-peptide levels (vs exogenous insulin use). ~ 10% of cases associated with MEN 1 syndrome. Treatment: surgical resection.

Somatostatinoma
Tumor of pancreatic δ cells → overproduction of somatostatin → ↓ secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP). May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria. Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Carcinoid syndrome
Rare syndrome caused by carcinoid tumors (neuroendocrine cells noted, note prominent rosettes [arrow]), especially metastatic small bowel tumors, which secrete high levels of serotonin (5-HT). Not seen if tumor is limited to GI tract (5-HT undergoes first-pass metabolism in liver). Results in recurrent diarrhea, cutaneous flushing, asthmatic wheezing, right-sided valvular heart disease (tricuspid regurgitation, pulmonic stenosis) due to lung MAO-A enzymatic breakdown of 5-HT before left heart return. ↑ 5-hydroxyindoleacetic acid (5-HIAA) in urine, niacin deficiency (pellagra). Associated with neuroendocrine tumor markers chromogranin A and synaptophysin. Treatment: surgical resection, somatostatin analog (eg, octreotide).

Rule of 1/3s:
1/3 metastasize
1/3 present with 2nd malignancy
1/3 are multiple
Most common malignancy in the small intestine.
**Zollinger-Ellison syndrome**

Gastrin-secreting tumor (gastrinoma) of pancreas or duodenum. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test: gastrin levels remain elevated after administration of secretin, which normally inhibits gastrin release. May be associated with MEN 1.

---

**Multiple endocrine neoplasias**

All MEN syndromes have autosomal dominant inheritance. “All MEN are dominant” (or so they think).

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>CHARACTERISTICS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN 1</strong></td>
<td>Pituitary tumors (prolactin or GH)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parathyroid adenomas</td>
<td>Associated with mutation of MEN1 (menin, a tumor suppressor, chromosome 11), angiofibromas, collagenomas, meningiomas</td>
</tr>
<tr>
<td><strong>MEN 2A</strong></td>
<td>Parathyroid hyperplasia</td>
<td>Medullary thyroid carcinoma—neoplasm of parafollicular or C cells; secretes calcitonin; prophylactic thyroidectomy required</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma (secretes catecholamines)</td>
<td>Associated with mutation in RET (codes for receptor tyrosine kinase) in cells of neural crest origin</td>
</tr>
<tr>
<td><strong>MEN 2B</strong></td>
<td>Medullary thyroid carcinoma</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Mucosal neuromas (oral/intestinal ganglioneuromatosis)</td>
<td>Associated with marfanoid habitus; mutation in ( RET ) gene</td>
</tr>
</tbody>
</table>

---

**MEN 1** = 3 P’s: Pituitary, Parathyroid, and Pancreas

**MEN 2A** = 2 P’s: Parathyroid and Pheochromocytoma

**MEN 2B** = 1 P: Pheochromocytoma
Diabetes mellitus management

All patients with diabetes mellitus should receive education on diet, exercise, blood glucose monitoring, and complication management. Treatment differs based on the type of diabetes:

- Type 1 DM—insulin replacement
- Type 2 DM—oral agents (metformin is first line), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose
- Gestational DM—insulin replacement if nutrition therapy and exercise alone fail

Regular (short-acting) insulin is preferred for DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>MECHANISM</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin preparations</td>
<td>Bind insulin receptor (tyrosine kinase activity).</td>
<td>Hypoglycemia, lipodystrophy, rare hypersensitivity reactions.</td>
</tr>
<tr>
<td>Short acting (2–3 hr peak): regular Intermediate acting (4–10 hr peak): NPH Long acting (no real peak): detemir, glargine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>↓ glucagon release, ↓ gastric emptying, ↑ satiety.</td>
<td>Hypoglycemia (in setting of mistimed prandial insulin), nausea.</td>
</tr>
<tr>
<td>Pramlintide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>↓ glucagon release, ↓ gastric emptying, ↑ glucose-dependent insulin release, ↑ satiety.</td>
<td>Nausea, vomiting, pancreatitis. Promote weight loss (often desired).</td>
</tr>
<tr>
<td>Exenatide, liraglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Inhibit hepatic gluconeogenesis and the action of glucagon, by inhibiting mGPD. ↑ glycolysis, peripheral glucose uptake (↑ insulin sensitivity).</td>
<td>GI upset, lactic acidosis (use with caution in renal insufficiency), B₁₂ deficiency. Promote weight loss (often desired).</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Close K⁺ channel in pancreatic β cell membrane → cell depolarizes → insulin release via ↑ Ca²⁺ influx.</td>
<td>Hypoglycemia (↑ risk with renal failure), weight gain. 1st generation: disulfiram-like effects. 2nd generation: hypoglycemia.</td>
</tr>
<tr>
<td>1st generation: chlorpropamide, tolbutamide 2nd generation: glimepiride, glipizide, glyburide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Close K⁺ channel in pancreatic β cell membrane → cell depolarizes → insulin release via ↑ Ca²⁺ influx (binding site differs from sulfonylureas).</td>
<td>Hypoglycemia (↑ risk with renal failure), weight gain.</td>
</tr>
<tr>
<td>Nateglinide, repaglinide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Diabetes mellitus management (continued)

### Oral drugs (continued)

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>MECHANISM</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 inhibitors</strong>&lt;br&gt;Linagliptin, saxagliptin, sitagliptin</td>
<td>Inhibit DPP-4 enzyme that deactivates GLP-1. ↓ glucagon release, gastric emptying. ↑ glucose-dependent insulin release, satiety.</td>
<td>Mild urinary or respiratory infections, weight neutral.</td>
</tr>
<tr>
<td><strong>Glitazones/thiazolidinediones</strong>&lt;br&gt;Pioglitazone, rosiglitazone</td>
<td>Binds to PPAR-γ nuclear transcription regulator → ↑ insulin sensitivity and levels of adiponectin → regulation of glucose metabolism and fatty acid storage.</td>
<td>Weight gain, edema, HF, ↑ risk of fractures. Delayed onset of action (several weeks).</td>
</tr>
<tr>
<td><strong>Sodium-glucose co-transporter 2 (SGLT2) inhibitors</strong>&lt;br&gt;Canagliflozin, dapagliflozin, empagliflozin</td>
<td>Block reabsorption of glucose in proximal convoluted tubule.</td>
<td>Glucosuria, UTIs, vaginal yeast infections, hyperkalemia, dehydration (orthostatic hypotension), weight loss.</td>
</tr>
<tr>
<td><strong>α-glucosidase inhibitors</strong>&lt;br&gt;Acarbose, miglitol</td>
<td>Inhibit intestinal brush-border α-glucosidases → delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.</td>
<td>GI upset. Not recommended if kidney function is impaired.</td>
</tr>
<tr>
<td><strong>Thioamides</strong>&lt;br&gt;Propylthiouracil, methimazole.</td>
<td>Block thyroid peroxidase, inhibiting the oxidation of iodide and the organification and coupling of iodine → inhibition of thyroid hormone synthesis. PTU also blocks 5'-deiodinase → ↓ peripheral conversion of T₄ to T₃.</td>
<td>Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity. Methimazole is a possible teratogen (can cause aplasia cutis).</td>
</tr>
<tr>
<td><strong>Levothyroxine (T₄), liothyronine (T₃)</strong>&lt;br&gt;Thyroid hormone replacement.</td>
<td>Hyperthyroidism. PTU blocks Peripheral conversion. PTU used in first trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with corticosteroids).</td>
<td>Tachycardia, heat intolerance, tremors, arrhythmias.</td>
</tr>
</tbody>
</table>

**MECHANISM**

- Block thyroid peroxidase, inhibiting the oxidation of iodide and the organification and coupling of iodine → inhibition of thyroid hormone synthesis. PTU also blocks 5'-deiodinase → ↓ peripheral conversion of T₄ to T₃.
- Hyperthyroidism. PTU blocks Peripheral conversion. PTU used in first trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with corticosteroids).

**CLINICAL USE**

- Hypothyroidism, myxedema. May be abused for weight loss.
- Thyroid hormone replacement.

**ADVERSE EFFECTS**

- Tachycardia, heat intolerance, tremors, arrhythmias.
### Hypothalamic/pituitary drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH antagonists (conivaptan, tolvaptan)</td>
<td>SIADH, block action of ADH at V₂-receptor.</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Central (not nephrogenic) DI, von Willebrand disease, sleep enuresis, hemophilia A.</td>
</tr>
<tr>
<td>GH</td>
<td>GH deficiency, Turner syndrome.</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Labor induction (stimulates uterine contractions), milk letdown; controls uterine hemorrhage.</td>
</tr>
<tr>
<td>Somatostatin (octreotide)</td>
<td>Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices.</td>
</tr>
</tbody>
</table>

#### Demeclocycline

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>ADH antagonist (member of tetracycline family).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Use</td>
<td>SIADH.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Nephrogenic DI, photosensitivity, abnormalities of bone and teeth.</td>
</tr>
</tbody>
</table>

#### Fludrocortisone

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Synthetic analog of aldosterone with little glucocorticoid effects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Use</td>
<td>Mineralocorticoid replacement in 1° adrenal insufficiency.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.</td>
</tr>
</tbody>
</table>

#### Cinacalcet

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Sensitizes Ca²⁺-sensing receptor (CaSR) in parathyroid gland to circulating Ca²⁺ → PTH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Use</td>
<td>Refractory hypercalcemia in 1° hyperparathyroidism, 2° hyperparathyroidism, or parathyroid carcinoma.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Hypocalcemia.</td>
</tr>
</tbody>
</table>

#### Sevelamer

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Use</td>
<td>Hyperphosphatemia in CKD.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Hypophosphatemia, GI upset.</td>
</tr>
</tbody>
</table>
“A good set of bowels is worth more to a man than any quantity of brains.”  
—Josh Billings

“Man should strive to have his intestines relaxed all the days of his life.”  
—Moses Maimonides

“Is life worth living? It all depends on the liver.”  
—William James

When studying the gastrointestinal system, be sure to understand the normal embryology, anatomy, and physiology and how it is affected in the various pathologic diseases. Study not only what a disease entails, but also its specific findings, so that you can differentiate between two similar diseases. For example, what specifically makes ulcerative colitis different than Crohn disease? Also, it is important to understand bile metabolism and which lab values increase or decrease depending on the disease process. Be comfortable reading abdominal X-rays, CT scans, and endoscopy exams.
Gastrointestinal—embryology

Normal gastrointestinal embryology

- **Foregut**—esophagus to upper duodenum.
- **Midgut**—lower duodenum to proximal 2/3 of transverse colon.
- **Hindgut**—distal 1/3 of transverse colon to anal canal above pectinate line.

**Midgut development**:
- 6th week—physiologic midgut herniates through umbilical ring
- 10th week—returns to abdominal cavity + rotates around superior mesenteric artery (SMA),
  total 270° counterclockwise

**Ventral wall defects**

Developmental defects due to failure of rostral fold closure (eg, sternal defects [ectopia cordis]), lateral fold closure (eg, omphalocele, gastroschisis), or caudal fold closure (eg, bladder extrophy).

**Gastrochisis**
- **Etiology**
  Extrusion of abdominal contents through abdominal folds (typically right of umbilicus)
- **Coverage**
  Not covered by peritoneum or amnion; “the abdominal contents are coming out of the G”
- **Associations**
  Not associated with chromosome abnormalities

**Omphalocele**
- **Etiology**
  Failure of lateral walls to migrate at umbilical ring → persistent midline herniation of abdominal contents into umbilical cord
- **Coverage**
  Surrounded by peritoneum (light gray shiny sac); “abdominal contents are sealed in the Θ”
- **Associations**
  Associated with congenital anomalies (eg, trisomies 13 and 18, Beckwith-Wiedemann syndrome) and other structural abnormalities (eg, cardiac, GU, neural tube)

**Congenital umbilical hernia**

Failure of umbilical ring to close after physiologic herniation of the intestines. Small defects usually close spontaneously.

**Tracheoesophageal anomalies**

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%) and often presents as polyhydramnios in utero (due to inability of fetus to swallow amniotic fluid). Neonates drool, choke, and vomit with first feeding. TEFs allow air to enter stomach (visible on CXR). Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach.

In **H**-type, the fistula resembles the letter H. In pure EA, CXR shows gasless abdomen.

**Diagram**: Normal anatomy, Pure EA (atresia or stenosis), Pure TEF (H-type), EA with distal TEF (most common)
Intestinal atresia

Presents with bilious vomiting and abdominal distension within first 1–2 days of life.

Duodenal atresia—failure to recanalize. Associated with “double bubble” (dilated stomach, proximal duodenum) on x-ray. Associated with Down syndrome.

Jejunal and ileal atresia—disruption of mesenteric vessels → ischemic necrosis → segmental resorption (bowel discontinuity or “apple peel”).

Hypertrophic pyloric stenosis

Most common cause of gastric outlet obstruction in infants (1:600). Palpable olive-shaped mass in epigastric region, visible peristaltic waves, and nonbilious projectile vomiting at ∼ 2–6 weeks old. More common in firstborn males; associated with exposure to macrolides. Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction). Ultrasound shows thickened and lengthened pylorus. Treatment is surgical incision (pyloromyotomy).

Pancreas and spleen embryology

Pancreas—derived from foregut. Ventral pancreatic buds contribute to uncinate process and main pancreatic duct. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct. Both the ventral and dorsal buds contribute to pancreatic head.

Annular pancreas—abnormal rotation of ventral pancreatic bud forms a ring of pancreatic tissue → encircles 2nd part of duodenum; may cause duodenal narrowing (arrows in image) and vomiting.

Pancreas divisum—ventral and dorsal parts fail to fuse at 8 weeks. Common anomaly; mostly asymptomatic, but may cause chronic abdominal pain and/or pancreatitis.

Spleen—arises in mesentery of stomach (hence is mesodermal) but has foregut supply (celiac trunk → splenic artery).
Retroperitoneal structures include GI structures that lack a mesentery and non-GI structures. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.

SAD PUCKER:
- Suprarenal (adrenal) glands [not shown]
- Aorta and IVC
- Duodenum (2nd through 4th parts)
- Pancreas (except tail)
- Ureters [not shown]
- Colon (descending and ascending)
- Kidneys
- Esophagus (thoracic portion) [not shown]
- Rectum (partially) [not shown]
### Important gastrointestinal ligaments

<table>
<thead>
<tr>
<th>Ligament</th>
<th>Connects</th>
<th>Structures Contained</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Falciform ligament</strong></td>
<td>Liver to anterior abdominal wall</td>
<td>Ligamentum teres hepatis (derivative of fetal umbilical vein), patent paraumbilical veins</td>
<td>Derivative of ventral mesentery</td>
</tr>
</tbody>
</table>
| **Hepatoduodenal ligament** | Liver to duodenum                      | Portal triad: proper hepatic artery, portal vein, common bile duct                    | Pringle maneuver—ligament may be compressed between thumb and index finger placed in omental foramen to control bleeding
Borders the omental foramen, which connects the greater and lesser sacs
Part of lesser omentum |
| **Gastrohepatic ligament** | Liver to lesser curvature of stomach    | Gastric vessels                                                                      | Separates greater and lesser sacs on the right
May be cut during surgery to access lesser sac
Part of lesser omentum |
| **Gastrocolic ligament**  | Greater curvature and transverse colon  | Gastroepiploic arteries                                                                | Part of greater omentum                                                                         |
| **Gastrosplenic ligament** | Greater curvature and spleen            | Short gastriics, left gastroepiploic vessels                                           | Separates greater and lesser sacs on the left
Part of greater omentum                                                                         |
| **Splenorenal ligament**  | Spleen to posterior abdominal wall      | Splenic artery and vein, tail of pancreas                                             |                                                                                                  |
Digestive tract anatomy

Layers of gut wall (inside to outside—MSMS):
- Mucosa—epithelium, lamina propria, muscularis mucosa
- Submucosa—includes Submucosal nerve plexus (Meissner), Secretes fluid
- Muscularis externa—includes Myenteric nerve plexus (Auerbach), Motility
- Serosa (when intraperitoneal), adventitia (when retroperitoneal)

Ulcers can extend into submucosa, inner or outer muscular layer. Erosions are in the mucosa only.

Frequencies of basal electric rhythm (slow waves):
- Stomach—3 waves/min
- Duodenum—12 waves/min
- Ileum—8–9 waves/min

Digestive tract histology

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>Nonkeratinized stratified squamous epithelium.</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastric glands.</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Villi and microvilli † absorptive surface. Brunner glands (HCO₃⁻-secreting cells of submucosa) and crypts of Lieberkühn (contain stem cells that replace enterocytes/goblet cells and Paneth cells that secrete defensins, lysozyme, and TNF).</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Plicae circulares (also present in distal duodenum) and crypts of Lieberkühn.</td>
</tr>
<tr>
<td>Ileum</td>
<td>Peyers patches (lymphoid aggregates in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn. Largest number of goblet cells in the small intestine.</td>
</tr>
<tr>
<td>Colon</td>
<td>Crypts of Lieberkühn but no villi; abundant goblet cells.</td>
</tr>
</tbody>
</table>
Arteries supplying GI structures are single and branch anteriorly.
Arteries supplying non-GI structures are paired and branch laterally and posteriorly.

**Superior mesenteric artery syndrome**—characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when SMA and aorta compress transverse (third) portion of duodenum. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).

Two areas of the colon have dual blood supply from distal arterial branches (“watershed regions”) susceptible in colonic ischemia:
- Splenic flexure—SMA and IMA
- Rectosigmoid junction—the last sigmoid arterial branch from the IMA and superior rectal artery

### Gastrointestinal blood supply and innervation

<table>
<thead>
<tr>
<th>EMBRYONIC GUT REGION</th>
<th>ARTERY</th>
<th>PARASYMPATHETIC INNERRATION</th>
<th>VERTEBRAL LEVEL</th>
<th>STRUCTURES SUPPLIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foregut</td>
<td>Celiac</td>
<td>Vagus</td>
<td>T12/L1</td>
<td>Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)</td>
</tr>
<tr>
<td>Midgut</td>
<td>SMA</td>
<td>Vagus</td>
<td>L1</td>
<td>Distal duodenum to proximal 2/3 of transverse colon</td>
</tr>
<tr>
<td>Hindgut</td>
<td>IMA</td>
<td>Pelvic</td>
<td>L3</td>
<td>Distal 1/3 of transverse colon to upper portion of rectum</td>
</tr>
</tbody>
</table>
Celiac trunk

Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the stomach.

Strong anastomoses exist between:
- Left and right gastroepiploics
- Left and right gastrics

Posterior duodenal ulcers penetrate gastroduodenal artery causing hemorrhage.

Anterior duodenal ulcers perforate into the anterior abdominal cavity, potentially leading to pneumoperitoneum.
Varices of gut, butt, and caput (medusae) are commonly seen with portal hypertension.

Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. Can precipitate hepatic encephalopathy.
**Pectinate (dentate) line**

Formed where endoderm (hindgut) meets ectoderm.

Above pectinate line—internal hemorrhoids, adenocarcinoma. Internal hemorrhoids receive visceral innervation and are therefore **not painful**.

Below pectinate line—external hemorrhoids, anal fissures, squamous cell carcinoma. External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed.

**Anal fissure**—tear in the anal mucosa below the Pectinate line. Pain while Pooping; blood on toilet Paper. Located Posteriorly because this area is Poorly Perfused. Associated with low-fiber diets and constipation.
The functional unit of the liver is made up of hexagonally arranged lobules surrounding the central vein with portal triads on the edges (consisting of a portal vein, hepatic artery, bile ducts, as well lymphatics). Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids. Kupffer cells, which are specialized macrophages, are located in the sinusoids (black arrows in A; 2 yellow arrows show hepatic venule). Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated). Responsible for hepatic fibrosis.

Zone I—periportal zone:
- Affected 1st by viral hepatitis
- Ingested toxins (eg, cocaine)

Zone II—intermediate zone:
- Yellow fever

Zone III—pericentral vein (centrilobular) zone:
- Affected 1st by ischemia
- High concentration of cytochrome P-450
- Most sensitive to metabolic toxins (eg, ethanol, CCl₄, halothane, rifampin)
- Site of alcoholic hepatitis
Gallstones that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder with painless jaundice (Courvoisier sign).

Cholangiography shows filling defects in gallbladder (blue arrow) and cystic duct (red arrow) A.

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**Femoral region**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral triangle</td>
<td>Contains femoral nerve, artery, vein.</td>
</tr>
<tr>
<td>Femoral sheath</td>
<td>Fascial tube 3–4 cm below inguinal ligament. Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve.</td>
</tr>
</tbody>
</table>

---

Lateral to medial: Nerve-Artery-Vein-Lymphatics.

You go from lateral to medial to find your NAVel.

Venous near the penis.
Inguinal canal

- Parietal peritoneum
- Extraperitoneal tissue
- Transversalis fascia
- Transversus abdominis muscle
- Internal oblique muscle
- Aponeurosis of external oblique muscle
- Inguinal ligament

Deep (internal) inguinal ring
Site of protrusion of indirect hernia

Superficial (external) inguinal ring

Inferior epigastric vessels

Abdominal wall
Site of protrusion of direct hernia

Medial umbilical ligament

Rectus abdominis muscle
Pyramidalis muscle
Conjoined tendon
Linea alba
Spermatic cord (ICE tie)

External spermatic fascia

External oblique

Internal spermatic fascia (transversalis fascia)
Cremasteric muscle and fascia (Internal oblique)

Internal spermatic fascia (external oblique)
Hernias

Protrusion of peritoneum through an opening, usually at a site of weakness. Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis). Complicated hernias can present with tenderness, erythema, fever.

Diaphragmatic hernia

Abdominal structures enter the thorax; may occur due to congenital defect of pleuroperitoneal membrane or from trauma. Commonly occurs on left side due to relative protection of right hemidiaphragm by liver. Most commonly a **hiatal hernia**, in which stomach herniates upward through the esophageal hiatus of the diaphragm.

**Sliding hiatal hernia**—gastroesophageal junction is displaced upward as gastric cardia slides into hiatus; “hourglass stomach.” Most common type.

**Paraesophageal hiatal hernia**—gastroesophageal junction is usually normal but gastric fundus protrudes into the thorax.

Indirect inguinal hernia

Goes through the internal (deep) inguinal ring, external (superficial) inguinal ring, and into the scrotum. Enters internal inguinal ring lateral to inferior epigastric vessels. Caused by failure of processus vaginalis to close (can form hydrocele). May be noticed in infants or discovered in adulthood. Much more common in males.

Direct inguinal hernia

Protrudes through the inguinal (Hesselbach) triangle. Bulges directly through parietal peritoneum medial to the inferior epigastric vessels but lateral to the rectus abdominis. Goes through the external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually occurs in older men due to an acquired weakness in the transversalis fascia.

Femoral hernia

Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in females, but overall inguinal hernias are the most common.

More likely to present with incarceration or strangulation than inguinal hernias.

**MDs don’t LIE:**

- Medial to inferior epigastric vessels = **Direct hernia**.
- Lateral to inferior epigastric vessels = **Indirect hernia**.

Inguinal (Hesselbach) triangle:

- Inferior epigastric vessels
- Lateral border of rectus abdominis
- Inguinal ligament
### Gastrointestinal regulatory substances

<table>
<thead>
<tr>
<th>REGULATORY SUBSTANCE</th>
<th>SOURCE</th>
<th>ACTION</th>
<th>REGULATION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrin</strong></td>
<td>G cells (antrum of stomach, duodenum)</td>
<td>↑ gastric H⁺ secretion</td>
<td>↑ by stomach distention/alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP)</td>
<td>↑ by chronic PPI use. ↑ in chronic atrophic gastritis (eg, <em>H pylori</em>). ↑↑ in Zollinger-Ellison syndrome (gastrinoma).</td>
</tr>
<tr>
<td><strong>Somatostatin</strong></td>
<td>D cells (pancreatic islets, GI mucosa)</td>
<td>↓ gastric acid and pepsinogen secretion</td>
<td>↑ by acid ↓ by vagal stimulation</td>
<td>Inhibits secretion of various hormones (encourages somatostasis). Octreotide is an analog used to treat acromegaly, carcinoid syndrome, and variceal bleeding.</td>
</tr>
<tr>
<td><strong>Cholecystokinin</strong></td>
<td>I cells (duodenum, jejunum)</td>
<td>↑ pancreatic secretion</td>
<td>↑ by fatty acids, amino acids</td>
<td>Acts on neural muscarinic pathways to cause pancreatic secretion.</td>
</tr>
<tr>
<td><strong>Secretin</strong></td>
<td>S cells (duodenum)</td>
<td>↑ pancreatic HCO₃⁻ secretion</td>
<td>↑ by acid fatty acids in lumen of duodenum</td>
<td>↑ HCO₃⁻ neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function.</td>
</tr>
<tr>
<td><strong>Glucose-dependent insulinoitropic peptide</strong></td>
<td>K cells (duodenum, jejunum)</td>
<td>Exocrine: ↓ gastric H⁺ secretion Endocrine: ↑ insulin release</td>
<td>↑ by fatty acids, amino acids, oral glucose</td>
<td>Also known as gastric inhibitory peptide (GIP). Oral glucose load leads to ↑ insulin compared to IV equivalent due to GIP secretion.</td>
</tr>
<tr>
<td><strong>Motilin</strong></td>
<td>Small intestine</td>
<td>Produces migrating motor complexes (MMCs)</td>
<td>↑ in fasting state</td>
<td>Motilin receptor agonists (eg, erythromycin) are used to stimulate intestinal peristalsis.</td>
</tr>
<tr>
<td><strong>Vasoactive intestinal polypeptide</strong></td>
<td>Parasympathetic ganglia in sphincters, gallbladder, small intestine</td>
<td>↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters</td>
<td>↑ by distention and vagal stimulation ↓ by adrenergic input</td>
<td>VιPοmα—non-α, non-β islet cell pancreatic tumor that secretes VIP. Watery Diarrhea, Hypokalemia, and Achlorhydria (WDHA syndrome).</td>
</tr>
<tr>
<td><strong>Nitric oxide</strong></td>
<td>↓ smooth muscle relaxation, including lower esophageal sphincter (LES)</td>
<td></td>
<td></td>
<td>Loss of NO secretion is implicated in ↑ LES tone of achalasia.</td>
</tr>
<tr>
<td><strong>Ghrelin</strong></td>
<td>Stomach</td>
<td>↑ appetite</td>
<td>↑ in fasting state ↓ by food</td>
<td>↑ in Prader-Willi syndrome. ↓ after gastric bypass surgery.</td>
</tr>
</tbody>
</table>
### Gastrointestinal secretory products

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SOURCE</th>
<th>ACTION</th>
<th>REGULATION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrinsic factor</strong></td>
<td>Parietal cells (stomach)</td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;–binding protein (required for B&lt;sub&gt;12&lt;/sub&gt; uptake in terminal ileum)</td>
<td>Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.</td>
<td></td>
</tr>
<tr>
<td><strong>Gastric acid</strong></td>
<td>Parietal cells (stomach)</td>
<td>↓ stomach pH</td>
<td>↑ by histamine, vagal stimulation (ACh), gastrin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ by somatostatin, GIP, prostaglandin, secretin</td>
<td></td>
</tr>
<tr>
<td><strong>Pepsin</strong></td>
<td>Chief cells (stomach)</td>
<td>Protein digestion</td>
<td>↑ by vagal stimulation (ACh), local acid</td>
<td>Pepsinogen (inactive) is converted to pepsin (active) in the presence of H&lt;sup&gt;+&lt;/sup&gt;.</td>
</tr>
<tr>
<td><strong>Bicarbonate</strong></td>
<td>Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum)</td>
<td>Neutralizes acid</td>
<td>↑ by pancreatic and biliary secretion with secretin</td>
<td>Trapped in mucus that covers the gastric epithelium.</td>
</tr>
</tbody>
</table>
Gastrin stimulates acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

### Pancreatic secretions

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>ROLE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-amylase</td>
<td>Starch digestion</td>
<td>Secreted in active form</td>
</tr>
<tr>
<td>Lipases</td>
<td>Fat digestion</td>
<td></td>
</tr>
<tr>
<td>Proteases</td>
<td>Protein digestion</td>
<td>Includes trypsin, chymotrypsin, elastase, carboxypeptidases. Secreted as proenzymes also known as zymogens</td>
</tr>
<tr>
<td>Trypsinogen</td>
<td>Converted to active enzyme trypsin by activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop)</td>
<td>Converted to trypsin by enterokinase/enteropeptidase, a brush-border enzyme on duodenal and jejunal mucosa</td>
</tr>
</tbody>
</table>

### Carbohydrate absorption

Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 (Na⁺ dependent). Fructose is taken up via facilitated diffusion by GLUT5. All are transported to blood by GLUT2. D-xylose absorption test: distinguishes GI mucosal damage from other causes of malabsorption.
**Vitamin/mineral absorption**

<table>
<thead>
<tr>
<th>Vitamin/mineral</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron</strong></td>
<td>Absorbed as Fe$^{2+}$ in duodenum.</td>
</tr>
<tr>
<td><strong>Folate</strong></td>
<td>Absorbed in small bowel.</td>
</tr>
<tr>
<td><strong>B$_12$</strong></td>
<td>Absorbed in terminal ileum along with bile salts, requires intrinsic factor.</td>
</tr>
</tbody>
</table>

**Iron Fist, Bro**
Clinically relevant in patients with small bowel disease or after resection.

---

**Peyer patches**

Unencapsulated lymphoid tissue found in lamina propria and submucosa of ileum. Contain specialized M cells that sample and present antigens to immune cells. B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Think of IgA, the Intra-gut Antibody. And always say “secretory IgA.”

---

**Bile**

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol 7α-hydroxylase catalyzes rate-limiting step of bile acid synthesis. Functions:

- Digestion and absorption of lipids and fat-soluble vitamins
- Cholesterol excretion (body’s 1º means of eliminating cholesterol)
- Antimicrobial activity (via membrane disruption)

 absorption of enteric bile salts at distal ileum (as in short bowel syndrome, Crohn disease) prevents normal fat absorption. Calcium, which normally binds oxalate, binds fat instead, so free oxalate is absorbed by gut → ↑ frequency of calcium oxalate kidney stones.
**Bilirubin**

Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin. Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile. Direct bilirubin—conjugated with glucuronic acid; water soluble. Indirect bilirubin—unconjugated; water insoluble.
Gastrointestinal—Pathology

Sialolithiasis

Stone(s) in salivary gland duct. Can occur in 3 major salivary glands (parotid, submandibular, sublingual). Single stone more common in submandibular gland (Wharton duct).

Presents as recurrent pre-/periprandial pain and swelling in affected gland.

Caused by dehydration or trauma.

Treat conservatively with NSAIDs, gland massage, warm compresses, sour candies (to promote salivary flow).

Sialadenitis

Inflammation of salivary gland due to obstruction, infection, or immune-mediated mechanisms.

Salivary gland tumors

Most commonly benign and in parotid gland. Tumors in smaller glands more likely malignant.

Typically present as painless mass/swelling. Facial pain or paralysis suggests malignant involvement of CN VII.

- Pleomorphic adenoma (benign mixed tumor)—most common salivary gland tumor.

  Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively. May undergo malignant transformation.

- Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous malignant components.

- Warthin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers. Typically found in smokers. Bilateral in 10%; multifocal in 10%. “Warriors from Germany love smoking.”

Achalasia

Failure of LES to relax due to loss of myenteric (Auerbach) plexus due to loss of postganglionic inhibitory neurons (which contain NO and VIP).

Manometry findings include uncoordinated or absent peristalsis with high LES resting pressure → progressive dysphagia to solids and liquids (vs obstruction—solids only). Barium swallow shows dilated esophagus with an area of distal stenosis (“bird’s beak”).

Associated with 1 risk of esophageal cancer.

A-chalasia = absence of relaxation.

2° achalasia (pseudoachalasia) may arise from Chagas disease (T cruzi infection) or extraesophageal malignancies (mass effect or paraneoplastic).
### Esophageal pathologies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boerhaave syndrome</strong></td>
<td>Transmural, usually distal esophageal rupture with pneumomediastinum (arrows in A) due to violent retching. Subcutaneous emphysema may be due to dissecting air (crepitus may be felt in the neck region or chest wall). Surgical emergency.</td>
</tr>
<tr>
<td><strong>Eosinophilic esophagitis</strong></td>
<td>Infiltration of eosinophils in the esophagus often in atopic patients. Food allergens → dysphagia, food impaction. Esophageal rings and linear furrows often seen on endoscopy. Typically unresponsive to GERD therapy.</td>
</tr>
<tr>
<td><strong>Esophageal strictures</strong></td>
<td>Associated with caustic ingestion and acid reflux.</td>
</tr>
<tr>
<td><strong>Esophageal varices</strong></td>
<td>Dilated submucosal veins (red arrows in B C) in lower ⅔ of esophagus 2° to portal hypertension. Common in cirrhotics, may be source of life-threatening hematemesis.</td>
</tr>
<tr>
<td><strong>Esophagitis</strong></td>
<td>Associated with reflux, infection in immunocompromised (Candida: white pseudomembrane; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or pill esophagitis (eg, bisphosphonates, tetracycline, NSAIDs, iron, and potassium chloride).</td>
</tr>
<tr>
<td><strong>Gastroesophageal reflux disease</strong></td>
<td>Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma. Transient decreases in LES tone.</td>
</tr>
<tr>
<td><strong>Mallory-Weiss syndrome</strong></td>
<td>Partial-thickness mucosal lacerations at gastroesophageal junction due to severe vomiting. Often presents with hematemesis. Usually found in alcoholics and bulimics.</td>
</tr>
<tr>
<td><strong>Plummer-Vinson syndrome</strong></td>
<td>Triad of Dysphagia, Iron deficiency anemia, and Esophageal webs. May be associated with glossitis. Increased risk of esophageal squamous cell carcinoma (“Plumbers DIE”).</td>
</tr>
<tr>
<td><strong>Sclerodermal esophageal dysmotility</strong></td>
<td>Esophageal smooth muscle atrophy → ↓ LES pressure and dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome.</td>
</tr>
</tbody>
</table>

![Image A](image-a.png)  ![Image B](image-b.png)  ![Image C](image-c.png)
Barrett esophagus

Specialized intestinal metaplasia — replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [stained blue]) in distal esophagus. Due to chronic gastroesophageal reflux disease (GERD). Associated with ↑ risk of esophageal adenocarcinoma.

Esophageal cancer

Typically presents with progressive dysphagia (first solids, then liquids) and weight loss; poor prognosis.

<table>
<thead>
<tr>
<th>CANCER</th>
<th>PART OF ESOPHAGUS AFFECTED</th>
<th>RISK FACTORS</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>Upper 2/3</td>
<td>Alcohol, hot liquids, caustic strictures, smoking, achalasia</td>
<td>More common worldwide</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Lower 1/3</td>
<td>Chronic GERD, Barrett esophagus, obesity, smoking, achalasia</td>
<td>More common in America</td>
</tr>
</tbody>
</table>
**Gastritis**

**Acute gastritis**

- Erosions can be caused by:
  - NSAIDs → PGE₂ → ↓ gastric mucosa protection
  - Burns (Curling ulcer) — hypovolemia → mucosal ischemia
  - Brain injury (Cushing ulcer) — ↑ vagal stimulation → ↑ ACh → ↑ H⁺ production

  Especially common among alcoholics and patients taking daily NSAIDs (eg, patients with rheumatoid arthritis).

  **Burned by the Curling iron.**

  Always **Cushion the brain.**

**Chronic gastritis**

- Mucosal inflammation, often leading to atrophy (hypochlorhydria → hypergastrinemia) and intestinal metaplasia (↑ risk of gastric cancers).

### H pylori

- Most common. ↑ risk of peptic ulcer disease, MALT lymphoma.

### Autoimmune

- Autoantibodies to parietal cells and intrinsic factor. ↑ risk of pernicious anemia.

Affects antrum first and spreads to body of stomach.

Affects body/fundus of stomach.

**Ménétrier disease**


  Presents with epigastric pain, anorexia, weight loss, vomiting, edema (due to protein loss).

**Gastric cancer**

- Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoïd (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, abdominal pain, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign. Associated with blood type A.

  - Intestinal — associated with H pylori; dietary nitrosamines (smoked foods), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.

  - Diffuse — not associated with H pylori; signet ring cells (mucin-filled cells with peripheral nuclei) A; stomach wall grossly thickened and leathery (limitis plastica).

  Virchow node — involvement of left supravacuicular node by metastasis from stomach.

  Krukenberg tumor — bilateral metastases to ovaries. Abundant mucin-secreting, signet ring cells.

  Sister Mary Joseph nodule — subcutaneous periumbilical metastasis.
Peptic ulcer disease

<table>
<thead>
<tr>
<th></th>
<th>Gastric ulcer</th>
<th>Duodenal ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAIN</strong></td>
<td>Can beGreater with meals—weight loss</td>
<td>Decreases with meals—weight gain</td>
</tr>
<tr>
<td><strong>H. PYLORI INFECTION</strong></td>
<td>~ 70%</td>
<td>~ 90%</td>
</tr>
<tr>
<td><strong>MECHANISM</strong></td>
<td>↓ mucosal protection against gastric acid</td>
<td>↑ mucosal protection or ↑ gastric acid secretion</td>
</tr>
<tr>
<td><strong>OTHER CAUSES</strong></td>
<td>NSAIDs</td>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td><strong>RISK OF CARCINOMA</strong></td>
<td>↑</td>
<td>Generally benign</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td>Biopsy margins to rule out malignancy</td>
<td>Hypertrophy of Brunner glands</td>
</tr>
</tbody>
</table>

Ulcer complications

**Hemorrhage**

Gastric, duodenal (posterior > anterior). Most common complication. Ruptured gastric ulcer on the lesser curvature of stomach → bleeding from left gastric artery. An ulcer on the posterior wall of duodenum → bleeding from gastroduodenal artery.

**Obstruction**

Pyloric channel, duodenal.

**Perforation**

Duodenal (anterior > posterior). May see free air under diaphragm with referred pain to the shoulder via irritation of phrenic nerve.
### Malabsorption Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Celiac Disease</strong></td>
<td>Gluten-sensitive enteropathy, celiac sprue. Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat) and steatorrhea. Associated with HLA-DQ2, HLA-DQ8, northern European descent, dermatitis herpetiformis, and bone density. Findings: IgA anti-tissue transglutaminase (IgA tTG), anti-endothelial, anti-deamidated gliadin peptide antibodies; villous atrophy (arrow in A shows blunting), crypt hyperplasia (double arrows in A), and intraepithelial lymphocytosis. Moderately high risk of malignancy (eg, T-cell lymphoma).</td>
</tr>
<tr>
<td><strong>Lactose Intolerance</strong></td>
<td>Lactase deficiency. Normal-appearing villi, except when 2nd to injury at tips of villi (eg, viral enteritis). Osmotic diarrhea with ↓ stool pH (colonic bacteria ferment lactose). Lactase hydrogen breath test: ✗ for lactose malabsorption if post-lactose breath hydrogen value rises &gt; 20 ppm compared with baseline.</td>
</tr>
<tr>
<td><strong>Pancreatic Insufficiency</strong></td>
<td>Due to chronic pancreatitis, cystic fibrosis, and obstructing cancer. Causes malabsorption of fat and fat-soluble vitamins (A, D, E, K) as well as vitamin B12. ↓ duodenal pH (bicarbonate) and fecal elastase.</td>
</tr>
<tr>
<td><strong>Tropical Sprue</strong></td>
<td>Similar findings as celiac sprue (affects small bowel), but responds to antibiotics. Cause is unknown, but seen in residents of or recent visitors to tropics. ↓ mucosal absorption affecting duodenum and jejunum but can involve ileum with time. Associated with megaloblastic anemia due to folate deficiency and, later, B12 deficiency.</td>
</tr>
<tr>
<td><strong>Whipple Disease</strong></td>
<td>Infection with <em>Tropheryma whippelii</em> (intracellular gram ✗); PAS ✗ foamy macrophages in intestinal lamina propria B and mesenteric nodes. Cardiac symptoms, arthralgias, and neurologic symptoms are common. Diarrhea/steatorrhea occur later in disease course. Most common in older men. Foamy Whipped cream in a CAN.</td>
</tr>
</tbody>
</table>
### Inflammatory bowel disease

<table>
<thead>
<tr>
<th>Crohn disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOCATION</strong></td>
<td>Any portion of the GI tract, usually the terminal ileum and colon. <em>Skip</em> lesions, <em>rectal sparing</em>.</td>
</tr>
<tr>
<td><strong>GROSS MORPHOLOGY</strong></td>
<td>Transmural inflammation $\rightarrow$ fistulas. A <em>Cobblestone</em> mucosa, creeping <em>fat</em>, bowel wall thickening (“string sign” on barium swallow x-ray <em>A</em>), linear ulcers, fissures.</td>
</tr>
<tr>
<td><strong>MICROSCOPIC MORPHOLOGY</strong></td>
<td>Noncaseating <em>granulomas</em> and lymphoid aggregates. Th1 mediated.</td>
</tr>
<tr>
<td><strong>COMPLICATIONS</strong></td>
<td>Malabsorption/malnutrition, colorectal cancer († risk with pancolitis).</td>
</tr>
<tr>
<td><strong>INTESTINAL MANIFESTATION</strong></td>
<td>Diarrhea that may or may not be bloody.</td>
</tr>
<tr>
<td><strong>EXTRAINTESTINAL MANIFESTATIONS</strong></td>
<td>Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis). A <em>Kidney stones</em> (usually calcium oxalate), gallstones. May be for anti-Saccharomyces cerevisiae antibodies (ASCA). A <em>1° sclerosing cholangitis</em>. Associated with <em>p-ANCA</em>.</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), infliximab, adalimumab. 5-aminosalicylic preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.</td>
</tr>
<tr>
<td><strong>For Crohn, think of a fat <em>granmy</em> and an old <em>crone</em> skipping down a <em>cobblestone</em> road away from the <em>wreck</em> (rectal sparing).</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Ulcerative colitis causes ULCCERS:**
- Ulcers
- Large intestine
- Continuous, Colorectal carcinoma, Crypt abscesses
- Extends proximally
- Red diarrhea
- Sclerosing cholangitis
Irritable bowel syndrome

Recurrent abdominal pain associated with ≥ 2 of the following:
- Related to defecation
- Change in stool frequency
- Change in form (consistency) of stool
No structural abnormalities. Most common in middle-aged women. Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted.
First-line treatment is lifestyle modification and dietary changes.

Appendicitis

Acute inflammation of the appendix (yellow arrows in A), can be due to obstruction by fecalith (red arrow in A) (in adults) or lymphoid hyperplasia (in children).
Initial diffuse periumbilical pain migrates to McBurney point (1/3 the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate → peritonitis; may elicit psoas, obturator, and Rovsing signs, guarding and rebound tenderness on exam.
Differential: diverticulitis (elderly), ectopic pregnancy (use β-hCG to rule out), pseudoappendicitis.
Treatment: appendectomy.

Diverticula of the GI tract

| Diverticulum | “True” diverticulum—all gut wall layers outpouch (eg, Meckel).
| False diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa. |
| Diverticulosis | Many false diverticula of the colon (commonly sigmoid. Common (in ~ 50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with obesity and diets low in fiber, high in total fat/red meat. |
| Diverticulitis | Often asymptomatic or associated with vague discomfort. Complications include diverticular bleeding (painless hematochezia), diverticulitis. |

Inflammation of diverticula with wall thickening classically causing LLQ pain, fever, leukocytosis. Treat with antibiotics.
Complications: abscess, fistula (colovesical fistula → pneumaturia), obstruction (inflammatory stenosis), perforation (→ peritonitis).
**Zenker diverticulum**

Pharyngoesophageal false diverticulum. Esophageal dysmotility causes herniation of mucosal tissue at Killian triangle between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor. Presenting symptoms: dysphagia, obstruction, gurgling, aspiration, foul breath, neck mass. Most common in elderly males.

**Elder MIKE has bad breath.**
- Elderly
- Males
- Inferior pharyngeal constrictor
- Killian triangle
- Esophageal dysmotility
- Halitosis

**Meckel diverticulum**

True diverticulum. Persistence of the vitelline (omphalomesenteric) duct. May contain ectopic acid–secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause hematochezia/melena (less commonly), RLQ pain, intussusception, volvulus, or obstruction near terminal ileum.

Contrast with omphalomesenteric cyst = cystic dilation of vitelline duct.
Diagnosis: pertechnetate study for uptake by heterotopic gastric mucosa.

**Hirschsprung disease**

Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in distal segment of colon. Due to failure of neural crest cell migration. Associated with mutations in RET.

Presents with bilious emesis, abdominal distention, and failure to pass meconium within 48 hours → chronic constipation. Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a "transition zone."

Risk ↑ with Down syndrome.
Explosive expulsion of feces (squirt sign)
- empty rectum on digital exam.
Diagnosed by absence of ganglionic cells on rectal suction biopsy.
Treatment: resection.
**RET** mutation in the **REcTum**.
**Malrotation**

Anomaly of midgut rotation during fetal development → improper positioning of bowel (small bowel clumped on the right side), formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

**Volvulus**

Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. Can occur throughout the GI tract. Midgut volvulus more common in infants and children. Sigmoid volvulus (coffee bean sign on x-ray) more common in elderly.

**Intussusception**

Telescoping of proximal bowel segment into a distal segment, commonly at ileocecal junction. Compromised blood supply → intermittent abdominal pain often with “currant jelly” stools. Patient may draw legs to chest to ease pain. Exam may reveal sausage-shaped mass. Ultrasound shows “target sign.” Often due to a lead point, but can be idiopathic. Most common pathologic lead point is a Meckel diverticulum (children) or intraluminal mass/tumor (adults). Majority of cases occur in children; unusual in adults.

May be associated with rotavirus vaccine, Henoch-Schönlein purpura, and recent viral infection (eg, adenovirus; Peyer patch hypertrophy creates lead point).
Other intestinal disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mesenteric ischemia</td>
<td>Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis → abdominal pain out of proportion to physical findings. May see red “currant jelly” stools.</td>
</tr>
<tr>
<td>Chronic mesenteric ischemia</td>
<td>“Intestinal angina”: atherosclerosis of celiac artery, SMA, or IMA → intestinal hypoperfusion → postprandial epigastric pain → food aversion and weight loss.</td>
</tr>
<tr>
<td>Adhesion</td>
<td>Fibrous band of scar tissue; commonly forms after surgery. Most common cause of small bowel obstruction, demonstrated by multiple dilated small bowel loops on x-ray (arrows in C).</td>
</tr>
<tr>
<td>Ileus</td>
<td>Intestinal hypomotility without obstruction → constipation and flatus; distended/tympanic abdomen with bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility).</td>
</tr>
<tr>
<td>Meconium ileus</td>
<td>In cystic fibrosis, meconium plug obstructs intestine, preventing stool passage at birth.</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (primarily colonic) with possible perforation, which can lead to pneumatosis intestinalis, free air in abdomen, portal venous gas.</td>
</tr>
</tbody>
</table>
Colonic polyps

- Growths of tissue within the colon. May be neoplastic or non-neoplastic. Grossly characterized as flat, sessile, or pedunculated (on a stalk) on the basis of protrusion into colonic lumen. Generally classified by histologic type.

### Histologic Type

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Histologic Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally non-neoplastic</td>
<td>Solitary lesions do not have significant risk of transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.</td>
</tr>
<tr>
<td>Small, usually &lt; 5 mm. Look similar to normal mucosa. Clinically insignificant.</td>
<td>Hamartomatous polyps</td>
</tr>
<tr>
<td>Due to mucosal erosion in inflammatory bowel disease.</td>
<td>Inflammatory pseudopolyps</td>
</tr>
<tr>
<td>May include lipomas, leiomyomas, fibromas, and other lesions.</td>
<td>Submucosal polyps</td>
</tr>
<tr>
<td>Most common; generally smaller and predominantly located in rectosigmoid region. Occasionally evolves into serrated polyps and more advanced lesions.</td>
<td>Hyperplastic polyps</td>
</tr>
</tbody>
</table>

### Malignant potential

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adenomatous polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplastic, via chromosomal instability pathway with mutations in APC and KRAS. Tubular histology has less malignant potential than villous (&quot;villous histology is villainous&quot;); tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding.</td>
<td></td>
</tr>
<tr>
<td>Premalignant. Characterized by CpG island methylator phenotype (CIMP; cytosine base followed by guanine, linked by a phosphodiester bond). Defect may silence MMR gene (DNA mismatch repair) expression. Mutations lead to microsatellite instability and mutations in BRAF. “Sawtooth” pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.</td>
<td>Serrated polyps</td>
</tr>
</tbody>
</table>

### Polyposis syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Autosomal dominant mutation of APC tumor suppressor gene on chromosome 5q21. 2-hit hypothesis. Thousands of polyps arise starting after puberty; pancolonic; always involves rectum. Prophylactic colectomy or else 100% progress to CRC.</td>
</tr>
<tr>
<td>Gardner syndrome</td>
<td>FAP + osseous and soft tissue tumors, congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth.</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>FAP/Lynch syndrome + malignant CNS tumor (eg, medulloblastoma, glioma). Turcot = Turban.</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented mouth, lips, hands, genitalia. Associated with 1 risk of breast and GI cancers (eg, colorectal, stomach, small bowel, pancreatic).</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome</td>
<td>Autosomal dominant syndrome in children (typically &lt; 5 years old) featuring numerous hamartomatous polyps in the colon, stomach, small bowel. Associated with 1 risk of CRC.</td>
</tr>
</tbody>
</table>
Lynch syndrome
Previously known as hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of DNA mismatch repair genes with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

Colorectal cancer

**Epidemiology**
Most patients are > 50 years old. ~ 25% have a family history.

**Risk Factors**
Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.

**Presentation**

**Diagnosis**
Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screen low-risk patients starting at age 50 with colonoscopy. Alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), and CT colonography. Patients with a first-degree relative who has colon cancer should be screened via colonoscopy at age 40, or starting 10 years prior to their relative’s presentation. Patients with IBD have a distinct screening protocol. "Apple core” lesion seen on barium enema x-ray. CEA tumor marker: good for monitoring recurrence, should not be used for screening.
**Molecular pathogenesis of colorectal cancer**

Chromosomal instability pathway: mutations in APC cause FAP and most sporadic CRC (via adenoma-carcinoma sequence; firing order of events is AK-53). Microsatellite instability pathway: mutations or methylation of mismatch repair genes (eg, MLH1) cause Lynch syndrome and some sporadic CRC (via serrated polypl pathway). Overexpression of COX-2 has been linked to colorectal cancer, NSAIDs may be chemopreventive.

**Cirrhosis and portal hypertension**

**Cirrhosis**—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (red arrows in A; white arrows show splenomegaly) disrupt normal architecture of liver; ↑ risk for hepatocellular carcinoma (HCC). Etiologies include alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

**Portal hypertension**—↑ pressure in portal venous system. Etiologies include cirrhosis (most common cause in Western countries), vascular obstruction (eg, portal vein thrombosis, Budd-Chiari syndrome), schistosomiasis.
Spontaneous bacterial peritonitis

Also known as 1° bacterial peritonitis. Common and potentially fatal bacterial infection in patients with cirrhosis and ascites. Often asymptomatic, but can cause fevers, chills, abdominal pain, ileus, or worsening encephalopathy. Commonly caused by aerobic gram — organisms (eg, E coli, Klebsiella) or less commonly gram + Streptococcus.

Diagnosis: paracentesis with ascitic fluid absolute neutrophil count (ANC) > 250 cells/mm³. Empiric first-line treatment is 3rd generation cephalosporin (eg, cefotaxime).

Serum markers of liver pathology

<table>
<thead>
<tr>
<th>ENZYMES RELEASED IN LIVER DAMAGE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase</td>
<td>↑ in most liver disease: ALT &gt; AST</td>
</tr>
<tr>
<td>and alanine aminotransferase</td>
<td>↑ in alcoholic liver disease: AST &gt; ALT</td>
</tr>
<tr>
<td></td>
<td>AST &gt; ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>↑ in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease</td>
</tr>
<tr>
<td>γ-glutamyl transpeptidase</td>
<td>↑ in various liver and biliary diseases (just as ALP can), but not in bone disease; associated with alcohol use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FUNCTIONAL LIVER MARKERS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>↑ in various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis</td>
</tr>
<tr>
<td>Albumin</td>
<td>↑ in advanced liver disease (marker of liver’s biosynthetic function)</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>↑ in advanced liver disease (↑ production of clotting factors, thereby measuring the liver’s biosynthetic function)</td>
</tr>
<tr>
<td>Platelets</td>
<td>↑ in advanced liver disease (↑ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration)</td>
</tr>
</tbody>
</table>

Reye syndrome

Rare, often fatal childhood hepatic encephalopathy. Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty change), hypoglycemia, vomiting, hepatomegaly, coma. Associated with viral infection (especially VZV and influenza) that has been treated with aspirin. Mechanism: aspirin metabolites ↑ β-oxidation by reversible inhibition of mitochondrial enzymes. Avoid aspirin in children, except in those with Kawasaki disease.

Reye of sunSHINE:

- Steatosis of liver/hepatocytes
- Hypoglycemia/Hepatomegaly
- Infection (VZV, influenza)
- Not awake (coma)
- Encephalopathy
### Alcoholic liver disease

#### Hepatic steatosis
Macrovesicular fatty change that may be reversible with alcohol cessation.

#### Alcoholic hepatitis
Requires sustained, long-term consumption.
- Swollen and necrotic hepatocytes with neutrophilic infiltration.
- Mallory bodies (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).

Make AST with alcohol: $\text{AST} > \text{ALT}$ (ratio usually $> 2:1$).

#### Alcoholic cirrhosis
Final and usually irreversible form.
- Sclerosis around central vein (arrows in image) may be seen in early disease.
- Regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal hypertension and end-stage liver disease.

### Nonalcoholic fatty liver disease
- Metabolic syndrome (insulin resistance);
- Obesity → fatty infiltration of hepatocytes → cellular “ballooning” and eventual necrosis.
- May cause cirrhosis and HCC. Independent of alcohol use.

$$\text{ALT} > \text{AST} \quad \text{(Lipids)}$$

### Hepatic encephalopathy
- Cirrhosis → portosystemic shunts → ↑ NH$_4^+$ metabolism → neuropsychiatric dysfunction.
- Reversible neuropsychiatric dysfunction ranging from disorientation/asterixis (mild) to difficult arousal or coma (severe).
- Triggers:
  * ↑ NH$_4^+$ production and absorption (due to dietary protein, GI bleed, constipation, infection).
  * ↓ NH$_4^+$ removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).
- Treatment: lactulose (↑ NH$_4^+$ generation) and rifaximin or neomycin (↓ NH$_4^+$ producing gut bacteria).
Hepatocellular carcinoma/hepatoma

Most common 1° malignant tumor of liver in adults. Associated with HBV (+/− cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and nonalcoholic fatty liver disease, autoimmune disease, hemochromatosis, α1-antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from *Aspergillus*). May lead to Budd-Chiari syndrome.

Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. Spreads hematogenously.

Diagnosis: 1 α-fetoprotein; ultrasound or contrast CT/MRI, biopsy.

Other liver tumors

Cavernous hemangioma

Most common benign liver tumor typically occurs at age 30–50 years. Biopsy contraindicated because of risk of hemorrhage.

Hepatic adenoma

Rare, benign liver tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock).

Angiosarcoma

Malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.

Metastases

GI malignancies, breast and lung cancer. Most common overall; metastases are rarely solitary.

Budd-Chiari syndrome

Thrombosis or compression of hepatic veins with centrilobular congestion and necrosis → congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure). Absence of JVD. Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC. May cause nutmeg liver (notted appearance).

α1-antitrypsin deficiency

Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS + globules in liver. Codominant trait. Often presents in young patients with liver damage and dyspnea without a history of smoking.

In lungs, 1 α1-antitrypsin → uninhibited elastase in alveoli → 1 elastic tissue → panacinar emphysema.
Jaundice

Abnormal yellowing of the skin and/or sclera due to bilirubin deposition. Hyperbilirubinemia 2° to 1 production or disposition (impaired hepatic uptake, conjugation, excretion).

HOT Liver—common causes of ↑ bilirubin level:
- Hemolysis
- Obstruction
- Tumor
- Liver disease

| Unconjugated (indirect) hyperbilirubinemia | Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome. |
| Conjugated (direct) hyperbilirubinemia | Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke. Biliary tract disease: * 1° sclerosing cholangitis * 1° biliary cholangitis Excretion defect: Dubin-Johnson syndrome, Rotor syndrome. |
| Mixed (direct and indirect) hyperbilirubinemia | Hepatitis, cirrhosis. |

Physiologic neonatal jaundice

At birth, immature UDP-glucuronosyltransferase → unconjugated hyperbilirubinemia → jaundice/ kernicterus (deposition of unconjugated, lipid-soluble bilirubin in the brain, particularly basal ganglia).

Occurs after first 24 hours of life and usually resolves without treatment in 1–2 weeks. Treatment: phototherapy (non-UV) isomerizes unconjugated bilirubin to water-soluble form.
### Hereditary hyperbilirubinemas

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Gilbert syndrome</strong></td>
<td>Mildly ↓ UDP-glucuronosyltransferase conjugation and impaired bilirubin uptake. Asymptomatic or mild jaundice usually with stress, illness, or fasting. ↑ unconjugated bilirubin without overt hemolysis.</td>
<td>Relatively common, benign condition. Go! (asymptomatic/benign)</td>
</tr>
<tr>
<td><strong>2 Crigler-Najjar syndrome, type I</strong></td>
<td>Absent UDP-glucuronosyltransferase. Presents early in life; patients die within a few years. Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin. Treatment: plasmapheresis and phototherapy. Liver transplant is curative.</td>
<td>Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis. No-go! (symptomatic)</td>
</tr>
<tr>
<td><strong>3 Dubin-Johnson syndrome</strong></td>
<td>Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black (Dark) liver. Benign.</td>
<td>Rotor syndrome is similar, but milder in presentation without black (Regular) liver. Due to impaired hepatic uptake and excretion.</td>
</tr>
</tbody>
</table>

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**Diagram:**
- **HEPATIC SINUSOID**
- **Circulating bilirubin** (albumin bound; unconjugated, water insoluble)
- **Hemoglobin**
- **Kupffer cell** (macrophage)
- **Endothelial cell**
- **Space of Disse**
- **Hepatocyte**
- **BILIRUBIN UPTAKE**
- **Unconjugated bilirubin**
- **Conjugation**
- **Conjugated bilirubin** (bilirubin diglucuronide, water soluble)
- **INTRACELLULAR TRANSPORT**
- **Bile canaliculus lumen**
- **Bile flow**
- **Obstructive jaundice (downstream)**
- **Stasis**

---

**Key Points:**
- Gilbert syndrome: Milder, UDP-glucuronosyltransferase deficiency, asymptomatic or mild jaundice.
- Crigler-Najjar syndrome, type I: Absent UDP-glucuronosyltransferase, early onset, jaundice, kernicterus, fatal if untreated.
- Dubin-Johnson syndrome: Conjugated hyperbilirubinemia due to liver excretion defect, black liver, benign.
- Rotor syndrome: Similar to Dubin-Johnson but milder presentation and response to treatment.

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**Notes:**
- All autosomal recessive.

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**Treatment Options:**
- Plasmapheresis and phototherapy for Crigler-Najjar syndrome and Dubin-Johnson syndrome.
- Phenobarbital for Crigler-Najjar syndrome type II.
- Liver transplant for Crigler-Najjar syndrome type I.

---

**References:**
**Wilson disease (hepatolenticular degeneration)**

Autosomal recessive mutations in hepatocyte copper-transporting ATPase (ATP7B gene; chromosome 13) ➔ ↓ copper incorporation into apoceruloplasmin and excretion into bile ➔ ↓ serum ceruloplasmin. Copper accumulates, especially in liver, brain, cornea, kidneys; ↑ urine copper.

Presents before age 40 with liver disease (eg, hepatitis, acute liver failure, cirrhosis), neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism), psychiatric disease, Kayser-Fleischer rings (deposits in Descemet membrane of cornea), hemolytic anemia, renal disease (eg, Fanconi syndrome).

Treatment: chelation with penicillamine or trientine, oral zinc.

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**Hemochromatosis**

Autosomal recessive. C282Y mutation > H63D mutation on HFE gene, located on chromosome 6; associated with HLA-A3. Leads to abnormal iron sensing and ↑ intestinal absorption (↑ ferritin, ↑ iron, ↓ TIBC ➔ ↑ transferrin saturation). Iron overload can also be 2nd to chronic transfusion therapy (eg, β-thalassemia major). Iron accumulates, especially in liver, pancreas, skin, heart, pituitary, joints. Hemosiderin (iron) can be identified on liver MRI or biopsy with Prussian blue stain.

Presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in women. Classic triad of cirrhosis, diabetes mellitus, skin pigmentation (“bronze diabetes”). Also causes restrictive cardiomyopathy (classic) or dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death.

Treatment: repeated phlebotomy, chelation with deferasirox, deferoxamine, oral deferiprone.

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**Biliary tract disease**

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP).

<table>
<thead>
<tr>
<th><strong>PATHOLOGY</strong></th>
<th><strong>EPIDEMIOLOGY</strong></th>
<th><strong>ADDITIONAL FEATURES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary sclerosing cholangitis</strong></td>
<td>Unknown cause of concentric “onion skin” bile duct fibrosis ➔ alternating strictures and dilation with “beading” of intra- and extrahepatic bile ducts on ERCP, magnetic resonance cholangiopancreatography (MRCP).</td>
<td>Classically in middle-aged men with IBD.</td>
</tr>
<tr>
<td></td>
<td>Associated with ulcerative colitis. p-ANCA ⊕. ↑ IgM. Can lead to 2nd biliary cholangitis. ↑ risk of cholangiocarcinoma and gallbladder cancer.</td>
<td></td>
</tr>
<tr>
<td><strong>Primary biliary cholangitis</strong></td>
<td>Autoimmune reaction ➔ lymphocytic infiltrate + granulomas ➔ destruction of lobular bile ducts.</td>
<td>Classically in middle-aged women.</td>
</tr>
<tr>
<td></td>
<td>Anti-mitochondrial antibody ⊕, ↑ IgM. Associated with other autoimmune conditions (eg, Sjögren syndrome, Hashimoto thyroiditis, CREST, rheumatoid arthritis, celiac disease).</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary biliary cholangitis</strong></td>
<td>Extrahepatic biliary obstruction ➔ ↑ pressure in intrahepatic ducts ➔ injury/fibrosis and bile stasis.</td>
<td>Patients with known obstructive lesions (gallstones, biliary strictures, pancreatic carcinoma).</td>
</tr>
<tr>
<td></td>
<td>May be complicated by ascending cholangitis.</td>
<td></td>
</tr>
</tbody>
</table>
Gallstones  
(cholelithiasis)

1. Gallstones are cholesterol and/or bilirubin, bile salts, and gallbladder stasis all cause stones.  
2. Risk factors (4 F’s):  
   1. Female  
   2. Fat  
   3. Fertile (multiparity)  
   4. Forty  
   Most common complication is cholecystitis; can also cause acute pancreatitis, ascending cholangitis.  
   Diagnose with ultrasound. Treat with elective cholecystectomy if symptomatic.

<table>
<thead>
<tr>
<th>RELATED PATHOLOGIES</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary colic</td>
<td>Associated with nausea/vomiting and dull RUQ pain. Neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing stone into cystic duct. Labs are normal, ultrasound shows cholelithiasis.</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>Presence of gallstone(s) in common bile duct, often leading to elevated ALP, CGT, direct bilirubin, and/or AST/ALT.</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Acute or chronic inflammation of gallbladder. Calculous cholecystitis—most common type; due to gallstone impaction in the cystic duct resulting in inflammation and gallbladder wall thickening (arrows in B); can produce 2nd infection. Acalculous cholecystitis—due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients. Murphy sign: inspiratory arrest on RUQ palpation due to pain. Pain may radiate to right shoulder (due to irritation of phrenic nerve). ↑ ALP if bile duct becomes involved (eg, ascending cholangitis). Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction. Gallstone ileus—fistula between gallbladder and GI tract → stone enters GI lumen → obstructs at ileocecal valve (narrowest point); can see air in biliary tree (pneumobilia).</td>
</tr>
<tr>
<td>Porcelain gallbladder</td>
<td>Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging C. Treatment: prophylactic cholecystectomy due to high rates of gallbladder cancer (mostly adenocarcinoma).</td>
</tr>
<tr>
<td>Ascending cholangitis</td>
<td>Infection of biliary tree usually due to obstruction that leads to stasis/bacterial overgrowth. Charcot triad of cholangitis includes jaundice, fever, RUQ pain. Reynolds pentad is Charcot triad plus altered mental status and shock (hypotension).</td>
</tr>
</tbody>
</table>
Acute pancreatitis

Autodigestion of pancreas by pancreatic enzymes (A shows pancreas [yellow arrows] surrounded by edema [red arrows]).
Causes: Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hypertriglyceridemia (> 1000 mg/dL), ERCP, Drugs (eg, sulfa drugs, NRTIs, protease inhibitors). I GET SMASHED.
Diagnosis by 2 of 3 criteria: acute epigastric pain often radiating to the back, ↑ serum amylase or lipase (more specific) to 3× upper limit of normal, or characteristic imaging findings.
Complications: pseudocyst (lined by granulation tissue, not epithelium), abscess, necrosis, hemorrhage, infection, organ failure (ARDS, shock, renal failure), hypocalcemia (precipitation of Ca²⁺ soaps).

Chronic pancreatitis

Chronic inflammation, atrophy, calcification of the pancreas (A). Major causes include alcohol abuse and genetic predisposition (ie, cystic fibrosis); can be idiopathic. Complications include pancreatic insufficiency and pseudocysts.
Pancreatic insufficiency (typically when <10% pancreatic function) may manifest with steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus.
Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).

Pancreatic adenocarcinoma

Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration (A); often metastatic at presentation, with average survival ~ 1 year after diagnosis. Tumors more common in pancreatic head (→ obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).
Risk factors:
* Tobacco use
* Chronic pancreatitis (especially > 20 years)
* Diabetes
* Age > 50 years
* Jewish and African-American males
Often presents with:
* Abdominal pain radiating to back
* Weight loss (due to malabsorption and anorexia)
* Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome)
* Obstructive jaundice with palpable, nontender gallbladder (Courvoisier sign)
Treatment: Whipple procedure, chemotherapy, radiation therapy.
Acid suppression therapy

Histamine-2 blockers  
- **Cimetidine**, ranitidine, famotidine, nizatidine. Take H<sub>2</sub> blockers before you dine. Think “**table for 2**” to remember H<sub>2</sub>.

  **MECHANISM**  
  - Reversible block of histamine H<sub>2</sub>-receptors → ↓ H<sup>+</sup> secretion by parietal cells.

  **CLINICAL USE**  
  - Peptic ulcer, gastritis, mild esophageal reflux.

  **ADVERSE EFFECTS**  
  - Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions); it also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males); can cross blood-brain barrier (confusion, dizziness, headaches) and placenta. Both cimetidine and ranitidine ↓ renal excretion of creatinine. Other H<sub>2</sub> blockers are relatively free of these effects.

Proton pump inhibitors  
- Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.

  **MECHANISM**  
  - Irreversibly inhibit H<sup>+</sup>/K<sup>+</sup> ATPase in stomach parietal cells.

  **CLINICAL USE**  
  - Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome, component of therapy for H<sub>p</sub>lori, stress ulcer prophylaxis.

  **ADVERSE EFFECTS**  
  - ↑ risk of C difficile infection, pneumonia, acute interstitial nephritis. ↓ serum Mg<sup>2+</sup> with long-term use; ↓ serum Mg<sup>2+</sup> and ↓ Ca<sup>2+</sup> absorption (potentially leading to increased fracture risk in elderly).
### Antacids

Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying. All can cause hypokalemia. Overuse can also cause the following problems.

<table>
<thead>
<tr>
<th>Antacid</th>
<th>Effect</th>
<th>Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aluminum hydroxide</strong></td>
<td>Constipation and hypophosphatemia; proximal muscle weakness, osteodystrophy, seizures</td>
<td>Aluminum amount of feces.</td>
</tr>
<tr>
<td><strong>Calcium carbonate</strong></td>
<td>Hypercalcemia (milk-alkali syndrome), rebound acid ↑</td>
<td>Can chelate and ↓ effectiveness of other drugs (eg, tetracycline).</td>
</tr>
<tr>
<td><strong>Magnesium hydroxide</strong></td>
<td>Diarrhea, hyporeflexia, hypotension, cardiac arrest</td>
<td>Mg²⁺ = Must go to the bathroom.</td>
</tr>
</tbody>
</table>

### Bismuth, sucralfate

**Mechanism**: Bind to ulcer base, providing physical protection and allowing HCO₃⁻ secretion to reestablish pH gradient in the mucus layer. Require acidic environment; usually not given with PPIs/H₂ blockers.

**Clinical Use**: ↑ ulcer healing, travelers' diarrhea (bismuth).

### Misoprostol

**Mechanism**: PGE₁ analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.

**Clinical Use**: Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE₁ production). Also used off-label for induction of labor (ripens cervix).

**Adverse Effects**: Diarrhea. Contraindicated in women of childbearing potential (abortifacient).

### Octreotide

**Mechanism**: Long-acting somatostatin analog; inhibits secretion of various splanchnic vasodilatory hormones.

**Clinical Use**: Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors.

**Adverse Effects**: Nausea, cramps, steatorrhea. ↑ risk of cholelithiasis due to CCK inhibition.

### Sulfasalazine

**Mechanism**: A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria.

**Clinical Use**: Ulcerative colitis, Crohn disease (colitis component).

**Adverse Effects**: Malaise, nausea, sulfonamide toxicity, reversible oligospermia.

### Loperamide

**Mechanism**: Agonist at μ-opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential).

**Clinical Use**: Diarrhea.

**Adverse Effects**: Constipation, nausea.
Ondansetron

**MECHANISM**
5-HT₃ antagonist; ↓ vagal stimulation. Powerful central-acting antiemetic.

**CLINICAL USE**
Control vomiting postoperatively and in patients undergoing cancer chemotherapy.

**ADVERSE EFFECTS**
Headache, constipation, QT interval prolongation, serotonin syndrome.

Metoclopramide

**MECHANISM**
D₂ receptor antagonist. ↑ resting tone, contractility, LES tone, motility, promotes gastric emptying. Does not influence colon transport time.

**CLINICAL USE**
Diabetic and postsurgery gastroparesis, antiemetic, persistent GERD.

**ADVERSE EFFECTS**
↑ parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction or Parkinson disease (due to D₂-receptor blockade).

Orlistat

**MECHANISM**
Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats.

**CLINICAL USE**
Weight loss.

**ADVERSE EFFECTS**
Abdominal pain, flatulence, bowel urgency/frequent bowel movements; ↓ absorption of fat-soluble vitamins.

Laxatives

Indicated for constipation or patients on opiates requiring a bowel regimen.

<table>
<thead>
<tr>
<th>EXAMPLES</th>
<th>MECHANISM</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-forming laxatives</td>
<td>Psyllium, methylcellulose</td>
<td>Soluble fibers draw water into gut lumen, forming a viscous liquid that promotes peristalsis</td>
</tr>
<tr>
<td>Osmotic laxatives</td>
<td>Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose</td>
<td>Provides osmotic load to draw water into GI lumen. Lactulose also treats hepatic encephalopathy: gut flora degrade lactulose into metabolites (lactic acid, acetic acid) that promote nitrogen excretion as NH₄⁺</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Senna</td>
<td>Enteric nerve stimulation → colonic contraction</td>
</tr>
<tr>
<td>Emollients</td>
<td>Docusate</td>
<td>Promotes incorporation of water and fat into stool</td>
</tr>
</tbody>
</table>

Aprepitant

**MECHANISM**
Substance P antagonist. Blocks NK₁ (neurokinin-1) receptors in brain.

**CLINICAL USE**
Antiemetic for chemotherapy-induced nausea and vomiting.
“Of all that is written, I love only what a person has written with his own blood.”
—Friedrich Nietzsche

“All the soarings of my mind begin in my blood.”
—Rainer Maria Rilke

“The best blood will at some time get into a fool or a mosquito.”
—Austin O’Malley

When studying hematology, pay close attention to the many cross connections to immunology. Make sure you master the different types of anemias. Be comfortable interpreting blood smears. Please note that solid tumors are covered in the other organ systems. When reviewing oncologic drugs, focus on mechanisms and adverse effects rather than details of clinical uses, which may be lower yield.
Carry O₂ to tissues and CO₂ to lungs. Anucleate and lack organelles; biconcave with large surface area-to-volume ratio for rapid gas exchange. Life span of 120 days. Source of energy is glucose (90% used in glycolysis, 10% used in HMP shunt). Membranes contain Cl⁻/HCO₃⁻ antipporter, which allow RBCs to export HCO₃⁻ and transport CO₂ from the periphery to the lungs for elimination.

Erythrocytosis = polycythemia = ↑ Hct.

Anisocytosis = varying sizes.

Poikilocytosis = varying shapes.

Reticulocyte = immature RBC; reflects erythroid proliferation.

Bluish color (polychromasia) on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

Involved in 1° hemostasis. Small cytoplasmic fragments derived from megakaryocytes. Life span of 8–10 days. When activated by endothelial injury, aggregate with other platelets and interact with fibrinogen to form platelet plug. Contain dense granules (ADP, Ca²⁺) and α granules (vWF, fibrinogen, fibronectin). Approximately ⅓ of platelet pool is stored in the spleen.

Thrombocytopenia or ↓ platelet function results in petechiae.

vWF receptor: GpIb.

Fibrinogen receptor: GpIIb/IIIa.

Thrombopoietin stimulates megakaryocyte proliferation.

Alfa granules contain vWF, fibrinogen, fibronectin.

Leukocytes

Divided into granulocytes (neutrophils, eosinophils, basophils, mast cells) and mononuclear cells (monocytes, lymphocytes). WBC differential count from highest to lowest (normal ranges per USMLE):

Neutrophils (~ 60%)

Lymphocytes (~ 30%)

Monocytes (~ 6%)

Eosinophils (~ 3%)

Basophils (~ 1%)

Important neutrophil chemotactic agents: C5a, IL-8, LTB₄, kallikrein, platelet-activating factor.


Hypersegmented neutrophils (nucleus has 6+ lobes) are seen in vitamin B₁₂/folate deficiency. ↑ band cells (immature neutrophils) reflect states of ↑ myeloid proliferation (bacterial infections, CML). Important neutrophil chemotactic agents: C5a, IL-8, LTB₄, kallikrein, platelet-activating factor.
Monocytes

- Found in blood, differentiate into macrophages in tissues.
- Large, kidney-shaped nucleus. Extensive “frosted glass” cytoplasm.

Macrophages

- Phagocytose bacteria, cellular debris, and senescent RBCs. Long life in tissues.
- Differentiate from circulating blood monocytes. Activated by interferon. Can function as antigen-presenting cell via MHC II.

Eosinophils

- Produce histaminase, major basic protein (MBP, a helminthotoxin), eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin.

Basophils

- Mediate allergic reaction. Densely basophilic granules contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand.
Mast cells

Mediate allergic reaction in local tissues. Contain basophilic granules and originate from the same precursor as basophils but are not the same cell type. Can bind the Fc portion of IgE to membrane. Activated by tissue trauma, C3a and C5a, surface IgE crosslinking by antigen (IgE receptor aggregation) → degranulation → release of histamine, heparin, tryptase, and eosinophil chemotactic factors. Involved in type I hypersensitivity reactions. Cromolyn sodium prevents mast cell degranulation (used for asthma prophylaxis).

Dendritic cells

Highly phagocytic antigen-presenting cells (APCs). Function as link between innate and adaptive immune systems. Express MHC class II and Fc receptors on surface. Called Langerhans cell in the skin.

Lymphocytes

Refer to B cells, T cells, and NK cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm.

B cells

Part of humoral immune response. Originate from stem cells in bone marrow and matures in marrow. Migrate to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC. B = Bone marrow.

T cells

Mediate cellular immune response. Originate from stem cells in the bone marrow, but mature in the thymus. Differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. Most circulating lymphocytes are T cells (80%). T is for Thymus. CD4+ helper T cells are the primary target of HIV. Rule of 8: MHC II × CD4 = 8; MHC I × CD8 = 8.
Plasma cells

Produce large amounts of antibody specific to a particular antigen. “Clock-face” chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (arrows in A). Found in bone marrow and normally do not circulate in peripheral blood.

Multiple myeloma is a plasma cell cancer.

Hematology and oncology—Physiology

Fetal erythropoiesis

Fetal erythropoiesis occurs in:
- Yolk sac (3–8 weeks)
- Liver (6 weeks–birth)
- Spleen (10–28 weeks)
- Bone marrow (18 weeks to adult)

Hemoglobin development

Embryonic globins: ζ and ε.
Fetal hemoglobin (HbF) = α₂γ₂.
Adult hemoglobin (HbA₃ = α₂β₂.
HbF has higher affinity for O₂ due to less avid binding of 2,3-BPG, allowing HbF to extract O₂ from maternal hemoglobin (HbA₁ and HbA₂) across the placenta. HbA₂ (α₂δ₂) is a form of adult hemoglobin present in small amounts.

From fetal to adult hemoglobin:
Alpha Always, Gamma Goes, Becomes Beta.

Young Liver Synthesizes Blood.
Blood groups

<table>
<thead>
<tr>
<th>ABO classification</th>
<th>Rh classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Rh+</td>
</tr>
<tr>
<td>B</td>
<td>Rh-</td>
</tr>
<tr>
<td>AB</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td></td>
</tr>
</tbody>
</table>

**RBC type**

- A
- B
- AB
- O

**Group antigens on RBC surface**

- A
- B
- A & B
- None

**Antibodies in plasma**

- Anti-B
- Anti-A
- None
- Anti-A
- Anti-B
- IgM, IgG
- IgG

**Clinical relevance**

- Receive B or AB → hemolytic reaction
- Receive A or AB → hemolytic reaction
- Universal recipient of RBCs; universal donor of plasma
- Universal donor of RBCs; universal recipient of plasma
- Can receive any non-O → hemolytic reaction
- Can receive either Rh(D) or Rh(D- blood
- Treat mother with anti-D Ig during and after each pregnancy to prevent anti-D IgG formation

Hemolytic disease of the newborn

Also known as erythroblastosis fetalis.

**Rh hemolytic disease of the newborn**

- First pregnancy: mother exposed to fetal blood (often during delivery) → formation of maternal anti-D IgG. Subsequent pregnancies: anti-D IgG crosses the placenta → HDN in the fetus.

**ABO hemolytic disease of the newborn**

- Pre-existing maternal anti-A and/or anti-B IgG antibodies cross placenta → HDN in the fetus.

**Presentation**

- Jaundice shortly after birth, kernicterus, hydrops fetalis.
- Mild jaundice in the neonate within 24 hours of birth. Usually less severe than Rh HDN.

**Treatment/Prevention**

- Prevent by administration of anti-D IgG to Rh- pregnant women during third trimester and early postpartum period (if fetus tests + for Rh). Prevents maternal anti-D IgG production.
- Treat newborn with phototherapy or exchange transfusion.
Hemoglobin electrophoresis

On a gel, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbF, HbS, and HbC. This is because the missense mutations in HbS and HbC replace glutamic acid with valine (neutral) and lysine, respectively, impacting the net protein charge.

Coagulation and kinin pathways

Collagen, basement membrane, activated platelets

Contact activation (intrinsic) pathway

Tissue factor (extrinsic) pathway

ANTICOAGULANTS: factor Xa
- LMWH (greatest efficacy)
- heparin
- direct Xa inhibitors (apixaban, rivaroxaban)
- fondaparinux

ANTICOAGULANTS: IIa (thrombin)
- heparin (greatest efficacy)
- LMWH (dalteparin, enoxaparin)
- direct thrombin inhibitors (argatroban, bivalirudin, dabigatran)

Hemophilia A: deficiency of factor VIII (XR)
Hemophilia B: deficiency of factor IX (DO)
Hemophilia C: deficiency of factor XI (ARI)

Note: Kallikrein activates bradykinin; ACE inactivates bradykinin
* = require Ca²⁺, phospholipid
= inhibited by vitamin K antagonist warfarin
= cofactor
= activates but not part of coagulation cascade
LMWH, low-molecular-weight heparin

Coagulation and kinin pathways

Contact activation (intrinsic) pathway

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Note: Kallikrein activates bradykinin; ACE inactivates bradykinin
* = require Ca²⁺, phospholipid
= inhibited by vitamin K antagonist warfarin
= cofactor
= activates but not part of coagulation cascade
LMWH, low-molecular-weight heparin
Coagulation cascade components

**Procoagulation**

Vitamin K deficiency: ↓ synthesis of factors II, VII, IX, X, protein C, protein S. Warfarin inhibits vitamin K epoxide reductase. Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis. FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding. Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy.

Factor VII—Shortest half life. Factor II—Longest half life.

**Anticoagulation**

Antithrombin inhibits activated forms of factors II, VII, IX, X, XI, XII. Heparin enhances the activity of antithrombin. Principal targets of antithrombin: thrombin and factor Xa. Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C. tPA is used clinically as a thrombolytic.
Platelet plug formation (primary hemostasis)

1. INJURY
   Endothelial damage → transient vasoconstriction via neural stimulation reflex and endothelin (released from damaged cell)

2. EXPOSURE
   vWF binds to exposed collagen
   vWF is from Weibel-Palade bodies of endothelial cells and α-granules of platelets

3. ADHESION
   Platelets bind vWF via GpIb receptor at the site of injury only (specific) → platelets undergo conformational change
   Platelets release ADP and Ca²⁺ (necessary for coagulation cascade), TXA₂
   ADP helps platelets adhere to endothelium

4. ACTIVATION
   ADP binding to P2Y₁₂ receptor induces GpIIb/IIIa expression at platelet surface

5. AGGREGATION
   Fibrinogen binds GpIIb/IIIa receptors and links platelets
   Balance between pro-aggregation factors: TXA₂ (released by platelets) ↓ blood flow ↑ platelet aggregation
   Anti-aggregation factors: PGI₂ and NO (released by endothelial cells) ↑ blood flow ↓ platelet aggregation

Temporary plug stops bleeding; unstable, easily dislodged

Thrombogenesis

Formation of insoluble fibrin mesh.
Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting TXA₂ synthesis.
Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa by irreversibly blocking P2Y₁₂ receptor.
Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.
Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome.
### Pathologic RBC forms

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Associated Pathology</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthocytes (“spur cells”)</td>
<td><img src="A.png" alt="Image" /></td>
<td>Liver disease, abetalipoproteinemia (states of cholesterol dysregulation).</td>
<td>Acantho = spiny.</td>
</tr>
<tr>
<td>Basophilic stippling</td>
<td><img src="B.png" alt="Image" /></td>
<td>Sideroblastic anemias (eg, lead poisoning, myelodysplastic syndromes), thalassemias.</td>
<td>Seen primarily in peripheral smear, vs ringed sideroblasts seen in bone marrow. Aggregation of residual ribosomes.</td>
</tr>
<tr>
<td>Dacrocytes (“teardrop cells”)</td>
<td><img src="C.png" alt="Image" /></td>
<td>Bone marrow infiltration (eg, myelofibrosis), thalassemias.</td>
<td>RBC “sheds a tear” because it’s mechanically squeezed out of its home in the bone marrow.</td>
</tr>
<tr>
<td>Degmacytes (“bite cells”)</td>
<td><img src="D.png" alt="Image" /></td>
<td>G6PD deficiency.</td>
<td></td>
</tr>
<tr>
<td>Echinocytes (“burr cells”)</td>
<td><img src="E.png" alt="Image" /></td>
<td>End-stage renal disease, liver disease, pyruvate kinase deficiency.</td>
<td>Different from acanthocyte; its projections are more uniform and smaller.</td>
</tr>
<tr>
<td>Elliptocytes</td>
<td><img src="F.png" alt="Image" /></td>
<td>Hereditary elliptocytosis, usually asymptomatic; caused by mutation in genes encoding RBC membrane proteins (eg, spectrin).</td>
<td></td>
</tr>
<tr>
<td>Macro-ovalocytes</td>
<td><img src="G.png" alt="Image" /></td>
<td>Megaloblastic anemia (also hypersegmented PMNs).</td>
<td></td>
</tr>
</tbody>
</table>
### Pathologic RBC forms (continued)

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EXAMPLE</th>
<th>ASSOCIATED PATHOLOGY</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ringed sideroblasts</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td>Sideroblastic anemia. Excess iron in mitochondria.</td>
<td>Seen in bone marrow with special staining (Prussian blue), vs basophilic stippling in peripheral smear.</td>
</tr>
<tr>
<td><strong>Schistocytes</strong></td>
<td><img src="image2.png" alt="Image" /></td>
<td>Microangiopathic hemolytic anemias, including DIC, TTP/HUS, HELLP syndrome, mechanical hemolysis (eg, heart valve prosthesis).</td>
<td>Fragmented RBCs (eg, helmet cells).</td>
</tr>
<tr>
<td><strong>Sickle cells</strong></td>
<td><img src="image3.png" alt="Image" /></td>
<td>Sickle cell anemia.</td>
<td>Sickling occurs with dehydration, deoxygenation, and at high altitude.</td>
</tr>
<tr>
<td><strong>Spherocytes</strong></td>
<td><img src="image4.png" alt="Image" /></td>
<td>Hereditary spherocytosis, drug- and infection-induced hemolytic anemia.</td>
<td>Small, spherical cells without central pallor.</td>
</tr>
<tr>
<td><strong>Target cells</strong></td>
<td><img src="image5.png" alt="Image" /></td>
<td>HbC disease, Asplenia, Liver disease, Thalassemia.</td>
<td>“HALT,” said the hunter to his target.</td>
</tr>
</tbody>
</table>

### Other RBC abnormalities

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EXAMPLE</th>
<th>ASSOCIATED PATHOLOGY</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heinz bodies</strong></td>
<td><img src="image6.png" alt="Image" /></td>
<td>Seen in G6PD deficiency.</td>
<td>Oxidation of Hb-SH groups to -S—S- → Hb precipitation (Heinz bodies), with subsequent phagocytic damage to RBC membrane → bite cells.</td>
</tr>
<tr>
<td><strong>Howell-Jolly bodies</strong></td>
<td><img src="image7.png" alt="Image" /></td>
<td>Seen in patients with functional hyposplenia or asplenia.</td>
<td>Basophilic nuclear remnants found in RBCs. Howell-Jolly bodies are normally removed from RBCs by splenic macrophages.</td>
</tr>
</tbody>
</table>
Anemias

**Microcytic, hypochromic anemia**

**Iron deficiency**

- Iron due to chronic bleeding (eg, GI loss, menorrhagia), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis.

- Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin, ↑ RDW. Microcytosis and hypochromasia (↑ central pallor).

- Symptoms: fatigue, conjunctival pallor, pica (consumption of nonfood substances), spoon nails (koilonychia).

- May manifest as glossitis, cheilosis, Plummer-Vinson syndrome (triad of iron deficiency anemia, esophageal webs, and dysphagia).

**α-thalassemia**

- α-globin gene deletions → ↓ α-globin synthesis. cis deletion (deletions occur on same chromosome) prevalent in Asian populations; trans deletion (deletions occur on separate chromosomes) prevalent in African populations. Normal is αα/αα.

<table>
<thead>
<tr>
<th>NUMBER OF α-GLLOBIN GENES DELETED</th>
<th>DISEASE</th>
<th>CLINICAL OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (αα/αα)</td>
<td>α-thalassemia minima</td>
<td>No anemia (silent carrier)</td>
</tr>
<tr>
<td>2 (αα/α–; trans) or (αα/αα; cis)</td>
<td>α-thalassemia minor</td>
<td>Mild microcytic, hypochromic anemia; cis deletion may worsen outcome for the carrier’s offspring</td>
</tr>
<tr>
<td>3 (–/– α)</td>
<td>Hemoglobin H disease (HbH); excess β-globin forms β4</td>
<td>Moderate to severe microcytic hypochromic anemia</td>
</tr>
<tr>
<td>4 (–/––)</td>
<td>Hemoglobin Barts disease (Hb Barts); no α-globin, excess γ-globin forms γ4</td>
<td>Hydrops fetalis; incompatible with life</td>
</tr>
</tbody>
</table>
Microcytic, hypochromic anemia (continued)

**β-thalassemia**  
Point mutations in splice sites and promoter sequences → ↓ β-globin synthesis. Prevalent in Mediterranean populations.  
**β-thalassemia minor** (heterozygote): β chain is underproduced. Usually asymptomatic. Diagnosis confirmed by ↑ HbA2 (> 3.5%) on electrophoresis.  
**β-thalassemia major** (homozygote): β chain is absent → severe microcytic, hypochromic anemia with target cells and increased anisopoikilocytosis (requiring blood transfusion (2° hemochromatosis). Marrow expansion (“crew cut” on skull x-ray) → skeletal deformities. “Chipmunk” facies. Extramedullary hematopoiesis → hepatosplenomegaly. ↑ risk of parvovirus B19-induced aplastic crisis. ↑ HbF (α2γ2), HbA2 (α2δ2). HbF is protective in the infant and disease becomes symptomatic only after 6 months, when fetal hemoglobin declines.  
**HbS/β-thalassemia heterozygote:** mild to moderate sickle cell disease depending on amount of β-globin production.

**Lead poisoning**  
Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↓ RBC protoporphyrin. Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling).  
Symptoms of LEAD poisoning:  
- **Lines** on gingivae (Burton lines) and on metaphyses of long bones on x-ray.  
- **Encephalopathy** and **erythrocyte basophilic stippling.**  
- **Abdominal colic** and sideroblastic Anemia.  
- **Drops—wrist and foot drop.** Dimercaprol and EDTA are 1st line of treatment.  
**Succe**imer used for chelation for kids (It “sucks” to be a kid who eats lead).  
Exposure risk ↑ in old houses with chipped paint.

**Sideroblastic anemia**  
Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead, vitamin B6 deficiency, copper deficiency, isoniazid, chloramphenicol).  
Lab findings: ↑ iron, normal/↑ TIBC, ↑ ferritin. Ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) seen in bone marrow. Peripheral blood smear: basophilic stippling of RBCs.  
Treatment: pyridoxine (B6, cofactor for ALA synthase).
<table>
<thead>
<tr>
<th>Anemia Type</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrocytic anemia</strong></td>
<td>MCV &gt; 100 fL.</td>
<td></td>
</tr>
<tr>
<td><strong>Megaloblastic anemia</strong></td>
<td>Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm.</td>
<td>RBC macrocytosis, hypersegmented neutrophils, glossitis.</td>
</tr>
<tr>
<td><strong>Folate deficiency</strong></td>
<td>Causes: malnutrition (eg, alcoholics), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), requirement (eg, hemolytic anemia, pregnancy).</td>
<td>↑ homocysteine, normal methylmalonic acid. No neurologic symptoms (vs B12 deficiency).</td>
</tr>
<tr>
<td><strong>Vitamin B12 (cobalamin) deficiency</strong></td>
<td>Causes: pernicious anemia, malabsorption (eg, Crohn disease), gastrectomy, insufficient intake (eg, veganism), <em>Diphyllobothrium latum</em> (fish tapeworm).</td>
<td>↑ homocysteine, ↑ methylmalonic acid. Neurologic symptoms: reversible dementia, subacute combined degeneration (due to involvement of B12 in fatty acid pathways and myelin synthesis): spino cerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Historically diagnosed with the Schilling test, a 4-stage test that determines if the cause is dietary insufficiency vs malabsorption. Anemia 2° to insufficient intake may take several years to develop due to liver’s ability to store B12 (as opposed to folate deficiency).</td>
</tr>
<tr>
<td><strong>Orotic aciduria</strong></td>
<td>Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase. Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B12. No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia).</td>
<td>Orotic acid in urine. Treatment: uridine monophosphate or uridine triacetate to bypass mutated enzyme.</td>
</tr>
<tr>
<td><strong>Nonmegaloblastic anemia</strong></td>
<td>Macrocytic anemia in which DNA synthesis is unimpaired. Causes: alcoholism, liver disease.</td>
<td>RBC macrocytosis without hypersegmented neutrophils.</td>
</tr>
<tr>
<td><strong>Diamond-Blackfan anemia</strong></td>
<td>Rapid-onset anemia within 1st year of life due to intrinsic defect in erythroid progenitor cells.</td>
<td>↑ % HbF (but ↓ total Hb). Short stature, craniofacial abnormalities, and upper extremity malformations (triphalangeal thumbs) in up to 50% of cases.</td>
</tr>
</tbody>
</table>
### Normocytic, normochromic anemia

Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of the hemolysis (intravascular vs extravascular). Hemolysis can lead to increases in LDH, reticulocytes, unconjugated bilirubin, urobilinogen in urine.

#### Intravascular hemolysis

Findings: ↓ haptoglobin, ↑ schistocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. May also see ↑ unconjugated bilirubin. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.

#### Extravascular hemolysis

Findings: macrophages in spleen clear RBCs. Spherocytes in peripheral smear (most commonly hereditary spherocytosis and autoimmune hemolytic anemia), no hemoglobinuria/ hemosiderinuria. Can present with urobilinogen in urine.

### Nonhemolytic, normocytic anemia

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia of chronic disease</td>
<td>Inflammation → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages and ↓ iron absorption from gut. Associated with conditions such as rheumatoid arthritis, SLE, neoplastic disorders, and chronic kidney disease. ↓ iron, ↓ TIBC, ↑ ferritin. Normocytic, but can become microcytic. Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesis-stimulating agents such as EPO (eg, in chronic kidney disease).</td>
</tr>
</tbody>
</table>
| Aplastic anemia | Caused by failure or destruction of myeloid stem cells due to:  
  • Radiation and drugs (eg, benzene, chloramphenicol, alkylating agents, antimetabolites)  
  • Viral agents (EBV, HIV, hepatitis viruses)  
  • Fanconi anemia (DNA repair defect causing bone marrow failure; macrocytosis may be seen on CBC); also short stature, ↑ incidence of tumors/leukemia, café-au-lait spots, thumb/radial defects  
  • Idiopathic (immune mediated, 1st stem cell defect); may follow acute hepatitis ↓ reticulocyte count, ↑ EPO. Pancytopenia characterized by anemia, leukopenia, and thrombocytopenia. Normal cell morphology, but hypocellular bone marrow with fatty infiltration (dry bone marrow tap). Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection. Treatment: withdrawal of offending agent, immunosuppressive regimens (eg, antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (eg, GM-CSF). |
Intrinsic hemolytic anemia

<table>
<thead>
<tr>
<th>Description</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyruvate kinase deficiency</td>
<td>Autosomal recessive pyruvate kinase defect → ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG → ↓ hemoglobin affinity for O₂.</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>HbS point mutation causes a single amino acid replacement in β chain (substitution of glutamic acid with valine). Causes extravascular and intravascular hemolysis. Pathogenesis: low O₂, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → anemia, vaso-occlusive disease. Newborns are initially asymptomatic because of ↑ Hbf and ↓ HbS. Heterozygotes (sickle cell trait) also have resistance to malaria. 8% of African Americans carry an HbS allele. Sickle cells are crescent-shaped RBCs. “Crew cut” on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias).</td>
</tr>
<tr>
<td>HbC disease</td>
<td>Glutamic acid→lysine (lysine) mutation in β-globin. Causes extravascular hemolysis.</td>
</tr>
</tbody>
</table>
### Extrinsic hemolytic anemia

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune hemolytic anemia</strong></td>
<td>Autoimmune hemolytic anemias are usually Coombs⁺. Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient’s RBCs. RBCs agglutinate if RBCs are coated with Ig. Indirect Coombs test—normal RBCs added to patient’s serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent added.</td>
</tr>
</tbody>
</table>

#### Autoimmune hemolytic anemia

| Warm (IgG)—chronic anemia seen in SLE and CLL and with certain drugs (eg, α-methyldopa) (“warm weather is Great”). Cold (IgM and complement)—acute anemia triggered by cold; seen in CLL, *Mycoplasma pneumoniae* infections, and infectious Mononucleosis (“cold weather is MMMiserable”). RBC agglutinates may cause painful, blue fingers and toes with cold exposure. Many warm and cold AIHAs are idiopathic. |

<table>
<thead>
<tr>
<th><strong>Direct Coombs</strong></th>
<th><strong>Indirect Coombs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs +/- anti-RBC Ab</td>
<td>Donor blood</td>
</tr>
<tr>
<td>Anti-human globulin (Coombs reagent)</td>
<td>Anti-human globulin (Coombs reagent)</td>
</tr>
<tr>
<td>☀ Result (agglutination)</td>
<td>☀ Result (agglutination)</td>
</tr>
<tr>
<td>☩ Result (no agglutination)</td>
<td>☩ Result (no agglutination)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Microangiopathic anemia</strong></th>
<th><strong>Schistocytes</strong> (eg, “helmet cells”) are seen on peripheral blood smear due to mechanical destruction (<em>schisto</em> = to split) of RBCs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenesis: RBCs are damaged when passing through obstructed or narrowed vessel lumina. Seen in DIC, TTP/HUS, SLE, HELLP syndrome, hypertensive emergency.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Macroangiopathic anemia</strong></th>
<th>Schistocytes on peripheral blood smear.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Infections</strong></th>
<th>† destruction of RBCs (eg, malaria, Babesia).</th>
</tr>
</thead>
</table>

---
Interpretation of iron studies

<table>
<thead>
<tr>
<th>Iron deficiency</th>
<th>Chronic disease</th>
<th>Hemochromatosis</th>
<th>Pregnancy/OCP use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Transferrin or TIBC</td>
<td>↑</td>
<td>↓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↓</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>% transferrin saturation (serum iron/TIBC)</td>
<td>↓↓</td>
<td>—</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

<sup>t↑ = 1° disturbance.</sup>

Transferrin—transports iron in blood.
TIBC—indirectly measures transferrin.
Ferritin—1° iron storage protein of body.

<sup>a</sup>Evolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

Leukopenias

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>CELL COUNT</th>
<th>CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Absolute neutrophil count &lt; 1500 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation</td>
</tr>
<tr>
<td></td>
<td>Severe infections typical when &lt; 500 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Absolute lymphocyte count &lt; 1500 cells/mm&lt;sup&gt;3&lt;/sup&gt; (&lt;3000 cells/mm&lt;sup&gt;3&lt;/sup&gt; in children)</td>
<td>HIV, DiGeorge syndrome, SCID, SLE, corticosteroids&lt;sup&gt;a&lt;/sup&gt;, radiation, sepsis, postoperative</td>
</tr>
<tr>
<td>Eosinopenia</td>
<td>Absolute eosinophil count &lt; 30 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Cushing syndrome, corticosteroids&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Corticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids ▲ activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, corticosteroids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

Left shift

▲ neutrophil precursors, such as band cells and metamyelocytes, in peripheral blood. Usually seen with neutrophilia in the acute response to infection or inflammation. Called leukoerythroblastic reaction when left shift is seen with immature RBCs. Occurs with severe anemia (physiologic response) or marrow response (eg, fibrosis, tumor taking up space in marrow).

A left shift is a shift to a more immature cell in the maturation process.
Heme synthesis, porphyrias, and lead poisoning

The porphyrias are hereditary or acquired conditions of defective heme synthesis that lead to the accumulation of heme precursors. Lead inhibits specific enzymes needed in heme synthesis, leading to a similar condition.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>AFFECTED ENZYME</th>
<th>ACCUMULATED SUBSTRATE</th>
<th>PRESENTING SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead poisoning</td>
<td>Ferrochelatase and ALA dehydratase</td>
<td>Protoporphyrin, ALA (blood)</td>
<td>Microcytic anemia (basophilic stippling in peripheral smear, ringed sideroblasts in bone marrow), GI and kidney disease. Children—exposure to lead paint → mental deterioration. Adults—environmental exposure (eg, batteries, ammunition) → headache, memory loss, demyelination.</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Porphobilinogen deaminase, previously known as uroporphyrinogen I synthase (autosomal dominant mutation)</td>
<td>Porphobilinogen, ALA</td>
<td>Symptoms (5 P’s): Painful abdomen, Port wine–colored urine, Polyneuropathy, Psychological disturbances, Precipitated by drugs (eg, cytochrome P-450 inducers), alcohol, starvation. Treatment: hemin and glucose, which inhibit ALA synthase.</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Uroporphyrinogen decarboxylase (autosomal dominant mutation)</td>
<td>Uroporphyrin (tea-colored urine)</td>
<td>Blistering cutaneous photosensitivity and hyperpigmentation. Most common porphyria. Exacerbated with alcohol consumption. Associated with hepatitis C.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Intermediates</th>
<th>Enzymes</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondria</td>
<td>Glycine + succinyl-CoA</td>
<td>Aminolevulinic acid</td>
<td>Aminolevulinate synthase (rate-limiting step)</td>
</tr>
<tr>
<td></td>
<td>B6</td>
<td>Glucose, hemin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydroxymethylbilane</td>
<td>Porphobilinogen deaminase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uroporphyrinogen III</td>
<td>Porphobilinogen deaminase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coproporphyrinogen III</td>
<td>Uroporphyrinogen decarboxylase</td>
<td></td>
</tr>
<tr>
<td>Cytoplasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Protoporphyrin</td>
<td>Ferrochelatase</td>
<td>Lead poisoning</td>
</tr>
<tr>
<td></td>
<td>Fe^{2+}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↓ heme → ↑ ALA synthase activity
↑ heme → ↓ ALA synthase activity
Iron poisoning

High mortality rate with accidental ingestion by children (adult iron tablets may look like candy).

**MECHANISM**
Cell death due to peroxidation of membrane lipids.

**SYMPTOMS/SIGNS**
Nausea, vomiting, gastric bleeding, lethargy, scarring leading to GI obstruction.

**TREATMENT**
Chelation (eg, IV deferoxamine, oral deferasirox) and dialysis.

---

Coagulation disorders

PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ PT (Play Tennis outside [extrinsic pathway]).

INR (international normalized ratio)—calculated from PT. 1 = normal, > 1 = prolonged. Most common test used to follow patients on warfarin.

PTT—tests function of common and intrinsic pathway (all factors except VII and XIII). Defect → ↑ PTT (Play Table Tennis inside).

Coagulation disorders can be due to clotting factor deficiencies or acquired inhibitors. Diagnosed with a mixing study, in which normal plasma is added to patient’s plasma. Clotting factor deficiencies should correct (the PT or PTT returns to within the appropriate normal range), whereas factor inhibitors will not correct.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PT</th>
<th>PTT</th>
<th>MECHANISM AND COMMENTS</th>
</tr>
</thead>
</table>
| Hemophilia A, B, or C | — | ↑ | Intrinsic pathway coagulation defect (↑ PTT).  
  * A: deficiency of factor VIII; X-linked recessive.  
  * B: deficiency of factor IX; X-linked recessive.  
  * C: deficiency of factor XI; autosomal recessive.  
  Hemorrhage in hemophilia—hemarthroses (bleeding into joints, eg, knee), easy bruising, bleeding after trauma or surgery (eg, dental procedures).  
  Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C). |
| Vitamin K deficiency | ↑ | ↑ | General coagulation defect. Bleeding time normal.  
  ↓ activity of factors II, VII, IX, X, protein C, protein S. |
Platelet disorders

Defects in platelet plug formation → ↑ bleeding time (BT).
Platelet abnormalities → microhemorrhage: mucous membrane bleeding, epistaxis, petechiae, purpura, ↑ bleeding time, possibly decreased platelet count (PC).

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PC</th>
<th>BT</th>
<th>MECHANISM AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard-Soulier syndrome</td>
<td>−/↑</td>
<td>↑</td>
<td>Defect in platelet plug formation. Large platelets.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ GpIb → defect in platelet-to-vWF adhesion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abnormal ristocetin test that does not correct with mixing studies.</td>
</tr>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>−</td>
<td>↑</td>
<td>Defect in platelet integrin αIIbβ3 (GpIIb/IIIa) → defect in platelet-to-platelet aggregation, and therefore platelet plug formation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Labs: blood smear shows no platelet clumping.</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>↓</td>
<td>↑</td>
<td>Characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Typical HUS is seen in children, accompanied by diarrhea and commonly caused by Shiga-like toxin of enterohemorrhagic E coli (EHEC) (eg, O157:H7). HUS in adults does not present with diarrhea; EHEC infection not required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Same spectrum as TTP, with a similar clinical presentation and same initial treatment of plasmapheresis.</td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td>↓</td>
<td>↑</td>
<td>Anti-GpIIb/IIIa antibodies → splenic macrophage consumption of platelet-antibody complex. May be 1° (idiopathic) or 2° to autoimmune disorder, viral illness, malignancy, or drug reaction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Labs: ↑ megakaryocytes on bone marrow biopsy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: steroids, IVIG; rituximab or splenectomy for refractory ITP.</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>↓</td>
<td>↑</td>
<td>Inhibition or deficiency of ADAMTS 13 (vWF metalloprotease) → ↓ degradation of vWF multimers.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pathogenesis: ↑ large vWF multimers → ↑ platelet adhesion → ↑ platelet aggregation and thrombosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Labs: schistocytes, ↑ LDH, normal coagulation parameters.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptoms (FAT RN): pentad of Fever, microangiopathic hemolytic Anemia, Thrombocytopenia, Renal failure, Neurologic symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: plasmapheresis, steroids.</td>
</tr>
</tbody>
</table>
### Mixed platelet and coagulation disorders

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PC</th>
<th>BT</th>
<th>PT</th>
<th>PTT</th>
<th>MECHANISM AND COMMENTS</th>
</tr>
</thead>
</table>

### Hereditary thrombosis syndromes leading to hypercoagulability

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>Inherited deficiency of antithrombin: has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following heparin administration. Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa.</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>Production of mutant factor V (G → A DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Most common cause of inherited hypercoagulability in Caucasians. Complications include DVT, cerebral vein thromboses, recurrent pregnancy loss.</td>
</tr>
<tr>
<td>Protein C or S deficiency</td>
<td>↓ ability to inactivate factors Va and VIIIa. ↑ risk of thrombotic skin necrosis with hemorrhage after administration of warfarin. If this occurs, think protein C deficiency. Together, protein C Cancels, and protein S Stops, coagulation.</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>Mutation in 3′ untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.</td>
</tr>
</tbody>
</table>
Blood transfusion therapy

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>DOSAGE EFFECT</th>
<th>CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed RBCs</td>
<td>↑ Hb and O₂ carrying capacity</td>
<td>Acute blood loss, severe anemia</td>
</tr>
<tr>
<td>Platelets</td>
<td>↑ platelet count (∼5000/mm³/unit)</td>
<td>Stop significant bleeding (thrombocytopenia, qualitative platelet defects)</td>
</tr>
<tr>
<td>Fresh frozen plasma/prothrombin complex concentrate</td>
<td>↑ coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, as well as protein C and S</td>
<td>DIC, cirrhosis, immediate anticoagulation reversal</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin</td>
<td>Coagulation factor deficiencies involving fibrinogen and factor VIII</td>
</tr>
</tbody>
</table>

Blood transfusion risks include infection transmission (low), transfusion reactions, iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a Ca²⁺ chelator), and hyperkalemia (RBCs may lyse in old blood units).

Leukemia vs lymphoma

Leukemia
Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.

Lymphoma
Discrete tumor mass arising from lymph nodes. Presentations often blur definitions.

Hodgkin vs non-Hodgkin lymphoma

Hodgkin
Both may present with constitutional (“B”) signs/symptoms: low-grade fever, night sweats, weight loss (patients are Bothered by B symptoms).

- Localized, single group of nodes; contiguous spread (stage is strongest predictor of prognosis). Overall prognosis better than that of non-Hodgkin lymphoma.
- Characterized by Reed-Sternberg cells.
- Bimodal distribution—young adulthood and > 55 years; more common in men except for nodular sclerosing type.
- Associated with EBV.

Non-Hodgkin
Majority involve B cells; a few are of T-cell lineage.

- Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread.
- Can occur in children and adults.
- May be associated with HIV and autoimmune diseases.

Hodgkin lymphoma
Contains Reed-Sternberg cells: distinctive tumor giant cells; binucleate or bilobed with the 2 halves as mirror images (“owl eyes”). 2 owl eyes × 15 = 30. RS cells are CD15+ and CD30+ B-cell origin.

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular sclerosis</td>
<td>Most common</td>
</tr>
<tr>
<td>Lymphocyte rich</td>
<td>Best prognosis</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>Eosinophilia, seen in immunocompromised patients</td>
</tr>
<tr>
<td>Lymphocyte depleted</td>
<td>Seen in immunocompromised patients</td>
</tr>
<tr>
<td>Neoplasms of mature B cells</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Burkitt lymphoma</strong></td>
<td>Adolescents or young adults t(8;14)—translocation of c-myc (8) and heavy-chain Ig (14) “Starry sky” appearance, sheets of lymphocytes with interspersed “tingible body” macrophages (arrows in A). Associated with EBV. Jaw lesion in endemic form in Africa; pelvis or abdomen in sporadic form.</td>
</tr>
<tr>
<td><strong>Diffuse large B-cell lymphoma</strong></td>
<td>Usually older adults, but 20% in children t(14;18)—translocation of heavy-chain Ig (14) and BCL-2 (18) Most common type of non-Hodgkin lymphoma in adults.</td>
</tr>
<tr>
<td><strong>Follicular lymphoma</strong></td>
<td>Adults t(14;18)—translocation of heavy-chain Ig (14) and BCL-2 (18) Indolent course; Bcl-2 inhibits apoptosis. Presents with painless “waxing and waning” lymphadenopathy.</td>
</tr>
<tr>
<td><strong>Mantle cell lymphoma</strong></td>
<td>Adult males t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD 5+ Very aggressive, patients typically present with late-stage disease.</td>
</tr>
<tr>
<td><strong>Marginal zone lymphoma</strong></td>
<td>Adults t(11;18) Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma]).</td>
</tr>
<tr>
<td><strong>Primary central nervous system lymphoma</strong></td>
<td>Adults Most commonly associated with HIV/AIDS; pathogenesis involves EBV infection Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. Mass lesion(s) (may be ring-enhancing in immunocompromised patient) on MRI needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neoplasms of mature T cells</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult T-cell lymphoma</strong></td>
<td>Adults Caused by HTLV (associated with IV drug abuse) Adults present with cutaneous lesions; common in Japan, West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.</td>
</tr>
<tr>
<td><strong>Mycosis fungoides/ Sézary syndrome</strong></td>
<td>Adults Mycosis fungoides: skin patches (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with “cerebriform” nuclei and intraepidermal neoplastic cell aggregates (Pautrier microabscess). May progress to Sézary syndrome (T-cell leukemia).</td>
</tr>
</tbody>
</table>
Multiple myeloma

Monoclonal plasma cell ("fried egg" appearance) cancer that arises in the marrow and produces large amounts of IgG (55%) or IgA (25%). Bone marrow > 10% monoclonal plasma cells. Most common 1° tumor arising within bone in people > 40–50 years old. Associated with:

* ↑ susceptibility to infection
* Primary amyloidosis (AL)
* Punched-out lytic bone lesions on x-ray
* M spike on serum protein electrophoresis
* Ig light chains in urine (Bence Jones protein)
* Rouleaux formation (RBCs stacked like poker chips in blood smear)

Numerous plasma cells with "clock-face" chromatin and intracytoplasmic inclusions containing immunoglobulin.

Monoclonal gammopathy of undetermined significance (MGUS)—monoclonal expansion of plasma cells (bone marrow < 10% monoclonal plasma cells), asymptomatic, may lead to multiple myeloma. No CRAB findings. Patients with MGUS develop multiple myeloma at a rate of 1–2% per year.

Think CRAB:

- Hypercalcemia
- Renal involvement
- Anemia
- Bone lytic lesions/Back pain

Multiple Myeloma: Monoclonal M protein spike

Distinguish from Waldenström macroglobulinemia — M spike = IgM

→ hyperviscosity syndrome (eg, blurred vision, Raynaud phenomenon); no CRAB findings.

Myelodysplastic syndromes

Stem-cell disorders involving ineffective hematopoiesis → defects in cell maturation of nonlymphoid lineages. Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

Pseudo–Pelger–Huet anomaly—neutrophils with bilobed ("duet") nuclei. Typically seen after chemotherapy.
Leukemias

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood); rare cases present with normal/↓ WBCs. Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

<table>
<thead>
<tr>
<th>Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia/lymphoma</td>
<td>Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑ lymphoblasts A. TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells). Most responsive to therapy. May spread to CNS and testes. t(12;21) → better prognosis.</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
<td>Age &gt; 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. CLL = Crushed Little Lymphocytes (smudge cells). Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).</td>
</tr>
<tr>
<td>Myeloid neoplasms</td>
<td>Median onset 65 years. Auer rods D; myeloperoxidase E cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑ circulating myeloblasts on peripheral smear; adults. Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome. APL: t(15;17), responds to all-trans retinoic acid (vitamin A), inducing differentiation of promyelocytes; DIC is a common presentation.</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>Occurs across the age spectrum with peak incidence 45–85 years, median age at diagnosis 64 years. Defined by the Philadelphia chromosome (t[9;22], BCR-ABL) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils E) and splenomegaly. May accelerate and transform to AML or ALL (“blast crisis”). Very low LAP as a result of low activity in malignant neutrophils (vs benign neutrophilia [leukemoid reaction], in which LAP is ↑). Responds to bcr-abl tyrosine kinase inhibitors (eg, imatinib, dasatinib).</td>
</tr>
</tbody>
</table>
The myeloproliferative disorders (polycythemia vera, essential thrombocythemia, myelofibrosis, and CML) are malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines. Associated with V617F JAK2 mutation.

**Polycythemia vera**

Primary polycythemia. Disorder of ↑ RBCs. May present as intense itching after hot shower. Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A. ↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO). Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor).

**Essential thrombocythemia** Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed B. Erythromelalgia may occur.

**Myelofibrosis** Obliteration of bone marrow with fibrosis C due to ↑ fibroblast activity. Often associated with massive splenomegaly and "teardrop" RBCs D. "Bone marrow is crying because it's fibrosed and is a dry tap."

<table>
<thead>
<tr>
<th></th>
<th>RBCs</th>
<th>WBCs</th>
<th>PLATELETS</th>
<th>PHILADELPHIA CHROMOSOME</th>
<th>JAK2 MUTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>⊕</td>
<td>⊕</td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td>–</td>
<td>–</td>
<td>↑</td>
<td>⊕</td>
<td>(30–50%)</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>↓</td>
<td>Variable</td>
<td>Variable</td>
<td>⊕</td>
<td>⊕ (30–50%)</td>
</tr>
<tr>
<td>CML</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>⊕</td>
<td>⊕</td>
</tr>
</tbody>
</table>

**Polycythemia**

<table>
<thead>
<tr>
<th></th>
<th>PLASMA VOLUME</th>
<th>RBC MASS</th>
<th>O₂ SATURATION</th>
<th>EPO LEVELS</th>
<th>ASSOCIATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Dehydration, burns.</td>
</tr>
<tr>
<td>Appropriate absolute</td>
<td>–</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Lung disease, congenital heart disease, high altitude.</td>
</tr>
<tr>
<td>Inappropriate absolute</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
<td>Malignancy (eg, renal cell carcinoma, hepatocellular carcinoma), hydronephrosis. Due to ectopic EPO secretion.</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>↑</td>
<td>↑↑</td>
<td>–</td>
<td>↓</td>
<td>EPO ↓ in PCV due to negative feedback suppressing renal EPO production.</td>
</tr>
</tbody>
</table>

↑↑ = 1° disturbance
### Chromosomal translocations

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Associated Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>Burkitt (Burk-8) lymphoma (c-myc activation)</td>
</tr>
<tr>
<td>t(9;22) (Philadelphia chromosome)</td>
<td>CML (BCR-ABL hybrid), ALL (less common, poor prognostic factor)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Mantle cell lymphoma (cyclin D1 activation)</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>Follicular lymphoma (BCL-2 activation)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>APL (M3 type of AML)</td>
</tr>
</tbody>
</table>

**Philadelphia CreaML cheese.**

The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, c-myc and BCL-2) are translocated next to this heavy chain gene region, they are overexpressed.

**t(11;14)** Mantle cell lymphoma (cyclin D1 activation)

**t(14;18)** Follicular lymphoma (BCL-2 activation)

**t(15;17)** APL (M3 type of AML)

Responds to all-trans retinoic acid.

### Langerhans cell histiocytosis

Collective group of proliferative disorders of dendritic (Langerhans) cells. Presents in a child as lytic bone lesions and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 (mesodermal origin) and CD1a. Birbeck granules (“tennis rackets” or rod shaped on EM) are characteristic.

### Tumor lysis syndrome

Oncologic emergency triggered by massive tumor cell lysis, most often in lymphomas/leukemias. Release of K⁺ → hyperkalemia, release of PO₄³⁻ → hyperphosphatemia, hypocalcemia due to Ca²⁺ sequestration by PO₄³⁻. ↑ nucleic acid breakdown → hyperuricemia → acute kidney injury. Prevention and treatment include aggressive hydration, allopurinol, rasburicase.
### Heparin

| MECHANISM | Activates antithrombin, which ↓ action of IIa (thrombin) and factor Xa. Short half-life. |
| CLINICAL USE | Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta). Follow PTT. |
| ADVERSE EFFECTS | Bleeding, thrombocytopenia (HIT), osteoporosis, drug-drug interactions. For rapid reversal (antidote), use protamine sulfate (positively charged molecule that binds negatively charged heparin). |
| NOTES | Low-molecular-weight heparins (eg, enoxaparin, dalteparin) act predominantly on factor Xa. Fondaparinux acts only on factor Xa. Have better bioavailability and 2–4× longer half life than unfractionated heparin; can be administered subcutaneously and without laboratory monitoring. Not easily reversible. Heparin-induced thrombocytopenia (HIT)—development of IgG antibodies against heparin-bound platelet factor 4 (PF4). Antibody-heparin-PF4 complex activates platelets → thrombosis and thrombocytopenia. |

### Direct thrombin inhibitors

| Direct thrombin inhibitors | Bivalirudin (related to hirudin, the anticoagulant used by leeches), Argatroban, Dabigatran (only oral agent in class). |
| MECHANISM | Directly inhibits activity of free and clot-associated thrombin. |
| CLINICAL USE | Venous thromboembolism, atrial fibrillation. Can be used in HIT, when heparin is BAD for the patient. Does not require lab monitoring. |
| ADVERSE EFFECTS | Bleeding; can reverse dabigatran with idarucizumab. Consider PCC and/or antifibrinolytics (eg, tranexamic acid) if no reversal agent available. |
Warfarin

**MECHANISM**
Interferes with $\gamma$-carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X, and proteins C and S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (VKORC1). In laboratory assay, has effect on EXtrinsic pathway and $\uparrow$ PT. Long half-life.

**CLINICAL USE**
Chronic anticoagulation (eg, venous thromboembolism prophylaxis, and prevention of stroke in atrial fibrillation). Not used in pregnant women (because warfarin, unlike heparin, crosses placenta). Follow PT/INR.

**ADVERSE EFFECTS**
Bleeding, teratogenic, skin/tissue necrosis, drug-drug interactions. Initial risk of hypercoagulation: protein C has a shorter half-life than factors II and X. Existing protein C depletes before existing factors II and X deplete, and before warfarin can reduce factors II and X production $\rightarrow$ hypercoagulation. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthrombosis.

For reversal of warfarin, give vitamin K. For rapid reversal, give fresh frozen plasma (FFP) or PCC. Heparin “bridging”: heparin frequently used when starting warfarin. Heparin’s activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis. Cytochrome P-450 inhibitors increase warfarin effect.

**Heparin vs warfarin**

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROUTE OF ADMINISTRATION</strong></td>
<td>Parenteral (IV, SC)</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>SITE OF ACTION</strong></td>
<td>Blood</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>ONSET OF ACTION</strong></td>
<td>Rapid (seconds)</td>
<td>Slow, limited by half-lives of normal clotting factors</td>
</tr>
<tr>
<td><strong>MECHANISM OF ACTION</strong></td>
<td>Activates antithrombin, which $\downarrow$ the action of IIa (thrombin) and factor Xa</td>
<td>Impairs synthesis of vitamin K–dependent clotting factors II, VII, IX, and X, and anticoagulation proteins C and S</td>
</tr>
<tr>
<td><strong>DURATION OF ACTION</strong></td>
<td>Hours</td>
<td>Days</td>
</tr>
<tr>
<td><strong>AGENTS FOR REVERSAL</strong></td>
<td>Protamine sulfate</td>
<td>Vitamin K, FFP, PCC</td>
</tr>
<tr>
<td><strong>MONITORING</strong></td>
<td>PTT (intrinsic pathway)</td>
<td>PT/INR (extrinsic pathway)</td>
</tr>
<tr>
<td><strong>CROSSES PLACENTA</strong></td>
<td>No</td>
<td>Yes (teratogenic)</td>
</tr>
</tbody>
</table>
**Direct factor Xa inhibitors**

**Antithrombin (Heparin)**
- **Mechanism:** Directly inhibit factor Xa.
- **Clinical Use:** Treatment and prophylaxis for DVT and PE; stroke prophylaxis in patients with atrial fibrillation. Oral agents do not usually require coagulation monitoring.
- **Adverse Effects:** Bleeding. Not easily reversible.

**Thrombolytics**

- **Alteplase (tPA), reteplase (rPA), streptokinase, tenecteplase (TNK-tPA).**
- **Mechanism:** Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots. ↑ PT, ↑ PTT, no change in platelet count.
- **Clinical Use:** Early MI, early ischemic stroke, direct thrombolysis of severe PE.
- **Adverse Effects:** Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diatheses, or severe hypertension. Nonspecific reversal with antifibrinolytics (eg, aminocaproic acid, tranexamic acid), platelet transfusions, and factor corrections (eg, cryoprecipitate, FFP, PCC).

**ADP receptor inhibitors**

- **Clopidogrel, prasugrel, ticagrelor (reversible), ticlopidine.**
- **Mechanism:** Inhibit platelet aggregation by irreversibly blocking ADP (P2Y12) receptor. Prevent expression of glycoproteins IIb/IIIa on platelet surface.
- **Clinical Use:** Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke.
- **Adverse Effects:** Neutropenia (ticlopidine). TTP may be seen.

**Cilostazol, dipyridamole**

- **Mechanism:** Phosphodiesterase inhibitors; ↑ cAMP in platelets, resulting in inhibition of platelet aggregation; vasodilators.
- **Clinical Use:** Intermittent claudication, coronary vasodilation, prevention of stroke or TIA's (combined with aspirin).
- **Adverse Effects:** Nausea, headache, facial flushing, hypotension, abdominal pain.

**Glycoprotein IIb/IIIa inhibitors**

- **Abciximab, eptifibatide, tirofiban.**
- **Mechanism:** Bind to the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation. Abciximab is made from monoclonal antibody Fab fragments.
- **Clinical Use:** Unstable angina, percutaneous coronary intervention.
- **Adverse Effects:** Bleeding, thrombocytopenia.
Cancer drugs—cell cycle

Cancer drugs—targets
### Antimetabolites

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM(^a)</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azathioprine, 6-mercaptopurine</strong></td>
<td>Purine (thiol) analogs → 4 de novo purine synthesis. Activated by HGPRT. Azathioprine is metabolized into 6-MP.</td>
<td>Preventing organ rejection, rheumatoid arthritis, IBD, SLE; used to wean patients off steroids in chronic disease and to treat steroid-refractory chronic disease.</td>
<td>Myelosuppression; GI, liver toxicity. Azathioprine and 6-MP are metabolized by xanthine oxidase; thus both have ↑ toxicity with allopurinol or febuxostat.</td>
</tr>
<tr>
<td><strong>Cladribine</strong></td>
<td>Purine analog → multiple mechanisms (eg, inhibition of DNA polymerase, DNA strand breaks).</td>
<td>Hairy cell leukemia.</td>
<td>Myelosuppression, nephrotoxicity, and neurotoxicity.</td>
</tr>
<tr>
<td><strong>Cytarabine (arabinofuranosyl cytidine)</strong></td>
<td>Pyrimidine analog → DNA chain termination. At higher concentrations, inhibits DNA polymerase.</td>
<td>Leukemias (AML), lymphomas.</td>
<td>Myelosuppression with megaloblastic anemia. Cytarabine causes panCYTopenia.</td>
</tr>
<tr>
<td><strong>5-fluorouracil</strong></td>
<td>Pyrimidine analog bioactivated to 5-FdUMP, which covalently complexes with thymidylate synthase and folic acid. Capecitabine is a prodrug with similar activity. This complex inhibits thymidylate synthase → 4 dTMP → 4 DNA synthesis.</td>
<td>Colon cancer, pancreatic cancer, actinic keratosis, basal cell carcinoma (topical). Effects enhanced with the addition of leucovorin.</td>
<td>Myelosuppression, palmar-plantar erythrodysesthesia (hand-foot syndrome).</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Folic acid analog that competitively inhibits dihydrofolate reductase → 4 dTMP → 4 DNA synthesis.</td>
<td>Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas. Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.</td>
<td>Myelosuppression, which is reversible with leucovorin “rescue.” Hepatotoxicity. Mucositis (eg, mouth ulcers). Pulmonary fibrosis. Folate deficiency, which may be teratogenic (neural tube defects) without supplementation. Nephrotoxicity (rare).</td>
</tr>
</tbody>
</table>

\(^a\) All are S-phase specific.
### Antitumor Antibiotics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin, daunorubicin</td>
<td>Generate free radicals. Intercalate in DNA → breaks in DNA → ↓ replication. Interferes with topoisomerase II enzyme.</td>
<td>Solid tumors, leukemias, lymphomas.</td>
<td>Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia. Dextrazoxane (iron chelating agent), used to prevent cardiotoxicity.</td>
</tr>
</tbody>
</table>

### Alkylating Agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan</td>
<td>Cross-links DNA.</td>
<td>Used to ablate patient’s bone marrow before bone marrow transplantation.</td>
<td>Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation.</td>
</tr>
<tr>
<td>Cyclophosphamide, ifosfamide</td>
<td>Cross-link DNA at guanine. Require bioactivation by liver. A nitrogen mustard.</td>
<td>Solid tumors, leukemia, lymphomas.</td>
<td>Myelosuppression; SIADH; hemorrhagic cystitis, prevented with mesna (thiol group of mesna binds toxic metabolites) or adequate hydration.</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Require bioactivation. Cross blood-brain barrier → CNS. Cross-link DNA.</td>
<td>Brain tumors (including glioblastoma multiforme).</td>
<td>CNS toxicity (convulsions, dizziness, ataxia).</td>
</tr>
</tbody>
</table>
### Microtubule Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Clinical Use</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel, other taxanes</td>
<td>Hyperstabilize polymerized microtubules in M phase so that mitotic spindle cannot break down (anaphase cannot occur).</td>
<td>Ovarian and breast carcinomas. Myelosuppression, neuropathy, hypersensitivity.</td>
<td><strong>Taxes stabilize</strong> society.</td>
</tr>
<tr>
<td>Vincristine, vinblastine</td>
<td>Vinca alkaloids that bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation (M-phase arrest).</td>
<td>Solid tumors, leukemias, Hodgkin (vinblastine) and non-Hodgkin (vincristine) lymphomas.</td>
<td>Vincristine: neurotoxicity (areflexia, peripheral neuritis), constipation (including paralytic ileus). Crisps the nerves. Vinblastine: bone marrow suppression. Blasts the bone marrow.</td>
</tr>
</tbody>
</table>

### Cisplatin, carboplatin

- **Mechanism**: Cross-link DNA.
- **Clinical Use**: Testicular, bladder, ovary, and lung carcinomas.
- **Adverse Effects**: Nephrotoxicity, peripheral neuropathy, ototoxicity. Prevent nephrotoxicity with amifostine (free radical scavenger) and chloride (saline) diuresis.

### Etoposide, teniposide

- **Mechanism**: Inhibit topoisomerase II → DNA degradation.
- **Clinical Use**: Solid tumors (particularly testicular and small cell lung cancer), leukemias, lymphomas.
- **Adverse Effects**: Myelosuppression, alopecia.

### Irinotecan, topotecan

- **Mechanism**: Inhibit topoisomerase I and prevent DNA unwinding and replication.
- **Clinical Use**: Colon cancer (irinotecan); ovarian and small cell lung cancers (topotecan).
- **Adverse Effects**: Severe myelosuppression, diarrhea.

### Hydroxyurea

- **Mechanism**: Inhibits ribonucleotide reductase → DNA Synthesis (S-phase specific).
- **Clinical Use**: Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell († HbF).
- **Adverse Effects**: Severe myelosuppression.
### Bevacizumab

**MECHANISM**
Monoclonal antibody against VEGF. Inhibits angiogenesis (Bevacizumab inhibits Blood Vessel formation).

**CLINICAL USE**
Solid tumors (colorectal cancer, renal cell carcinoma), wet age-related macular degeneration.

**ADVERSE EFFECTS**
Hemorrhage, blood clots, and impaired wound healing.

### Erlotinib

**MECHANISM**
EGFR tyrosine kinase inhibitor.

**CLINICAL USE**
Non-small cell lung carcinoma.

**ADVERSE EFFECTS**
Rash.

### Cetuximab

**MECHANISM**
Monoclonal antibody against EGFR.

**CLINICAL USE**
Stage IV colorectal cancer (wild-type KRAS), head and neck cancer.

**ADVERSE EFFECTS**
Rash, elevated LFTs, diarrhea.

### Imatinib

**MECHANISM**
Tyrosine kinase inhibitor of BCR-ABL (Philadelphia chromosome fusion gene in CML) and c-kit (common in GI stromal tumors).

**CLINICAL USE**
CML, GI stromal tumors (GIST).

**ADVERSE EFFECTS**
Fluid retention.

### Rituximab

**MECHANISM**
Monoclonal antibody against CD20, which is found on most B-cell neoplasms.

**CLINICAL USE**
Non-Hodgkin lymphoma, CLL, ITP, rheumatoid arthritis.

**ADVERSE EFFECTS**
1 risk of progressive multifocal leukoencephalopathy.

### Bortezomib, carfilzomib

**MECHANISM**
Proteasome inhibitors, induce arrest at G2-M phase and apoptosis.

**CLINICAL USE**
Multiple myeloma, mantle cell lymphoma.

**ADVERSE EFFECTS**
Peripheral neuropathy, herpes zoster reactivation.
Tamoxifen, raloxifene

**MECHANISM**
Selective estrogen receptor modulators (SERMs)—receptor antagonists in breast and agonists in bone. Block the binding of estrogen to ER cells.

**CLINICAL USE**
Breast cancer treatment (tamoxifen only) and prevention. Raloxifene also useful to prevent osteoporosis.

**ADVERSE EFFECTS**
Tamoxifen—partial agonist in endometrium, which ↑ the risk of endometrial cancer; “hot flashes.” Raloxifene—no ↑ in endometrial carcinoma (so you can relax!), because it is an estrogen receptor antagonist in endometrial tissue. Both ↑ risk of thromboembolic events (eg, DVT, PE).

Trastuzumab (Herceptin)

**MECHANISM**
Monoclonal antibody against HER-2 (c-erbB2), a tyrosine kinase receptor. Helps kill cancer cells that overexpress HER-2 through inhibition of HER-2 initiated cellular signaling and antibody-dependent cytotoxicity.

**CLINICAL USE**
HER-2 + breast cancer and gastric cancer (tras2umab).

**ADVERSE EFFECTS**
Cardiotoxicity. “Heartceptin” damages the heart.

Vemurafenib

**MECHANISM**
Small molecule inhibitor of BRAF oncogene + melanoma. VEmuRAF-enib is for V600E-mutated BRAF inhibition.

**CLINICAL USE**
Metastatic melanoma.

Rasburicase

**MECHANISM**
Recombinant uricase that catalyzes metabolism of uric acid to allantoin.

**CLINICAL USE**
Prevention and treatment of tumor lysis syndrome.

Common chemotoxicities

- Cisplatin/Carboplatin → ototoxicity
- Vincristine → peripheral neuropathy
- Bleomycin, Busulfan → pulmonary fibrosis
- Doxorubicin → cardiotoxicity
- Trastuzumab (Herceptin) → cardiotoxicity
- Cisplatin/Carboplatin → nephrotoxicity
- CYclophosphamide → hemorrhagic cystitis
“Rigid, the skeleton of habit alone upholds the human frame.”
—Virginia Woolf

“Beauty may be skin deep, but ugly goes clear to the bone.”
—Redd Foxx

“The function of muscle is to pull and not to push, except in the case of the genitals and the tongue.”
—Leonardo da Vinci

“To thrive in life you need three bones. A wishbone. A backbone. And a funny bone.”
—Reba McEntire

This chapter provides information you will need to understand certain anatomical dysfunctions, rheumatic diseases, and dermatologic conditions. Be able to interpret 3D anatomy in the context of radiologic imaging. For the rheumatic diseases, create instructional cases or personas that includes the most likely presentation and symptoms: risk factors, gender, important markers (eg, autoantibodies), and other epidemiologic factors. Doing so will allow you to answer the higher order questions that are likely to be asked on the exam.
Musculoskeletal, skin, and connective tissue anatomy and physiology

Arm abduction

<table>
<thead>
<tr>
<th>DEGREE</th>
<th>MUSCLE</th>
<th>NERVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0°–15°</td>
<td>Supraspinatus</td>
<td>Suprascapular</td>
</tr>
<tr>
<td>15°–100°</td>
<td>Deltoid</td>
<td>Axillary</td>
</tr>
<tr>
<td>&gt; 90°</td>
<td>Trapezius</td>
<td>Accessory</td>
</tr>
<tr>
<td>&gt; 100°</td>
<td>Serratus Anterior</td>
<td>Long Thoracic (SALT)</td>
</tr>
</tbody>
</table>

Rotator cuff muscles

- **Supraspinatus** (suprascapular nerve)—abducts arm initially (before the action of the deltoid); most common rotator cuff injury (trauma or degeneration and impingement → tendinopathy or tear [arrow in A]), assessed by “empty/full can” test.
- **Infraspinatus** (suprascapular nerve)—externally rotates arm; pitching injury.
- **Teres minor** (axillary nerve)—adducts and externally rotates arm.
- **Subscapularis** (upper and lower subscapular nerves)—internally rotates and adducts arm. Innervated primarily by C5-C6.

**SHS** (small t is for teres minor).

Overuse injuries of the elbow

- **Medial epicondylitis** (golfer’s elbow) → Repetitive flexion (forehand shots) or idiopathic → pain near medial epicondyle.
- **Lateral epicondylitis** (tennis elbow) → Repetitive extension (backhand shots) or idiopathic → pain near lateral epicondyle.
### Wrist region

Scaphoid, Lunate, Triquetrum, Pisiform, Hamate, Capitate, Trapezoid, Trapezium (So Long To Pinky, Here Comes The Thumb).

Scaphoid (palpable in anatomic snuff box) is the most commonly fractured carpal bone, typically due to a fall on an outstretched hand. Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply. Fracture not always seen on initial x-ray. Dislocation of lunate may cause acute carpal tunnel syndrome.

### Metacarpal neck fracture

Also called boxer’s fracture. Common fracture caused by direct blow with a closed fist (eg, from punching a wall or individual). Most commonly seen in 4th and 5th metacarpals.

### Carpal tunnel syndrome

Entrapment of median nerve in carpal tunnel (between transverse carpal ligament and carpal bones); nerve compression → paresthesia, pain, and numbness in distribution of median nerve. Thenar eminence atrophies but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel. Suggested by ⊕ Tinel sign (percussion of wrist causes tingling) and Phalen maneuver (90° flexion of wrist causes tingling). Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may be associated with repetitive use.

### Guyon canal syndrome

Compression of ulnar nerve at wrist. Classically seen in cyclists due to pressure from handlebars.

---

![Diagram of the wrist region and carpal tunnel](image-url)
Common pediatric fractures

Greenstick fracture  Incomplete fracture extending partway through width of bone following bending stress; bone fails on tension side; compression side intact (compare to torus fracture). Bone is bent like a green twig.

Torus (buckle) fracture  Axial force applied to immature bone → cortex buckles on compression side and fractures. Tension side (other side of cortex) remains intact.

Hand muscles

Thenar (median)—Opponens pollicis, Abductor pollicis brevis, Flexor pollicis brevis, superficial head (deep head by ulnar nerve).
Hypothenar (ulnar)—Opponens digiti minimi, Abductor digiti minimi, Flexor digiti minimi brevis.
Dorsal interossei (ulnar)—abduct the fingers.
Palmar interossei (ulnar)—adduct the fingers.
Lumbricals (1st/2nd, median; 3rd/4th, ulnar)—flex at the MCP joint, extend PIP and DIP joints.

Both groups perform the same functions: Oppose, Abduct, and Flex (OAF).

Dorsals = DAB duct.
Palmars = PAD duct.
## Upper extremity nerves

<table>
<thead>
<tr>
<th>NERVE</th>
<th>CAUSES OF INJURY</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary (C5-C6)</td>
<td>Fractured surgical neck of humerus, Anterior dislocation of humerus</td>
<td>Flattened deltoid, Loss of arm abduction at shoulder (&gt; 15°), Loss of sensation over deltoid muscle and lateral arm</td>
</tr>
<tr>
<td>Musculocutaneous (C5-C7)</td>
<td>Upper trunk compression</td>
<td>Loss of forearm flexion and supination, Loss of sensation over lateral forearm</td>
</tr>
<tr>
<td>Radial (C5-T1)</td>
<td>Compression of axilla, eg, due to crutches or sleeping with arm over chair (“Saturday night palsy”), Midshaft fracture of humerus, Repetitive pronation/supination of forearm, eg, due to screwdriver use (“finger drop”)</td>
<td>Wrist drop: loss of elbow, wrist, and finger extension, ↓ grip strength (wrist extension necessary for maximal action of flexors), Loss of sensation over posterior arm/forearm and dorsal hand</td>
</tr>
<tr>
<td>Median (C5-T1)</td>
<td>Supracondylar fracture of humerus (proximal lesion), Carpal tunnel syndrome and wrist laceration (distal lesion)</td>
<td>“Ape hand” and “Pope’s blessing”, Loss of wrist flexion, flexion of lateral fingers, thumb opposition, lumbricals of 2nd and 3rd digits, Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 3½ fingers with proximal lesion</td>
</tr>
<tr>
<td>Ulnar (C8-T1)</td>
<td>Fracture of medial epicondyle of humerus “funny bone” (proximal lesion), Fractured hook of hamate (distal lesion) from fall on outstretched hand</td>
<td>“Ulnar claw” on digit extension, Radial deviation of wrist upon flexion (proximal lesion), Loss of wrist flexion, flexion of median fingers, abduction and adduction of fingers (interossei), actions of medial 2 lumbrical muscles, Loss of sensation over medial 1½ fingers including hypothenar eminence</td>
</tr>
<tr>
<td>Recurrent branch of median nerve (C5-T1)</td>
<td>Superficial laceration of palm</td>
<td>“Ape hand”, Loss of thenar muscle group: opposition, abduction, and flexion of thumb, No loss of sensation</td>
</tr>
</tbody>
</table>

Humerus fractures, proximally to distally, follow the **ARM** (Axillary → Radial → Median)
### Brachial Plexus Lesions

- **Erb palsy ("waiter’s tip")**
  - Traction or tear of upper ("Erb-er") trunk: C5-C6 roots
  - **Injury:** Traction or tear of upper ("Erb-er") trunk, C5-C6 roots
  - **Causes:** Infants—lateral traction on neck during delivery, Adults—trauma
  - **Muscle Deficit:** Deltoid, supraspinatus
  - **Functional Deficit:** Abduction (arm hangs by side)
  - **Presentation:** Infraspinatus

- **Klumpke palsy**
  - Traction or tear of lower trunk: C8-T1 root
  - **Injury:** Traction or tear of lower trunk, C8-T1 root
  - **Causes:** Infants—upward force on arm during delivery, Adults—trauma (e.g., grabbing a tree branch to break a fall)
  - **Muscle Deficit:** Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar
  - **Functional Deficit:** Total claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints

- **Thoracic Outlet Syndrome**
  - Compression of lower trunk and subclavian vessels
  - **Injury:** Compression of lower trunk and subclavian vessels
  - **Causes:** Cervical rib (arrows in A), Pancoast tumor
  - **Muscle Deficit:** Same as Klumpke palsy
  - **Functional Deficit:** Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression

- **Winged Scapula**
  - Lesion of long thoracic nerve, roots C5-C7 ("wings of heaven")
  - **Injury:** Lesion of long thoracic nerve, roots C5-C7 ("wings of heaven")
  - **Causes:** Axillary node dissection after mastectomy, stab wounds
  - **Muscle Deficit:** Serratus anterior
  - **Functional Deficit:** Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position
Distortions of the hand At rest, a balance exists between the extrinsic flexors and extensors of the hand, as well as the intrinsic muscles of the hand—particularly the lumbrical muscles (flexion of MCP, extension of DIP and PIP joints).

“Clawing”—seen best with distal lesions of median or ulnar nerves. Remaining extrinsic flexors of the digits exaggerate the loss of the lumbricals → fingers extend at MCP, flex at DIP and PIP joints.

Deficits less pronounced in proximal lesions; deficits present during voluntary flexion of the digits.

<table>
<thead>
<tr>
<th>PRESENTATION</th>
<th>CONTEXT</th>
<th>LOCATION OF Lesion</th>
<th>SIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extending fingers/at rest</td>
<td>Distal ulnar nerve</td>
<td>“Ulnar claw”</td>
</tr>
<tr>
<td></td>
<td>Making a fist</td>
<td>Proximal median nerve</td>
<td>“Pope’s blessing”</td>
</tr>
<tr>
<td></td>
<td>Extending fingers/at rest</td>
<td>Distal median nerve</td>
<td>“Median claw”</td>
</tr>
<tr>
<td></td>
<td>Making a fist</td>
<td>Proximal ulnar nerve</td>
<td>“OK gesture”</td>
</tr>
</tbody>
</table>

Note: Atrophy of the thenar eminence (unopposable thumb → “ape hand”) can be seen in median nerve lesions, while atrophy of the hypothenar eminence can be seen in ulnar nerve lesions.
Knee exam

Lateral femoral condyle to anterior tibia: ACL.
Medial femoral condyle to posterior tibia: PCL.
LAMP.

<table>
<thead>
<tr>
<th>Test</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior drawer sign</strong></td>
<td>Bending knee at 90° angle; ↑ anterior gliding of tibia (relative to femur) due to ACL injury. Lachman test also tests ACL, but is more sensitive (↑ anterior gliding of tibia [relative to femur] with knee bent at 30° angle).</td>
</tr>
<tr>
<td><strong>Posterior drawer sign</strong></td>
<td>Bending knee at 90° angle; ↑ posterior gliding of tibia due to PCL injury.</td>
</tr>
<tr>
<td><strong>Abnormal passive abduction</strong></td>
<td>Knee either extended or at ~ 30° angle, lateral (valgus) force → medial space widening of tibia → MCL injury.</td>
</tr>
<tr>
<td><strong>Abnormal passive adduction</strong></td>
<td>Knee either extended or at ~ 30° angle, medial (varus) force → lateral space widening of tibia → LCL injury.</td>
</tr>
<tr>
<td><strong>McMurray test</strong></td>
<td>During flexion and extension of knee with rotation of tibia/foot:</td>
</tr>
<tr>
<td></td>
<td>• Pain, “popping” on external rotation → medial meniscal tear (external rotation stresses medial meniscus)</td>
</tr>
<tr>
<td></td>
<td>• Pain, “popping” on internal rotation → lateral meniscal tear (internal rotation stresses lateral meniscus)</td>
</tr>
</tbody>
</table>
Common hip and knee conditions

**Trochanteric bursitis**
Inflammation of the gluteal tendon and bursa lateral to greater trochanter of femur. Treat pain with NSAIDs, heat, stretching.

**“Unhappy triad”**
Common injury in contact sports due to lateral force applied to a planted leg. Classically, consists of damage to the ACL, MCL, and medial meniscus (attached to MCL); however, lateral meniscus injury is more common. Presents with acute knee pain and signs of joint injury/instability.

**Prepatellar bursitis**
Inflammation of the prepatellar bursa in front of the kneecap (red arrow in image). Can be caused by repeated trauma or pressure from excessive kneeling (also called “housemaid’s knee”).

**Baker cyst**
Popliteal fluid collection (red arrow in image) in gastrocnemius-semimembranosus bursa commonly communicating with synovial space and related to chronic joint disease (eg, osteoarthritis, rheumatoid arthritis).

---

**Ankle sprains**
Anterior Talofibular ligament—most common ankle sprain overall, classified as a low ankle sprain. Due to overinversion/supination of foot. Always Tears First. Anterior inferior tibiofibular ligament—most common high ankle sprain.
### Lower Extremity Nerves

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Innervation</th>
<th>Cause of Injury</th>
<th>Presentation/Comments</th>
</tr>
</thead>
</table>
| Iliohypogastric (T12-L1)     | Sensory—suprapubic region  
Motor—transversus abdominis and internal oblique | Abdominal surgery                      | Burning or tingling pain in surgical incision site radiating to inguinal and suprapubic region |
| Genitofemoral nerve (L1-L2)  | Sensory—scrotum/labia majora, medial thigh  
Motor—cremaster | Laparoscopic surgery                  | ↓ anterior thigh sensation beneath inguinal ligament; absent cremasteric reflex |
| Lateral femoral cutaneous (L2-L3) | Sensory—anterior and lateral thigh | Tight clothing, obesity, pregnancy, pelvic procedures | ↓ thigh sensation (anterior and lateral) |
| Obturator (L2-L4)            | Sensory—medial thigh  
Motor—obturator externus, adductor longus, adductor brevis, gracilis, pectineus, adductor magnus | Pelvic surgery                          | ↓ thigh sensation (medial) and adduction |
| Femoral (L2-L4)              | Sensory—anterior thigh, medial leg  
Motor—quadriceps, iliacus, pectineus, sartorius | Pelvic fracture                        | ↓ thigh flexion and leg extension |
| Sciatic (L4-S3)              | Motor—semitendinosus, semimembranosus, biceps femoris, adductor magnus       | Herniated disc, posterior hip dislocation | Splits into common peroneal and tibial nerves |
| Common peroneal (L4-S2)      | Superficial peroneal nerve:  
- Sensory—dorsum of foot (except webspace between hallux and 2nd digit)  
- Motor—peroneus longus and brevis  
Deep peroneal nerve:  
- Sensory—webspace between hallux and 2nd digit  
- Motor—tibialis anterior | Trauma or compression of lateral aspect of leg, fibular neck fracture | **PED** = Peroneal Everts and Dorsiflexes; if injured, foot drop **PED**  
Loss of sensation on dorsum of foot  
**Foot drop**—inverted and plantarflexed at rest, loss of eversion and dorsiflexion; “steppage gait” |
| Tibial (L4-S3)               | Sensory—sole of foot  
Motor—biceps femoris (long head), triceps surae, plantaris, popliteus, flexor muscles of foot | Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion) | **TIP** = Tibial Inverts and Plantarflexes; if injured, can’t stand on **TIP** toes  
Inability to curl toes and loss of sensation on sole; in proximal lesions, foot everted at rest with loss of inversion and plantarflexion |
## Lower extremity nerves (continued)

<table>
<thead>
<tr>
<th>NERVE</th>
<th>INNERSATION</th>
<th>CAUSE OF INJURY</th>
<th>PRESENTATION/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superior gluteal</strong> (L4-S1)</td>
<td>Motor—gluteus medius, gluteus minimus, tensor fascia latae</td>
<td>Iatrogenic injury during intramuscular injection to superomedial gluteal region (prevent by choosing superolateral quadrant, preferably anterolateral region)</td>
<td>Trendelenburg sign/gait—pelvis tilts because weight-bearing leg cannot maintain alignment of pelvis through hip abduction. Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands.</td>
</tr>
<tr>
<td>Normal/Trendelenburg sign</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inferior gluteal</strong> (L5-S2)</td>
<td>Motor—gluteus maximus</td>
<td>Posterior hip dislocation</td>
<td>Difficulty climbing stairs, rising from seated position; loss of hip extension</td>
</tr>
<tr>
<td><strong>Pudendal</strong> (S2-S4)</td>
<td>Sensory—perineum</td>
<td>Stretch injury during childbirth</td>
<td>↓ sensation in perineum and genital area; can cause fecal or urinary incontinence. Can be blocked with local anesthetic during childbirth using ischial spine as a landmark for injection.</td>
</tr>
<tr>
<td></td>
<td>Motor—external urethral and anal sphincters</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Actions of hip muscles

<table>
<thead>
<tr>
<th>ACTION</th>
<th>MUSCLES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abductors</strong></td>
<td>Gluteus medius, gluteus minimus</td>
</tr>
<tr>
<td><strong>Adductors</strong></td>
<td>Adductor magnus, adductor longus, adductor brevis</td>
</tr>
<tr>
<td><strong>Extensors</strong></td>
<td>Gluteus maximus, semitendinosus, semimembranosus</td>
</tr>
<tr>
<td><strong>Flexors</strong></td>
<td>Iliopsoas, rectus femoris, tensor fascia lata, pectineus, sartorius</td>
</tr>
<tr>
<td><strong>Internal rotation</strong></td>
<td>Gluteus medius, gluteus minimus, tensor fascia latae</td>
</tr>
<tr>
<td><strong>External rotation</strong></td>
<td>Iliopsoas, gluteus maximus, piriformis, obturator</td>
</tr>
</tbody>
</table>
### Common musculoskeletal conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliotibial band syndrome</td>
<td>Overuse injury of lateral knee that occurs primarily in runners. Pain develops due to friction of iliotibial band against lateral femoral epicondyle.</td>
</tr>
<tr>
<td>Medial tibial stress syndrome</td>
<td>Also called shin splints. Common cause of shin pain and diffuse tenderness in runners and military recruits. Caused by bone resorption that outpaces bone formation in tibial cortex.</td>
</tr>
<tr>
<td>Limb compartment syndrome</td>
<td>Pressure within a fascial compartment of a limb (defined by compartment pressure to diastolic blood pressure gradient of &lt; 30 mm Hg) → venous outflow obstruction and arteriolar collapse → anoxia and necrosis. Causes include significant long bone fractures, reperfusion injury, animal venoms. Presents with severe pain and tense, swollen compartments with limb flexion. Motor deficits are late sign of irreversible muscle and nerve damage.</td>
</tr>
<tr>
<td>Plantar fasciitis</td>
<td>Inflammation of plantar aponeurosis characterized by heel pain (worse with first steps in the morning or after period of inactivity) and tenderness.</td>
</tr>
<tr>
<td>De Quervain tenosynovitis</td>
<td>Noninflammatory thickening of abductor pollicis longus and extensor pollicis brevis tendons characterized by pain or tenderness at radial styloid. ⊕ Finkelstein test (pain at radial styloid with active or passive stretch of thumb tendons).</td>
</tr>
<tr>
<td>Ganglion cyst</td>
<td>Fluid-filled swelling overlying joint or tendon sheath, most commonly at dorsal side of wrist. Arises from herniation of dense connective tissue.</td>
</tr>
</tbody>
</table>

### Childhood musculoskeletal conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental dysplasia of the hip</td>
<td>Abnormal acetabulum development in newborns. Results in hip instability/dislocation. Commonly tested with Ortolani and Barlow maneuvers (manipulation of newborn hip reveals a “chunk”). Confirmed via ultrasound (x-ray not used until ~4–6 months because cartilage is not ossified). Treatment: splint/harness.</td>
</tr>
<tr>
<td>Legg-Calvé-Perthes disease</td>
<td>Idiopathic avascular necrosis of femoral head. Commonly presents between 5–7 years with insidious onset of hip pain that may cause child to limp. More common in males (4:1 ratio). Initial x-ray often normal.</td>
</tr>
<tr>
<td>Slipped capital femoral epiphysis</td>
<td>Classically presents in an obese ~12-year-old child with hip/knee pain and altered gait. Increased axial force on femoral head → epiphysis displaces relative to femoral neck (like a scoop of ice cream slipping off a cone). Diagnosed via x-ray. Treatment: surgery.</td>
</tr>
<tr>
<td>Radial head subluxation (nursemaid’s elbow)</td>
<td>Common elbow injury in children &lt; 5 years. Caused by a sudden pull on the arm → immature annular ligament slips over head of radius. Injured arm held in flexed and pronated position.</td>
</tr>
</tbody>
</table>
### Signs of lumbosacral radiculopathy

Paresthesia and weakness related to specific lumbosacral spinal nerves. Usually, the intervertebral disc herniates into central canal, affecting the inferior nerves (eg, herniation of L3/4 disc affects L4 spinal nerve, but not L3). Intervertebral discs generally herniate posterolaterally, due to the thin posterior longitudinal ligament and thicker anterior longitudinal ligament along the midline of the vertebral bodies.

<table>
<thead>
<tr>
<th>SPINAL LEVEL</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3–L4</td>
<td>Weakness of knee extension, ↓ patellar reflex</td>
</tr>
<tr>
<td>L4–L5</td>
<td>Weakness of dorsiflexion, difficulty in heel-walking</td>
</tr>
<tr>
<td>L5–S1</td>
<td>Weakness of plantar flexion, difficulty in toe-walking, ↓ Achilles reflex</td>
</tr>
</tbody>
</table>

### Neurovascular pairing

Nerves and arteries are frequently named together by the bones/regions with which they are associated. The following are exceptions to this naming convention.

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>NERVE</th>
<th>ARTERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axilla/lateral thorax</td>
<td>Long thorac</td>
<td>Lateral thorac</td>
</tr>
<tr>
<td>Surgical neck of humerus</td>
<td>Axillary</td>
<td>Posterior circumflex</td>
</tr>
<tr>
<td>Midshaft of humerus</td>
<td>Radial</td>
<td>Deep brachial</td>
</tr>
<tr>
<td>Distal humerus/ cubital fossa</td>
<td>Median</td>
<td>Brachial</td>
</tr>
<tr>
<td>Popliteal fossa</td>
<td>Tibial</td>
<td>Popliteal</td>
</tr>
<tr>
<td>Posterior to medial malleolus</td>
<td>Tibial</td>
<td>Posterior tibial</td>
</tr>
</tbody>
</table>
Motoneuron action potential to muscle contraction

T-tubules are extensions of plasma membrane in contact with the sarcoplasmic reticulum, allowing for coordinated contraction of striated muscles.

1. Action potential opens presynaptic voltage-gated Ca\(^{2+}\) channels, inducing acetylcholine (ACh) release.
2. Postsynaptic ACh binding leads to muscle cell depolarization at the motor end plate.
3. Depolarization travels over the entire muscle cell and deep into the muscle via the T-tubules.
4. Membrane depolarization induces conformational changes in the voltage-sensitive dihydropyridine receptor (DHPR) and its mechanically coupled ryanodine receptor (RR) → Ca\(^{2+}\) release from the sarcoplasmic reticulum into the cytoplasm.
5. Tropomyosin is blocking myosin-binding sites on the actin filament. Released Ca\(^{2+}\) binds to troponin C (TnC), shifting tropomyosin to expose the myosin-binding sites.
6. The myosin head binds strongly to actin, forming a crossbridge. Pi is then released, initiating the power stroke.
7. During the power stroke, force is produced as myosin pulls on the thin filament. Muscle shortening occurs, with shortening of H and I bands and between Z lines (HIZ shrinkage). The A band remains the same length (A band is always the same length). ADP is released at the end of the power stroke.
8. Binding of new ATP molecule causes detachment of myosin head from actin filament. Ca\(^{2+}\) is resequestered.
9. ATP hydrolysis into ADP and Pi results in myosin head returning to high-energy position (cocked). The myosin head can bind to a new site on actin to form a crossbridge if Ca\(^{2+}\) remains available.
Types of muscle fibers

**Type 1 muscle**  
Slow twitch; red fibers resulting from  
↑ mitochondria and myoglobin concentration  
(↑ oxidative phosphorylation) → sustained  
contraction. Proportion ↑ after endurance  
training.

**Think “1 slow red ox.”**

**Type 2 muscle**  
Fast twitch; white fibers resulting from  
↑ mitochondria and myoglobin concentration  
(↑ anaerobic glycolysis). Proportion ↑ after  
weight/resistance training, sprinting.

Smooth muscle contraction and relaxation

Bone formation

**Endochondral ossification**  
Bones of axial skeleton, appendicular skeleton, and base of skull. Cartilaginous model of bone is  
first made by chondrocytes. Osteoclasts and osteoblasts later replace with woven bone and then  
remodel to lamellar bone. In adults, woven bone occurs after fractures and in Paget disease.  
Defective in achondroplasia.

**Membranous ossification**  
Bones of calvarium, facial bones, and clavicle. Woven bone formed directly without cartilage. Later  
remodeled to lamellar bone.
**Cell biology of bone**

**Osteoblast**  Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum. Osteoblastic activity measured by bone ALP, osteocalcin, propeptides of type I procollagen.

**Osteoclast**  Dissolves (“crushes”) bone by secreting H⁺ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors. RANK receptors on osteoclasts are stimulated by RANKL (RANK ligand, secreted by osteoblasts). RANK receptors blocked by OPG (osteoprotegerin, a RANKL decoy receptor) → ↓ osteoclast activity.

**Parathyroid hormone**  At low, intermittent levels, exerts anabolic effects (building bone) on osteoblasts and osteoclasts (indirect). Chronically ↑ PTH levels (1° hyperparathyroidism) cause catabolic effects (osteitis fibrosa cystica).

**Estrogen**  Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Causes closure of epiphyseal plate during puberty. Estrogen deficiency (surgical or postmenopausal) → ↑ cycles of remodeling and bone resorption → ↑ risk of osteoporosis.

**Achondroplasia**  Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is affected → large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Associated with ↑ paternal age. Most common cause of dwarfism.
Osteoporosis

Trabecular (spongy) and cortical bone lose mass and interconnections despite normal bone mineralization and lab values (serum Ca\(^{2+}\) and PO\(_4^{3-}\)).

Most commonly due to ↑ bone resorption related to ↓ estrogen levels and old age. Can be 2° to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other medical conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes).

Diagnosed by bone mineral density measurement by DEXA (dual-energy X-ray absorptiometry) at the lumbar spine, total hip, and femoral neck, with a T-score of ≤ −2.5 or by a fragility fracture (eg, fall from standing height, minimal trauma) at hip or vertebra. One time screening recommended in women ≥ 65 years old.

Prophylaxis: regular weight-bearing exercise and adequate Ca\(^{2+}\) and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL.).

Can lead to vertebral compression fractures — acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).

Osteopetrosis

Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. Overgrowth of cortical bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Can result in cranial nerve impingement and palsies due to narrowed foramina.

X-rays show diffuse symmetric sclerosis (bone-in-bone, “stone bone”). Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.
Osteomalacia/rickets

Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

X-rays show osteopenia and “Looser zones” (pseudofractures) in osteomalacia, epiphyseal widening and metaphyseal cupping/fraying in rickets. Children with rickets have pathologic bow legs (genu varum), beak-like costochondral junctions (rachitic rosary), craniotabes (soft skull).

↑ vitamin D → ↓ serum \( \text{Ca}^{2+} \) → ↑ PTH secretion → ↓ serum \( \text{PO}_4^{3-} \).

Hyperactivity of osteoblasts → ↑ ALP.

Paget disease of bone (osteitis deformans)

Common, localized disorder of bone remodeling caused by ↑ osteoclastic activity followed by ↑ osteoblastic activity that forms poor-quality bone. Serum \( \text{Ca}^{2+} \), phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone (osteocytes within lacunae in chaotic juxtapositions); long bone chalk-stick fractures. ↑ blood flow from arteriovenous shunts may cause high-output heart failure. ↑ risk of osteogenic sarcoma.

Hat size can be increased due to skull thickening; hearing loss is common due to auditory foramen narrowing.

Stages of Paget disease:
- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Treatment: bisphosphonates.

Osteonecrosis (avascular necrosis)

Infarction of bone and marrow, usually very painful. Most common site is femoral head (watershed zone) (due to insufficiency of medial circumflex femoral artery). Causes include Corticosteroids, Alcoholism, Sickle cell disease, Trauma, “the Bends” (caisson/decompression disease), LEgg-Calvé-Perthes disease (idiopathic), Gaucher disease, Slipped capital femoral epiphysis—CAST Bent LEGS.
### Lab values in bone disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>SERUM Ca(^{2+})</th>
<th>PO(_{4}^{3-})</th>
<th>ALP</th>
<th>PTH</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ bone mass</td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>—/↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Dense, brittle bones. Ca(^{2+}) ↓ in severe, malignant disease</td>
</tr>
<tr>
<td>Paget disease of bone</td>
<td>—</td>
<td>—</td>
<td>↑</td>
<td>—</td>
<td>Abnormal “mosaic” bone architecture</td>
</tr>
<tr>
<td>Osteitis fibrosa cystica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>“Brown tumors” due to fibrous replacement of bone, subperiosteal thinning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Idiopathic or parathyroid hyperplasia, adenoma, carcinoma</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Often as compensation for CKD (↑ PO(_{4}^{3-}) excretion and production of activated vitamin D)</td>
</tr>
<tr>
<td>Osteomalacia/rickets</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Soft bones; vitamin D deficiency also causes 2° hyperparathyroidism</td>
</tr>
<tr>
<td>Hypervitaminosis D</td>
<td>↑/↓</td>
<td>—</td>
<td>—</td>
<td>↓</td>
<td>Caused by oversupplementation or granulomatous disease (eg, sarcoidosis)</td>
</tr>
</tbody>
</table>

↑ ↓ = 1° change.
Primary bone tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Epidemiology</th>
<th>Location</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteochondroma</td>
<td>Most common benign bone tumor.</td>
<td>Metaphysis of long bones.</td>
<td>Lateral bony projection of growth plate (continuous with marrow space) covered by cartilaginous cap. Rarely transforms to chondrosarcoma.</td>
</tr>
<tr>
<td>Osteoma</td>
<td>Middle age.</td>
<td>Surface of facial bones.</td>
<td>Associated with Gardner syndrome.</td>
</tr>
<tr>
<td>Osteoid osteoma</td>
<td>Adults &lt; 25 years old.</td>
<td>Cortex of long bones.</td>
<td>Presents as bone pain (worse at night) that is relieved by NSAIDs. Bony mass (&lt; 2 cm) with radiolucent osteoid core.</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td></td>
<td>Vertebrae.</td>
<td>Similar histology to osteoid osteoma. Larger size (&gt; 2 cm), pain unresponsive to NSAIDs.</td>
</tr>
<tr>
<td>Chondroma</td>
<td>Medulla of small bones of hand and feet.</td>
<td></td>
<td>Benign tumor of cartilage.</td>
</tr>
</tbody>
</table>

**Malignant tumors**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Epidemiology</th>
<th>Location</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma (Osteogenic sarcoma)</td>
<td>Accounts for 20% of 1° bone cancers. Peak incidence of 1° tumor in males &lt; 20 years. Less common in elderly; usually 2° to predisposing factors, such as Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li-Fraumeni syndrome.</td>
<td>Metaphysis of long bones (often in knee region)</td>
<td>Pleomorphic osteoid-producing cells (malignant osteoblasts). Presents as painful enlarging mass or pathologic fractures. Codman triangle (from elevation of periosteum) or sunburst pattern on x-ray. Think of an osteococ (bone fish) swimming in the sun. Aggressive. 1° usually responsive to treatment (surgery, chemotherapy), poor prognosis for 2°.</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>Medulla of pelvis and central skeleton.</td>
<td></td>
<td>Tumor of malignant chondrocytes.</td>
</tr>
</tbody>
</table>
### Primary bone tumors (continued)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Epidemiology</th>
<th>Location</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ewing sarcoma</strong></td>
<td>Most common in Caucasians. Generally boys &lt; 15 years old.</td>
<td>Diaphysis of long bones (especially femur), pelvic flat bones.</td>
<td>Anaplastic small blue cells of neuroectodermal origin (resemble lymphocytes). Differentiate from conditions with similar morphology (eg, lymphoma, chronic osteomyelitis) by testing for t(11;22) (fusion protein EWS-FLI1). “Onion skin” periosteal reaction in bone. Aggressive with early metastases, but responsive to chemotherapy. 11 + 22 = 33 (Patrick Ewing’s jersey number).</td>
</tr>
</tbody>
</table>

**Diaphysis**
- Round cell lesions
- Ewing sarcoma
- Myeloma
- Osteoid osteoma
- Simple bone cyst

**Epiphysis, Metaphysis**
- Osteosarcoma
- Osteochondroma
- Physic
- Giant cell tumor

---

*Images: A, B, C, D*
### Osteoarthritis and rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>Osteoarthritis</th>
<th>Rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Mechanical—wear and tear destroys articular cartilage (degenerative joint disorder)  ♦ inflammation with inadequate repair. Chondrocytes mediate degradation and inadequate repair.</td>
<td>Autoimmune—immunological mechanisms induce formation of pannus (proliferative granulation tissue), which erodes articular cartilage and bone.</td>
</tr>
<tr>
<td><strong>Predisposing factors</strong></td>
<td>Age, female, obesity, joint trauma.</td>
<td>Female, HLA-DR4 (4-walled &quot;rheum&quot;), smoking, rheumatoid factor (IgM antibody that targets IgG Fc region; in 80%), anti-cyclic citrullinated peptide antibody (more specific).</td>
</tr>
<tr>
<td><strong>Joint findings</strong></td>
<td>Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid noninflammatory (WBC &lt; 2000/mm³). Involves DIP (Heberden nodes) and PIP (Bouchard nodes), and 1st CMC; not MCP.</td>
<td>Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing. Deformities: cervical subluxation, ulnar finger deviation, swan neck, boutonniere. Involves MCP, PIP, wrist; not DIP or 1st CMC. Synovial fluid inflammatory.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Acetaminophen, NSAIDs, intra-articular glucocorticoids.</td>
<td>NSAIDs, glucocorticoids, disease-modifying agents (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), biologic agents (eg, TNF-α inhibitors).</td>
</tr>
</tbody>
</table>

*Extraarticular manifestations include rheumatoid nodules (fibrinoid necrosis with palisading histiocytes) in subcutaneous tissue and lung (+ pneumoconiosis → Caplan syndrome), interstitial lung disease, pleuritis, pericarditis, anemia of chronic disease, neutropenia + splenomegaly (Felty syndrome), AA amyloidosis, Sjögren syndrome, scleritis, carpal tunnel syndrome.*

---

**Osteoarthritis**

- Normal
- **Joint capsule and synovial lining**
- Synovial cavity
- Cartilage
- Thickened capsule
- Slight synovial hypertrophy
- Osteophyte
- Ulcerated cartilage
- Sclerotic bone
- Joint space narrowing
- Subchondral bone cyst

**Rheumatoid arthritis**

- Normal
- Joint capsule and synovial lining
- Synovial cavity
- Cartilage
- Bone and cartilage erosion
- Increased synovial fluid
- Pannus formation

---

![Image of Osteoarthritis and Rheumatoid Arthritis](images)
Gout

**FINDINGS**
Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints A. Risk factors: male sex, hypertension, obesity, diabetes, dyslipidemia. Strongest risk factor is hyperuricemia, which can be caused by:
* Underexcretion of uric acid (90% of patients)—largely idiopathic, potentiated by renal failure; can be exacerbated by certain medications (eg, thiazide diuretics).
* Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, cell turnover (eg, tumor lysis syndrome), von Gierke disease.
Crystals are needle shaped and \( \Theta \) birefringent under polarized light (yellow under parallel light, blue under perpendicular light \( \uparrow \)).

**SYMPTOMS**
Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation C (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal with foods rich in purines (eg, red meat, seafood), trauma, surgery, dehydration, diuresis, or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid \( \rightarrow \) uric acid secretion and subsequent buildup in blood).

**TREATMENT**
Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine.
Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).

Calcium pyrophosphate deposition disease

Previously called pseudogout. Deposition of calcium pyrophosphate crystals within the joint space. Occurs in patients > 50 years old; both sexes affected equally. Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.

Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Knee most commonly affected joint.

Chondrocalcinosis (cartilage calcification) on x-ray.

Crystals are rhomboid and weakly \( \Theta \) birefringent under polarized light (blue when parallel to light \( \uparrow \)).

Acute treatment: NSAIDs, colchicine, glucocorticoids.
Prophylaxis: colchicine.

The blue P’s—blue (when Parallel), Positive birefringent, calcium Pyrophosphate, Pseudogout
Systemic juvenile idiopathic arthritis

Childhood arthritis seen in < 12 year olds. Usually presents with daily spiking fevers, salmon-pink macular rash, uveitis, and arthritis (commonly 2+ joints). Frequently presents with leukocytosis, thrombocytosis, anemia, ↑ ESR, ↑ CRP. Treatment: NSAIDs, steroids, methotrexate, TNF inhibitors.

Sjögren syndrome

Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates. Predominantly affects women 40–60 years old. Findings:
- Inflammatory joint pain
- Keratoconjunctivitis sicca (↑ tear production and subsequent corneal damage)
- Xerostomia (↑ saliva production)
- Presence of antinuclear antibodies, rheumatoid factor (can be in the absence of rheumatoid arthritis), antiribonucleoprotein antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement
Anti-SSA and anti-SSB may also be seen in SLE. ⊕ Anti-SSA in pregnant women with SLE → ↑ risk of congenital heart block in the newborn.

Septic arthritis

*S. aureus, Streptococcus,* and *Neisseria gonorrhoeae* are common causes. Affected joint is swollen, red, and painful. Synovial fluid purulent (WBC > 50,000/mm³). Gonococcal arthritis—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).
### Seronegative spondyloarthritis
Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (MHC class I serotype). Subtypes (PAIR) share variable occurrence of inflammatory back pain (associated with morning stiffness, improves with exercise), peripheral arthritis, enthesitis (inflamed insertion sites of tendons, e.g., Achilles), dactylitis (“sausage fingers”), uveitis.

### Psoriatic arthritis
Associated with skin psoriasis and nail lesions. Asymmetric and patchy involvement. Dactylitis and “pencil-in-cup” deformity of DIP on x-ray.

### Ankylosing spondylitis
Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation.

### Inflammatory bowel disease
Crohn disease and ulcerative colitis are often associated with spondyloarthritis.

### Reactive arthritis
Formerly known as Reiter syndrome. Classic triad:
* Conjonctivitis
* Urethritis
* Arthritis

“Can’t see, can’t pee, can’t bend my knee.”
Shigella, Yersinia, Chlamydia, Campylobacter, Salmonella (ShY ChiCS).

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Systemic lupus erythematosus

Systemic, remitting, and relapsing autoimmune disease. Organ damage primarily due to a type III hypersensitivity reaction and, to a lesser degree, a type II hypersensitivity reaction. Associated with deficiency of early complement proteins (eg, C1q, C4, C2) → i clearance of immune complexes. Classic presentation: rash, joint pain, and fever in a female of reproductive age (especially of African-American or Hispanic descent).

Libman-Sacks Endocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface). LSE in SLE.

Lupus nephritis (glomerular deposition of DNA-anti-DNA immune complexes) can be nephritid or nephrotic (causing hematuria or proteinuria). Most common and severe type is diffuse proliferative. Common causes of death in SLE: Renal disease (most common), Infections, Cardiovascular disease (accelerated CAD).

RASH OR PAIN:

- Rash (malar or discoid)
- Arthritis (nonerosive)
- Serositis (eg, pleuritis, pericarditis)
- Hematologic disorders (eg, cytopenias)
- Oral/nasopharyngeal ulcers (usually painless)
- Renal disease
- Photosensitivity
- Antinuclear antibodies
- Immunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)
- Neurologic disorders (eg, seizures, psychosis)

Lupus patients die with Redness In their Cheeks.

Antiphospholipid syndrome

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnose based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, antiphospholipid, anti-β2 glycoprotein antibodies.

Treat with systemic anticoagulation.

Anticardiolipin antibodies can cause false-positive VDRL/RPR, and lupus anticoagulant can cause prolonged PTT that is not corrected by the addition of normal platelet-free plasma.

Mixed connective tissue disease

Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

Polymyalgia rheumatica

Pain and stiffness in proximal muscles (eg, shoulders, hips), often with fever, malaise, weight loss. Does not cause muscular weakness. More common in women > 50 years old; associated with giant cell (temporal) arteritis.

ESR, CRP, normal CK.

Rapid response to low-dose corticosteroids.

Fibromyalgia

Most common in women 20–50 years old. Chronic, widespread musculoskeletal pain associated with “tender points,” stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance (“fibro fog”). Treatment: regular exercise, antidepressants (TCA, SNRI), neuropathic pain agents (eg, gabapentin).
**Polymyositis/dermatomyositis**

† CK, ⊕ ANA (nonspecific), ⊕ anti-Jo-1 (histidyl-tRNA synthetase) (specific), ⊕ anti-SRP (specific), ⊕ anti-Mi-2 (specific) antibodies. Both disorders associated with interstitial lung disease.

**Polymyositis**
Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.

**Dermatomyositis**
Clinically similar to polymyositis, but also involves malar rash (similar to that in SLE but involves nasolabial folds), Gottron papules, heliotrope (violaceous periorbital) rash, “shawl and face” rash, darkening and thickening of fingertips and sides resulting in irregular, “dirty”-appearing marks. † risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.

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**Neuromuscular junction diseases**

<table>
<thead>
<tr>
<th></th>
<th>Myasthenia gravis</th>
<th>Lambert-Eaton myasthenic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREQUENCY</strong></td>
<td>Most common NMJ disorder</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>PATHOPHYSIOLOGY</strong></td>
<td>Autoantibodies to postsynaptic ACh receptor</td>
<td>Autoantibodies to presynaptic Ca^{2+} channel → ACh release</td>
</tr>
<tr>
<td><strong>CLINICAL</strong></td>
<td>Ptosis, diplopia, weakness (respiratory muscle involvement can lead to dyspnea)</td>
<td>Proximal muscle weakness, autonomic symptoms (dry mouth, impotence)</td>
</tr>
<tr>
<td></td>
<td>Worsens with muscle use</td>
<td>Improves with muscle use</td>
</tr>
<tr>
<td></td>
<td>Improvement after edrophonium (tensilon) test</td>
<td></td>
</tr>
<tr>
<td><strong>ASSOCIATED WITH</strong></td>
<td>Thymoma, thymic hyperplasia</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td><strong>ACHE INHIBITOR ADMINISTRATION</strong></td>
<td>Reverses symptoms (edrophonium to diagnose, pyridostigmine to treat)</td>
<td>Minimal effect</td>
</tr>
</tbody>
</table>

**Raynaud phenomenon**

† blood flow to skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers and toes. Called Raynaud disease when 1° (idiopathic), Raynaud syndrome when 2° to a disease process such as mixed connective tissue disease, SLE, or CREST syndrome (limited form of systemic sclerosis). Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with Ca^{2+} channel blockers.
Scleroderma (systemic sclerosis)

Triad of autoimmunity, noninflammatory vasculopathy, and collagen deposition with fibrosis. Commonly sclerosis of skin, manifesting as puffy, taut skin without wrinkles, fingertip pitting. Can involve other systems, eg, renal (scleroderma renal crisis; treat with ACE inhibitors), pulmonary (interstitial fibrosis, pulmonary HTN), GI (esophageal dysmotility and reflux), cardiovascular. 75% female. 2 major types:

- **Diffuse scleroderma**—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase I antibody).

- **Limited scleroderma**—limited skin involvement confined to fingers and face. Also with CREST syndrome: Calcinosis cutis, anti-Centromere antibody, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. More benign clinical course.
Skin layers

Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis).
Epidermis layers from surface to base:
- Stratum Corneum (keratin)
- Stratum Lucidum (most prominent in palms and soles)
- Stratum Granulosum
- Stratum Spinosum (desmosomes)
- Stratum Basale (stem cell site)

Epithelial cell junctions

- **Tight junction** (zonula occludens)—prevents paracellular movement of solutes; composed of claudins and occludins.
- **Adherens junction** (belt desmosome, zonula adherens)—below tight junction, forms “belt” connecting actin cytoskeletons of adjacent cells with **E-cadherin** (Ca$^2+$-dependent adhesive proteins). Loss of E-cadherin promotes metastasis.
- **Desmosome** (spot desmosome, macula adherens)—structural support via intermediate filament interactions. Autoantibodies to desmoglein → pemphigus vulgaris.
- **Gap junction**—channel proteins called connexons permit electrical and chemical communication between cells.
- **Hemidesmosome**—connects keratin in basal cells to underlying basement membrane. Autoantibodies → **bullous** pemphigoid. (Hemidesmosomes are down “bullo”w).

Californians Like Girls in String Bikinis.
### Dermatologic macroscopic terms

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macule</td>
<td>Flat lesion with well-circumscribed change in skin color &lt; 1 cm</td>
<td>Freckle, labial macule A</td>
</tr>
<tr>
<td>Patch</td>
<td>Macule &gt; 1 cm</td>
<td>Large birthmark (congenital nevus) B</td>
</tr>
<tr>
<td>Papule</td>
<td>Elevated solid skin lesion &lt; 1 cm</td>
<td>Mole (nevus) C, acne</td>
</tr>
<tr>
<td>Plaque</td>
<td>Papule &gt; 1 cm</td>
<td>Psoriasis D</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Small fluid-containing blister &lt; 1 cm</td>
<td>Chickenpox (varicella), shingles (zoster) E</td>
</tr>
<tr>
<td>Bulla</td>
<td>Large fluid-containing blister &gt; 1 cm</td>
<td>Bullous pemphigoid F</td>
</tr>
<tr>
<td>Pustule</td>
<td>Vesicle containing pus</td>
<td>Pustular psoriasis G</td>
</tr>
<tr>
<td>Wheal</td>
<td>Transient smooth papule or plaque</td>
<td>Hives (urticaria) H</td>
</tr>
<tr>
<td>Scale</td>
<td>Flaking off of stratum corneum</td>
<td>Eczema, psoriasis, SCC I</td>
</tr>
<tr>
<td>Crust</td>
<td>Dry exudate</td>
<td>Impetigo J</td>
</tr>
</tbody>
</table>

### Dermatologic microscopic terms

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkeratosis</td>
<td>↑ thickness of stratum corneum</td>
<td>Psoriasis, calluses</td>
</tr>
<tr>
<td>Parakeratosis</td>
<td>Retention of nuclei in stratum corneum</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Hypergranulosis</td>
<td>↑ thickness of stratum granulosum</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>Spongiosis</td>
<td>Epidermal accumulation of edematous fluid in intercellular spaces</td>
<td>Eczematous dermatitis</td>
</tr>
<tr>
<td>Acantholysis</td>
<td>Separation of epidermal cells</td>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td>Acanthosis</td>
<td>Epidermal hyperplasia (↑ spinosum)</td>
<td>Acanthosis nigricans</td>
</tr>
</tbody>
</table>
### Pigmented skin disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albinism</td>
<td>Normal melanocyte number with ↓ melanin production due to ↓ tyrosinase activity or defective tyrosine transport. ↑ risk of skin cancer.</td>
</tr>
<tr>
<td>Melasma (chloasma)</td>
<td>Hyperpigmentation associated with pregnancy (“mask of pregnancy”) or OCP use.</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Irregular patches of complete depigmentation. Caused by autoimmune destruction of melanocytes.</td>
</tr>
</tbody>
</table>

#### Seborrheic dermatitis

Erythematous, well-demarcated plaques with greasy yellow scales in areas rich in sebaceous glands, such as scalp, face, and periocular region. Common in both infants and adults, associated with Parkinson disease. Sebaceous glands are not inflamed, but play a role in disease development. Possibly associated with Malassezia spp. Treat with topical antifungals and corticosteroids.
### Common skin disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acne</strong></td>
<td>Multifactorial etiology—↑ sebum/androgen production, abnormal keratinocyte desquamation, <em>Cutibacterium</em> (formerly <em>Propionibacterium</em>) <em>acnes</em> colonization of the pilosebaceous unit (comedones), and inflammation (papules/pustules, nodules, cysts). Treatment includes retinoids, benzoyl peroxide, and antibiotics.</td>
</tr>
<tr>
<td><strong>Atopic dermatitis (eczema)</strong></td>
<td>Pruritic eruption, commonly on skin flexures. Associated with other atopic diseases (asthma, allergic rhinitis, food allergies); ↑ serum IgE. Mutations in filaggrin gene predispose (via skin barrier dysfunction). Often appears on face in infancy and then in antecubital fossa in children and adults.</td>
</tr>
<tr>
<td><strong>Allergic contact dermatitis</strong></td>
<td>Type IV hypersensitivity reaction that follows exposure to allergen. Lesions occur at site of contact (eg, nickel, poison ivy, neomycin).</td>
</tr>
<tr>
<td><strong>Melanocytic nevus</strong></td>
<td>Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular. Junctional nevi are flat macules.</td>
</tr>
<tr>
<td><strong>Pseudofolliculitis barbae</strong></td>
<td>Foreign body inflammatory facial skin disorder characterized by firm, hyperpigmented papules and pustules that are painful and pruritic. Located on cheeks, jawline, and neck. Commonly occurs as a result of shaving (“razor bumps”), primarily affects African-American males.</td>
</tr>
<tr>
<td><strong>Psoriasis</strong></td>
<td>Papules and plaques with silvery scaling, especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. ↑ stratum spinosum, ↓ stratum granulosum. Auspitz sign—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Associated with nail pitting and psoriatic arthritis.</td>
</tr>
<tr>
<td><strong>Rosacea</strong></td>
<td>Inflammatory facial skin disorder characterized by erythematous papules and pustules, but no comedones. May be associated with facial flushing in response to external stimuli (eg, alcohol, heat). Phymatous rosacea can cause rhinophyma (bullaous deformation of nose).</td>
</tr>
<tr>
<td><strong>Seborrheic keratosis</strong></td>
<td>Flat, greasy, pigmented squamous epithelial proliferation with keratin-filled cysts (horn cysts). Looks “stuck on.” Lesions occur on head, trunk, and extremities. Common benign neoplasm of older persons. Leser-Trelat sign—sudden appearance of multiple seborrheic keratoses, indicating an underlying malignancy (eg, GI, lymphoid).</td>
</tr>
<tr>
<td><strong>Urticaria</strong></td>
<td>Hives. Pruritic wheals that form after mast cell degranulation. Characterized by superficial dermal edema and lymphatic channel dilation.</td>
</tr>
</tbody>
</table>

![Image of skin disorders](image)
### Vascular tumors of skin

| **Angiosarcoma** | Rare blood vessel malignancy typically occurring in the head, neck, and breast areas. Usually in elderly, on sun-exposed areas. Associated with radiation therapy and chronic postmastectomy lymphedema. Hepatic angiosarcoma associated with vinyl chloride and arsenic exposures. Very aggressive and difficult to resect due to delay in diagnosis. |
| **Bacillary angiomatosis** | Benign capillary skin papules found in AIDS patients. Caused by *Bartonella* infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate. |
| **Cherry hemangioma** | Benign capillary hemangioma of the elderly. Does not regress. Frequency ↑ with age. |
| **Cystic hygroma** | Cavernous lymphangioma of the neck. Associated with Turner syndrome. |
| **Glomus tumor** | Benign, painful, red-blue tumor, commonly under fingernails. Arises from modified smooth muscle cells of the thermoregulatory glomus body. |
| **Kaposi sarcoma** | Endothelial malignancy most commonly of the skin, but also mouth, GI tract, and respiratory tract. Associated with HHV-8 and HIV. Rarely mistaken for bacillary angiomatosis, but has lymphocytic infiltrate. |
| **Pyogenic granuloma** | Polypoid lobulated capillary hemangioma that can ulcerate and bleed. Associated with trauma and pregnancy. |
| **Strawberry hemangioma** | Benign capillary hemangioma of infancy. Appears in first few weeks of life (1/200 births); grows rapidly and regresses spontaneously by 5–8 years old. |
Skin infections

Bacterial infections

**Impetigo**
Very superficial skin infection. Usually from *S. aureus* or *S. pyogenes*. Highly contagious. Honey-colored crusting. Bullous impetigo has bullae and is usually caused by *S. aureus*.

**Erysipelas**
Infection involving upper dermis and superficial lymphatics, usually from *S. pyogenes*. Presents with well-defined, raised demarcation between infected and normal skin.

**Cellulitis**
Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from *S. pyogenes* or *S. aureus*. Often starts with a break in skin from trauma or another infection.

**Abscess**
Collection of pus from a walled-off infection within deeper layers of skin. Offending organism is almost always *S. aureus*.

**Necrotizing fasciitis**
Deeper tissue injury, usually from anaerobic bacteria or *S. pyogenes*. Pain may be out of proportion to exam findings. Results in crepitus from methane and CO₂ production. “Flesh-eating bacteria.” Causes bullae and a purple color to the skin. Surgical emergency.

**Staphylococcal scalded skin syndrome**
Exotoxin destroys keratinocyte attachments in stratum granulosum only (vs toxic epidermal necrolysis, which destroys epidermal-dermal junction). Characterized by fever and generalized erythematous rash with sloughing of the upper layers of the epidermis that heals completely. Nikolsky sign (separation of epidermis upon manual stroking of skin). Seen in newborns and children, adults with renal insufficiency.

Viral infections

**Herpes**
Herpes virus infections (HSV1 and HSV2) of skin can occur anywhere from mucosal surfaces to normal skin. These include herpes labialis, herpes genitalis, herpetic whitlow (finger).

**Molluscum contagiosum**
Umbilicated papules caused by a poxvirus. While frequently seen in children, it may be sexually transmitted in adults.

**Varicella zoster virus**
Causes varicella (chickenpox) and zoster (shingles). Varicella presents with multiple crops of lesions in various stages from vesicles to crusts. Zoster is a reactivation of the virus in dermatomal distribution (unless it is disseminated).

**Hairy leukoplakia**
Irregular, white, painless plaques on lateral tongue that cannot be scraped off. EBV mediated. Occurs in HIV-positive patients, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).
**Blistering skin disorders**

**Pemphigus vulgaris**
- Potentially fatal autoimmune skin disorder with IgG antibody against desmoglein (component of desmosomes, which connect keratinocytes in the stratum spinosum).
- Flaccid intraepidermal bullae caused by acantholysis (separation of keratinocytes, resembling a “row of tombstones”); oral mucosa is also involved. Type II hypersensitivity reaction.
- Immunofluorescence reveals antibodies around epidermal cells in a reticular (net-like) pattern. Nikolsky sign.

**Bullous pemphigoid**
- Less severe than pemphigus vulgaris. Type II hypersensitivity reaction: involves IgG antibody against hemidesmosomes (epidermal basement membrane; antibodies are “bullow” the epidermis).
- Tense blisters containing eosinophils affect skin but spare oral mucosa. Immunofluorescence reveals linear pattern at epidermal-dermal junction. Nikolsky sign.

**Dermatitis herpetiformis**
- Pruritic papules, vesicles, and bullae (often found on elbows). Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.

**Erythema multiforme**
- Associated with infections (eg, *Mycoplasma pneumoniae*, HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin), cancers, autoimmune disease. Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption).

**Stevens-Johnson syndrome**
- Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction, high mortality rate. Typically 2 mucous membranes are involved and targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. A more severe form of Stevens-Johnson syndrome (SJS) with > 30% of the body surface area involved is toxic epidermal necrolysis (TEN). 10–30% involvement denotes SJS-TEN.
Miscellaneous skin disorders

**Acanthosis nigricans**
Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck. Associated with insulin resistance (eg, diabetes, obesity, Cushing syndrome), visceral malignancy (eg, gastric adenocarcinoma).

**Actinic keratosis**
Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia.

**Erythema nodosum**
Painful, raised inflammatory lesions of subcutaneous fat (panniculitis), usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections, leprosy, inflammatory bowel disease.

**Lichen Planus**
Pruritic, Purple, Polygonal Planar Papules and Plaques are the 6 P’s of lichen Planus. Mucosal involvement manifests as Wickham striae (reticular white lines) and hypergranulosis. Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.

**Pityriasis rosea**
“Herald patch” followed days later by other scaly erythematous plaques, often in a “Christmas tree” distribution on trunk. Multiple pink plaques with collarette scale. Self-resolving in 6–8 weeks.

**Sunburn**
Acute cutaneous inflammatory reaction due to excessive UV irradiation. Causes DNA mutations, inducing apoptosis of keratinocytes. UVB is dominant in sunburn, UVA in tanning and photoAging. Exposure to UVA and UVB ↑ risk of skin cancer. Can also lead to impetigo.

**Burn classifications**

<table>
<thead>
<tr>
<th>Degree of Burn</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-degree burn</strong></td>
<td>Superficial, through epidermis (eg, common sunburn).</td>
</tr>
<tr>
<td><strong>Second-degree burn</strong></td>
<td>Partial-thickness burn through epidermis and dermis. Skin is blistered and usually heals without scarring.</td>
</tr>
<tr>
<td><strong>Third-degree burn</strong></td>
<td>Full-thickness burn through epidermis, dermis, and hypodermis. Skin scars with wound healing.</td>
</tr>
</tbody>
</table>
Skin cancer

**Basal cell carcinoma**

Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Waxy, pink, pearly nodules, commonly with telangiectasias, rolled borders, central crusting or ulceration. BCCs also appear as nonhealing ulcers with infiltrating growth or as a scaling plaque (superficial BCC). Basal cell tumors have “palisading” nuclei.

**Squamous cell carcinoma**

Second most common skin cancer. Associated with excessive exposure to sunlight, immunosuppression, chronically draining sinuses, and occasionally arsenic exposure. Commonly appears on face, lower lip, ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions with frequent scale. Histopathology: keratin “pearls.”

**Actinic keratosis**, a scaly plaque, is a precursor to squamous cell carcinoma. **Keratoacanthoma** is a variant that grows rapidly (4–6 weeks) and may regress spontaneously over months.

**Melanoma**

Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with sunlight exposure and dysplastic nevi; fair-skinned persons are at risk. Depth of tumor (Breslow thickness) correlates with risk of metastasis. Look for the **ABCDEs**: Asymmetry, Border irregularity, Color variation, Diameter > 6 mm, and Evolution over time. At least 4 different types of melanoma, including superficial spreading, nodular, lentigo maligna, and acral lentiginous (highest prevalence in African-Americans and Asians). Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Metastatic or unresectable melanoma in patients with **BRAF V600E** mutation may benefit from vemurafenib, a BRAF kinase inhibitor.
Arachidonic acid pathway

\[ \text{MEMBRANE PHOSPHOLIPIDS} \]

\[ \text{LEUKOTRIENE SYNTHESIS (5-lipoxygenase)} \]

\[ \text{Zileuton} \]

\[ \text{LEUKOTRIENE RECEPTOR ANTAGONISTS} \]

\[ \text{Montelukast} \]

\[ \text{Zafirlukast} \]

\[ \text{Arachidonic acid} \]

\[ \text{5-Lipoxygenase} \]

\[ \text{LTC}_4, \text{ LTD}_4, \text{ LTE}_4, \text{ LTB}_4 \]

\[ \uparrow \text{branchoal tone} \]

\[ \downarrow \text{neutrophil chemotaxis} \]

\[ \text{5-HPETE} \]

\[ \text{Leukotrienes} \]

\[ \text{Phospholipase A}_2 \]

\[ \text{ANTI-INFLAMMATORY AGENTS} \]

\[ \text{Glucocorticoids (corticosteroids)} \]

\[ \text{ENDOPEROXIDE SYNTHESIS (cyclooxygenase)} \]

\[ \text{COX-2 ONLY} \]

\[ \text{Celecoxib} \]

\[ \text{Celecoxib} \]

\[ \text{COX-1, COX-2} \]

\[ \text{Aspirin (irreversible)} \]

\[ \text{Diclofenac} \]

\[ \text{Ketorolac} \]

\[ \text{Ibuprofen} \]

\[ \text{Naproxen} \]

\[ \text{Indomethacin} \]

\[ \text{LEUKOTRIENE RECEPTOR ANTAGONISTS} \]

\[ \text{Montelukast} \]

\[ \text{Zafirlukast} \]

\[ \text{Cyclic endoperoxides} \]

\[ \text{Prostacyclin} \]

\[ \text{Prostaglandins} \]

\[ \text{Thromboxane} \]

\[ \text{PGI}_2 \]

\[ \downarrow \text{platelet aggregation} \]

\[ \downarrow \text{vascular tone} \]

\[ \text{Epoprostenol} \]

\[ \text{Alprostadil} \]

\[ \text{Dinoprostone} \]

\[ \text{Carboprost} \]

\[ \text{PGF}_{2\alpha} \]

\[ \uparrow \text{uterine tone} \]

\[ \text{TXA}_2 \]

\[ \uparrow \text{platelet aggregation} \]

\[ \uparrow \text{vascular tone} \]

\[ \text{LTB}_4 \]

\[ \text{is a neutrophil chemotactic agent.} \]

\[ \text{Neutrophils arrive “B4” others.} \]

\[ \text{Platelet-Gathering Inhibitor.} \]

Acetaminophen

**MECHANISM**

Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.

**CLINICAL USE**

Antipyretic, analgesic, but not anti-inflammatory. Used instead of aspirin to avoid Reye syndrome in children with viral infection.

**ADVERSE EFFECTS**

Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.
### Aspirin

**MECHANISM**
NSAID that irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) by covalent acetylation → ↓ synthesis of TXA₂ and prostaglandins. ↑ bleeding time. No effect on PT, PTT. Effect lasts until new platelets are produced.

**CLINICAL USE**

**ADVERSE EFFECTS**
Gastric ulceration, tinnitus (CN VII), allergic reactions (especially in patients with asthma or nasal polyps). Chronic use can lead to acute renal failure, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated with aspirin for viral infection. Toxic doses cause respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis.

### Celecoxib

**MECHANISM**
Reversibly and selectively inhibits the cyclooxygenase (COX) isoform 2 ("Selecoxib"), which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as TXA₂ production is dependent on COX-1.

**CLINICAL USE**
Rheumatoid arthritis, osteoarthritis.

**ADVERSE EFFECTS**
↑ risk of thrombosis. Sulfur allergy.

### Nonsteroidal anti-inflammatory drugs

**MECHANISM**
Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.

**CLINICAL USE**
Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA.

**ADVERSE EFFECTS**
Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole), aplastic anemia.

### Leflunomide

**MECHANISM**
Reversibly inhibits dihydroorotate dehydrogenase, preventing pyrimidine synthesis. Suppresses T-cell proliferation.

**CLINICAL USE**
Rheumatoid arthritis, psoriatic arthritis.

**ADVERSE EFFECTS**
Diarrhea, hypertension, hepatotoxicity, teratogenicity.

### Bisphosphonates

**MECHANISM**
Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.

**CLINICAL USE**
Osteoporosis, hypercalcemia, Paget disease of bone, metastatic bone disease, osteogenesis imperfecta.

**ADVERSE EFFECTS**
Esophagitis (if taken orally, patients are advised to take with water and remain upright for 30 minutes), osteonecrosis of jaw, atypical femoral stress fractures.
Teriparatide

**MECHANISM**
Recombinant PTH analog. ↑ osteoblastic activity when administered in pulsatile fashion.

**CLINICAL USE**
Osteoporosis. Causes ↑ bone growth compared to antiresorptive therapies (eg, bisphosphonates).

**ADVERSE EFFECTS**
↑ risk of osteosarcoma (avoid use in patients with Paget disease of the bone or unexplained elevation of alkaline phosphatase). Avoid in patients who have had prior cancers or radiation therapy. Transient hypercalcemia.

Gout drugs

<table>
<thead>
<tr>
<th>Chronic gout drugs (preventive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probenecid</strong></td>
</tr>
<tr>
<td>Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.</td>
</tr>
</tbody>
</table>

| Allopurinol |
| Competitive inhibitor of xanthine oxidase → ↓ conversion of hypoxanthine and xanthine to urate. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. ↑ concentrations of azathioprine and 6-MP (both normally metabolized by xanthine oxidase). |

| Pegloticase |
| Recombinant uricase catalyzing uric acid to allantoin (a more water-soluble product). |

| Febuxostat |
| Inhibits xanthine oxidase. |

**Acute gout drugs**

| NSAIDs |
| Any NSAID. Use salicylates with caution (may decrease uric acid excretion, particularly at low doses). |

| Glucocorticoids |
| Oral, intra-articular, or parenteral. |

| Colchicine |
| Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI, neuromyopathic side effects. |

**TNF-α inhibitors**

<table>
<thead>
<tr>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etanercept</strong></td>
</tr>
<tr>
<td>Fusion protein (decoy receptor for TNF-α + IgG1 Fc), produced by recombinant DNA. <strong>Etanercept intercepts TNF.</strong></td>
</tr>
<tr>
<td>Rheumatoid arthritis, psoriasis, ankylosing spondylitis</td>
</tr>
<tr>
<td>Predisposition to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization. Can also lead to drug-induced lupus.</td>
</tr>
</tbody>
</table>

| **Infliximab, adalimumab, certolizumab, golimumab** |
| Anti-TNF-α monoclonal antibody. |
| Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis |
“We are all now connected by the Internet, like neurons in a giant brain.”
—Stephen Hawking

“Anything’s possible if you’ve got enough nerve.”
—J.K. Rowling, Harry Potter and the Order of the Phoenix

“I like nonsense; it wakes up the brain cells.”
—Dr. Seuss

“I believe in an open mind, but not so open that your brains fall out.”
—Arthur Hays Sulzberger

“The chief function of the body is to carry the brain around.”
—Thomas Edison

“Exactly how [the brain] operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find.”
—Neil deGrasse Tyson

Know how to clinically interpret common patterns of neurologic symptoms and findings. Questions on the exam often correlate clinical scenarios with gross pathologic specimens or cross-sectional CT/MR imaging. With regard to neuropharmacology, antiparkinsonism, antiepileptic and opioid drugs tend to be highly testable.
**Neural development**


Alar plate (dorsal): sensory
Basal plate (ventral): motor

Same orientation as spinal cord.

**Regional specification of developing brain**

Telencephalon is the 1st part. Diencephalon is the 2nd part. The rest are arranged alphabetically:

- mesencephalon
- metencephalon
- myelencephalon

<table>
<thead>
<tr>
<th>Adult derivatives of:</th>
<th>Walls</th>
<th>Cavities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemispheres</td>
<td>Lateral ventricles</td>
<td></td>
</tr>
<tr>
<td>Thalamus, Hypothalamus</td>
<td>Third ventricle</td>
<td></td>
</tr>
<tr>
<td>Midbrain</td>
<td>Cerebral aqueduct</td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>Upper part of fourth ventricle</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medulla</td>
<td>Lower part of fourth ventricle</td>
<td></td>
</tr>
</tbody>
</table>

**Central and peripheral nervous systems origins**

- Neuroepithelia in neural tube—CNS neurons, ependymal cells (inner lining of ventricles, make CSF), oligodendrocytes, astrocytes.
- Neural crest—PNS neurons, Schwann cells.
- Mesoderm—Microglia (like Macrophages).
Neural tube defects  Neurupores fail to fuse (4th week) → persistent connection between amniotic cavity and spinal canal. Associated with maternal diabetes as well as low folic acid intake before conception and during pregnancy. ↑ α-fetoprotein (AFP) in amniotic fluid and maternal serum (except spina bifida occulta = normal AFP). ↑ acetycholinesterase (AChE) in amniotic fluid is a helpful confirmatory test.

Spina bifida occulta  Failure of caudal neuropore to close, but no herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect.

Meningocele  Meninges (but no neural tissue) herniate through bony defect. Associated with spina bifida cystica.

Meningomyelocele  Meninges and neural tissue (eg, cauda equina) herniate through bony defect.

Myeloschisis  Also known as rachischisis. Exposed unfused neural tissue without skin/meningeal covering.

Anencephaly  Failure of rostral neuropore to close → no forebrain, open calvarium. Clinical findings: polyhydramnios (no swallowing center in brain).

Holoprosencephaly  Failure of left and right hemispheres to separate; usually occurs during weeks 5–6. May be related to mutations in sonic hedgehog signaling pathway. Moderate form has cleft lip/palate, most severe form results in cyclopia. Seen in trisomy 13 and fetal alcohol syndrome. MRI reveals monoventricle and fusion of basal ganglia (star in A).
Posterior fossa malformations

**Chiari I malformation**
Ectopia of cerebellar tonsils (1 structure) \[A\]. Congenital, usually asymptomatic in childhood, manifests in adulthood with headaches and cerebellar symptoms. Associated with spinal cavitations (eg, syringomyelia).

**Chiari II malformation**
Herniation of low-lying cerebellar vermis and tonsils (2 structures) through foramen magnum with aqueductal stenosis → hydrocephalus. Usually associated with lumbosacral meningomyelocele (may present as paralysis/sensory loss at and below the level of the lesion).

**Dandy-Walker syndrome**
Agenesis of cerebellar vermis leads to cystic enlargement of 4th ventricle (arrow in \[B\]) that fills the enlarged posterior fossa. Associated with noncommunicating hydrocephalus, spina bifida.

---

**Syringomyelia**
Cystic cavity (syrinx) within central canal of spinal cord (yellow arrows in \[A\]). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a “cape-like,” bilateral symmetrical loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved). Associated with Chiari malformations (red arrow shows low-lying cerebellar tonsils in \[A\]) and other congenital malformations; acquired causes include trauma and tumors.

Syrinx = tube, as in syringe. Most common at C8–T1.
**Tongue development**

1st and 2nd branchial arches form anterior 2/3 (thus sensation via CN V₃, taste via CN VII).
3rd and 4th branchial arches form posterior 1/3 (thus sensation and taste mainly via CN IX, extreme posterior via CN X).

Motor innervation is via CN XII to hyoglossus (retracts and depresses tongue), genioglossus (protrudes tongue), and styloglossus (draws sides of tongue upward to create a trough for swallowing).

Motor innervation is via CN X to palatoglossus (elevates posterior tongue during swallowing).

Taste—CN VII, IX, X (solitary nucleus).
Pain—CN V₃, IX, X.
Motor—CN X, XII.

The Genie sticks out his tongue.

**Neurons**

Signal-transmitting cells of the nervous system. Permanent cells—do not divide in adulthood.
Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output). Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon.

Injury to axon → **Wallerian degeneration**—degeneration of axon distal to site of injury and axonal retraction proximally; allows for potential regeneration of axon (if in PNS). Macrophages remove debris and myelin.

**Astrocytes**


Derived from neuroectoderm. Astrocyte marker: GFAP.

**Microglia**


HIV-infected microglia fuse to form multinucleated giant cells in CNS.

**Ependymal cells**

Glial cells with a ciliated simple columnar form that line the ventricles and central canal of spinal cord. Apical surfaces are covered in cilia (which circulate CSF) and microvilli (which help in CSF absorption).
Myelin

† conduction velocity of signals transmitted down axons → saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of Na+ channels. Synthesis of myelin by oligodendrocytes in CNS (including CN I and II) and Schwann cells in PNS (including CN III-XII).

Wraps and insulates axons (arrow in A): † space constant and † conduction velocity.
COPS: CNS = Oligodendrocytes, PNS = Schwann cells.

Schwann cells

Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration. Derived from neural crest.
Injured in Guillain-Barré syndrome.

Oligodendrocytes

Myelinates axons of neurons in CNS. Each oligodendrocyte can myelinate many axons (∼30). Predominant type of glial cell in white matter.
Derived from neuroectoderm. “Fried egg” appearance histologically.
Injured in multiple sclerosis, progressive multifocal leukoencephalopathy (PML), leukodystrophies.

Sensory receptors

<table>
<thead>
<tr>
<th>RECEPTOR TYPE</th>
<th>SENSORY NEURON FIBER TYPE</th>
<th>LOCATION</th>
<th>SENSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free nerve endings</td>
<td>C—slow, unmyelinated fibers Aδ—fast, myelinated fibers</td>
<td>All skin, epidermis, some viscera</td>
<td>Pain, temperature</td>
</tr>
<tr>
<td>Meissner corpuscles</td>
<td>Large, myelinated fibers; adapt quickly</td>
<td>Glabrous (hairless) skin</td>
<td>Dynamic, fine/light touch, position sense</td>
</tr>
<tr>
<td>Pacinian corpuscles</td>
<td>Large, myelinated fibers; adapt quickly</td>
<td>Deep skin layers, ligaments, joints</td>
<td>Vibration, pressure</td>
</tr>
<tr>
<td>Merkel discs</td>
<td>Large, myelinated fibers; adapt slowly</td>
<td>Finger tips, superficial skin</td>
<td>Pressure, deep static touch (eg, shapes, edges), position sense</td>
</tr>
<tr>
<td>Ruffini corpuscles</td>
<td>Dendritic endings with capsule; adapt slowly</td>
<td>Finger tips, joints</td>
<td>Pressure, slippage of objects along surface of skin, joint angle change</td>
</tr>
</tbody>
</table>
Peripheral nerve

Endoneurium—invests single nerve fiber layers (inflammatory infiltrate in Guillain-Barré syndrome).

Perineurium (blood-nerve Permeability barrier)—surrounds a fascicle of nerve fibers. Must be rejoined in microsurgery for limb reattachment.

Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

Chromatolysis

Reaction of neuronal cell body to axonal injury. Changes reflect ↑ protein synthesis in effort to repair the damaged axon. Characterized by:

* Round cellular swelling
* Displacement of the nucleus to the periphery
* Dispersion of Nissl substance throughout cytoplasm

Concurrent with Wallerian degeneration.

Neurotransmitter changes with disease

<table>
<thead>
<tr>
<th>Location of Synthesis</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Schizophrenia</th>
<th>Alzheimer Disease</th>
<th>Huntington Disease</th>
<th>Parkinson Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Basal nucleus of Meynert</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Ventral tegmentum, SNc</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>GABA</td>
<td>Nucleus accumbens</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Locus ceruleus</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>Raphe nucleus</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meninges

Three membranes that surround and protect the brain and spinal cord:

* Dura mater—thick outer layer closest to skull. Derived from mesoderm.
* Arachnoid mater—middle layer, contains web-like connections. Derived from neural crest.
* Pia mater—thin, fibrous inner layer that firmly adheres to brain and spinal cord. Derived from neural crest.

CSF flows in the subarachnoid space, located between arachnoid and pia mater.

Epidural space—a potential space between the dura mater and skull containing fat and blood vessels.
Blood-brain barrier
Prevents circulating blood substances (e.g., bacteria, drugs) from reaching the CSF/CNS. Formed by 3 structures:
- Tight junctions between nonfenestrated capillary endothelial cells
- Basement membrane
- Astrocyte foot processes
Glucose and amino acids cross slowly by carrier-mediated transport mechanisms.
Nonpolar/lipid-soluble substances cross rapidly via diffusion.
A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (e.g., area postrema—vomiting after chemo; OVLT [organum vasculosum lamina terminalis]—osmotic sensing) or neurosecretory products to enter circulation (e.g., neurohypophysis—ADH release).
Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema.
Other notable barriers include:
- Blood-testis barrier
- Maternal-fetal blood barrier of placenta

Hypothalamus
Maintains homeostasis by regulating Thirst and water balance, controlling Adenohypophysis (anterior pituitary) and Neurohypophysis (posterior pituitary) release of hormones produced in the hypothalamus, and regulating Hunger, Autonomic nervous system, Temperature, and Sexual urges (TAN HATS).
Inputs (areas not protected by blood-brain barrier): OVLT (senses change in osmolarity), area postrema (found in medulla, responds to emetics).

Lateral nucleus
Hunger. Destruction → anorexia, failure to thrive (infants). Stimulated by ghrelin, inhibited by leptin.
Lateral injury makes you Lean.

Ventromedial nucleus
Satiety. Destruction (e.g., craniopharyngioma) → hyperphagia. Stimulated by leptin.
VentralMedial injury makes you Very Massive.

Anterior nucleus
Cooling, parasympathetic.
Anterior nucleus = cool off (cooling, pArasympathetic). A/C = anterior cooling.

Posterior nucleus
Heating, sympathetic.
Heating controlled by Posterior hypothalamus ("Hot Pot"). If you zap your posterior hypothalamus, you become a poikilotherm (cold-blooded, like a snake).

Suprachiasmatic nucleus
Circadian rhythm.
You need sleep to be charismatic (chiasmatic).

Supraoptic and paraventricular nuclei
Synthesize ADH and oxytocin.
ADH and oxytocin are carried by neurophysins down axons to posterior pituitary, where these hormones are stored and released.

Preoptic nucleus
Thermoregulation, sexual behavior. Releases GnRH. Failure of GnRH-producing neurons to migrate from olfactory pit → Kallmann syndrome.
Vomiting center

Coordinated by nucleus tractus solitarius (NTS) in the medulla, which receives information from the chemoreceptor trigger zone (CTZ, located within area postrema in 4th ventricle), GI tract (via vagus nerve), vestibular system, and CNS. CTZ and adjacent vomiting center nuclei receive input from 5 major receptors: muscarinic (M₁), dopamine (D₂), histamine (H₁), serotonin (5-HT₃), and neurokinin (NK-1) receptors.

* 5-HT₃, D₂, and NK-1 antagonists used to treat chemotherapy-induced vomiting.
* M₁ and H₁ antagonists used to treat motion sickness and hyperemesis gravidarum.

Sleep physiology

Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of hypothalamus. Circadian rhythm controls nocturnal release of ACTH, prolactin, melatonin, norepinephrine: SCN → norepinephrine release → pineal gland → melatonin. SCN is regulated by environment (eg, light).

Two stages: rapid-eye movement (REM) and non-REM.

Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and delta wave sleep; norepinephrine also ↓ REM sleep.

Benzodiazepines are useful for night terrors and sleepwalking by ↓ N3 and REM sleep.

<table>
<thead>
<tr>
<th>SLEEP STAGE (% OF TOTAL SLEEP TIME IN YOUNG ADULTS)</th>
<th>DESCRIPTION</th>
<th>EEG WAVEFORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake (eyes open)</td>
<td>Alert, active mental concentration.</td>
<td>Beta (highest frequency, lowest amplitude)</td>
</tr>
<tr>
<td>Awake (eyes closed)</td>
<td>Alpha</td>
<td></td>
</tr>
<tr>
<td>Non-REM sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage N1 (5%)</td>
<td>Light sleep.</td>
<td>Theta</td>
</tr>
<tr>
<td>Stage N2 (45%)</td>
<td>Deeper sleep; when bruxism (teeth grinding) occurs.</td>
<td>Sleep spindles and K complexes “Twooth” grinding</td>
</tr>
<tr>
<td>Stage N3 (25%)</td>
<td>Deepest non-REM sleep (slow-wave sleep); when sleepwalking, night terrors, and bedwetting occur.</td>
<td>Delta (lowest frequency, highest amplitude)</td>
</tr>
<tr>
<td>REM sleep (25%)</td>
<td>Loss of motor tone, ↑ brain O₂ use, ↑ and variable pulse and blood pressure ↑ ACh; when dreaming, nightmares, and penile/clitoral tumescence occur; may serve memory processing function. Depression increases total REM sleep but decreases REM latency. Extraocular movements due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center). Occurs every 90 minutes, and duration ↑ through the night.</td>
<td>Beta At night, BATS Drink Blood</td>
</tr>
</tbody>
</table>
Neurology and Special Senses

**Thalamus**

Major relay for all ascending sensory information except olfaction.

<table>
<thead>
<tr>
<th>Nuclei</th>
<th>Input</th>
<th>Senses</th>
<th>Destination</th>
<th>Mnemonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral Postero-Lateral nucleus</td>
<td>Spinothalamic and dorsal columns/medial lemniscus</td>
<td>Vibration, Pain, Pressure, Proprioception, Light touch, temperature</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; somatosensory cortex</td>
<td></td>
</tr>
<tr>
<td>Ventral posteromedial nucleus</td>
<td>Trigeminal and gustatory pathway</td>
<td>Face sensation, taste</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; somatosensory cortex</td>
<td>Makeup goes on the face</td>
</tr>
<tr>
<td>Lateral geniculate nucleus</td>
<td>CN II, optic chiasm, optic tract</td>
<td>Vision</td>
<td>Calcarine sulcus</td>
<td>Lateral = Light</td>
</tr>
<tr>
<td>Medial geniculate nucleus</td>
<td>Superior olive and inferior colliculus of tectum</td>
<td>Hearing</td>
<td>Auditory cortex of temporal lobe</td>
<td>Medial = Music</td>
</tr>
<tr>
<td>Ventral lateral nucleus</td>
<td>Basal ganglia, cerebellum</td>
<td>Motor</td>
<td>Motor cortex</td>
<td></td>
</tr>
</tbody>
</table>

**Limbic system**

Collection of neural structures involved in emotion, long-term memory, olfaction, behavior modulation, ANS function. Consists of hippocampus (red arrows in A), amygdalae, mammillary bodies, anterior thalamic nuclei, cingulate gyrus (yellow arrows in A), entorhinal cortex. Responsible for Feeding, Fleeing, Fighting, Feeling, and Sex. The famous 5 F’s.

**Dopaminergic pathways**

Commonly altered by drugs (eg, antipsychotics) and movement disorders (eg, Parkinson disease).

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Symptoms of altered activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesocortical</td>
<td>↓ activity → “negative” symptoms (eg, anergia, apathy, lack of spontaneity).</td>
<td>Antipsychotic drugs have limited effect.</td>
</tr>
<tr>
<td>Mesolimbic</td>
<td>↓ activity → “positive” symptoms (eg, delusions, hallucinations).</td>
<td>↓ therapeutic target of antipsychotic drugs.</td>
</tr>
<tr>
<td>Nigrostriatal</td>
<td>↓ activity → extrapyramidal symptoms (eg, dystonia, akathisia, parkinsonism, tardive dyskinesia).</td>
<td>Major dopaminergic pathway in brain. Significantly affected by movement disorders and antipsychotic drugs.</td>
</tr>
<tr>
<td>Tuberoinfundibular</td>
<td>↓ activity → ↑ prolactin → ↓ libido, sexual dysfunction, galactorrhea, gynecomastia (in men).</td>
<td></td>
</tr>
</tbody>
</table>
Cerebellum

Modulates movement; aids in coordination and balance. Arrow in A.

Input:
- Contralateral cortex via middle cerebellar peduncle.
- Ipsilateral proprioceptive information via inferior cerebellar peduncle from spinal cord.

Output:
- The only output of cerebellar cortex = Purkinje cells (always inhibitory) → deep nuclei of cerebellum → contralateral cortex via superior cerebellar peduncle.
- Deep nuclei (lateral → medial) — Dentate, Emboliform, Globose, Fastigial.

Lateral lesions — affect voluntary movement of extremities (lateral structures); when injured, propensity to fall toward injured (ipsilateral) side.

Medial lesions (eg, vermis, fastigial nuclei, flocculonodular lobe) — truncal ataxia (wide-based cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature (medial structures).

Don’t Eat Greasy Foods
**Basal ganglia**

Important in voluntary movements and making postural adjustments.
Receives cortical input, provides negative feedback to cortex to modulate movement.
Striatum = putamen (motor) + caudate (cognitive).
Lentiform = putamen + globus pallidus.

\[ \text{D}_1\text{-Receptor} = \text{DIRECT pathway.} \]
\[ \text{Indirect (D}_2\text{)} = \text{INHIBITORY.} \]

Direct (excitatory) pathway—SNC input stimulates the striatum, stimulating the release of GABA, which inhibits GABA release from the GPi, disinhibiting the thalamus via the GPi (↑ motion).
Indirect (inhibitory) pathway—SNC input stimulates the striatum, releasing GABA that disinhibits STN via GPe inhibition, and STN stimulates GPi to inhibit the thalamus (↓ motion).
Dopamine binds to \( \text{D}_1 \), stimulating the excitatory pathway, and to \( \text{D}_2 \), inhibiting the inhibitory pathway → ↑ motion.
Cerebral cortex regions

Homunculus

Topographic representation of motor (shown) and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having larger cortical representation.
Cerebral perfusion

Brain perfusion relies on tight autoregulation. Cerebral perfusion is primarily driven by \( P_{\text{CO}_2} \) (\( P_{\text{O}_2} \) also modulates perfusion in severe hypoxia). Cerebral perfusion relies on a pressure gradient between mean arterial pressure (MAP) and ICP. ↓ blood pressure or ↓ ICP → ↓ cerebral perfusion pressure (CPP).

Therapeutic hyperventilation → ↓ \( P_{\text{CO}_2} \)

→ vasoconstriction → ↓ cerebral blood flow

→ ↓ intracranial pressure (ICP). May be used to treat acute cerebral edema (eg, 2° to stroke) unresponsive to other interventions.

CPP = MAP – ICP. If CPP = 0, there is no cerebral perfusion → brain death.

Hypoxemia increases CPP only if \( P_{\text{O}_2} \) < 50 mm Hg.

CPP is directly proportional to \( P_{\text{CO}_2} \) until \( P_{\text{CO}_2} \) > 90 mm Hg.

Cerebral arteries—cortical distribution

Anterior cerebral artery (supplies anteromedial surface)

Middle cerebral artery (supplies lateral surface)

Posterior cerebral artery (supplies posterior and inferior surfaces)

Watershed zones

Between anterior cerebral/middle cerebral, posterior cerebral/middle cerebral arteries (cortical border zones) (blue areas in A), or may also occur between the superficial and deep vascular territories of the middle cerebral artery (internal border zones) (red areas in B).

Damage by severe hypotension → proximal upper and lower extremity weakness (if internal border zone stroke), higher order visual dysfunction (if posterior cerebral/middle cerebral cortical border zone stroke).
Circle of Willis

System of anastomoses between anterior and posterior blood supplies to brain.

Dural venous sinuses

Large venous channels that run through the periosteal and meningeal layers of the dura mater. Drain blood from cerebral veins (arrow) and receive CSF from arachnoid granulations. Empty into internal jugular vein.

Venous sinus thrombosis—presents with signs/symptoms of ICP (eg, headache, seizures, focal neurologic deficits). May lead to venous hemorrhage. Associated with hypercoagulable states (eg, pregnancy, OCP use, factor V Leiden).
Ventricular system

Lateral ventricles → 3rd ventricle via right and left interventricular foramina of Monro.
3rd ventricle → 4th ventricle via cerebral aqueduct of Sylvius.
4th ventricle → subarachnoid space via:
* Foramina of Luschka = Lateral.
* Foramen of Magendie = Medial.

CSF made by ependymal cells of choroid plexus. Travels to subarachnoid space via foramina of Luschka and Magendie, is reabsorbed by arachnoid granulations, and then drains into dural venous sinuses.

Brain stem—ventral view

4 CN are above pons (I, II, III, IV).
4 CN exit the pons (V, VI, VII, VIII).
4 CN are in medulla (IX, X, XI, XII).
4 CN nuclei are medial (III, IV, VI, XII).
“Factors of 12, except 1 and 2.”

Brain stem—dorsal view (cerebellum removed)

Pineal gland—melatonin secretion, circadian rhythms.
Superior colliculi—direct eye movements to stimuli (noise/movements) or objects of interest.
Inferior colliculi—auditory.
Your eyes are above your ears, and the superior colliculus (visual) is above the inferior colliculus (auditory).
**Cranial nerve nuclei**

Located in tegmentum portion of brain stem (between dorsal and ventral portions):

- Midbrain—nuclei of CN III, IV
- Pons—nuclei of CN V, VI, VII, VIII
- Medulla—nuclei of CN IX, X, XII
- Spinal cord—nucleus of CN XI

Lateral nuclei = sensory (alar plate).
—Sulcus limitans—
Medial nuclei = Motor (basal plate).

---

**Cranial nerve and vessel pathways**

- **Anterior cranial fossa**
  - Optic canal
  - Superior orbital fissure

- **Middle cranial fossa** (through sphenoid bone)
  - Foramen Rotundum
  - Foramen Ovale
  - Foramen spinosum

- **Posterior cranial fossa** (through temporal or occipital bone)
  - Internal auditory meatus
  - Jugular foramen
  - Hypoglossal canal
  - Foramen magnum

Divisions of CN V exit owing to Standing Room Only

- CN I
  - CN II
  - Ophthalmic artery
- CN III
  - CN IV
  - CN VI
- CN V₁
  - Middle meningeal artery
- CN V₂
- CN V₃
  - CN VII
  - CN VIII
  - CN IX
  - CN X
  - CN XI
  - Jugular vein
  - CN XII
  - Brain stem
  - Spinal root of CN XI
  - Vertebral arteries
### Cranial nerves

<table>
<thead>
<tr>
<th>NERVE</th>
<th>CN</th>
<th>FUNCTION</th>
<th>TYPE</th>
<th>MNEMONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory</td>
<td>I</td>
<td>Smell (only CN without thalamic relay to cortex)</td>
<td>Sensory</td>
<td>Some</td>
</tr>
<tr>
<td>Optic</td>
<td>II</td>
<td>Sight</td>
<td>Sensory</td>
<td>Say</td>
</tr>
<tr>
<td>Oculomotor</td>
<td>III</td>
<td>Eye movement (SR, IR, MR, IO), pupillary constriction (sphincter pupillae: Edinger-Westphal nucleus, muscarinic receptors), accommodation, eyelid opening (levator palpebrae)</td>
<td>Motor</td>
<td>Marry</td>
</tr>
<tr>
<td>Trochlear</td>
<td>IV</td>
<td>Eye movement (SO)</td>
<td>Motor</td>
<td>Money</td>
</tr>
<tr>
<td>Trigeminal</td>
<td>V</td>
<td>Mastication, facial sensation (ophthalmic, maxillary, mandibular divisions), somatosensation from anterior 2/3 of tongue</td>
<td>Both</td>
<td>But</td>
</tr>
<tr>
<td>Abducens</td>
<td>VI</td>
<td>Eye movement (LR)</td>
<td>Motor</td>
<td>My</td>
</tr>
<tr>
<td>Facial</td>
<td>VII</td>
<td>Facial movement, taste from anterior 2/3 of tongue (chorda tympani), lacrimation, salivation (submandibular and sublingual glands are innervated by CN seven), eyelid closing (orbicularis oculi), auditory volume modulation (stapedius)</td>
<td>Both</td>
<td>Brother</td>
</tr>
<tr>
<td>Vestibulocochlear</td>
<td>VIII</td>
<td>Hearing, balance</td>
<td>Sensory</td>
<td>Says</td>
</tr>
<tr>
<td>Glossopharyngeal</td>
<td>IX</td>
<td>Taste and sensation from posterior 1/3 of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemosensory receptors, and elevation of pharynx/larynx (stylopharyngeus)</td>
<td>Both</td>
<td>Big</td>
</tr>
<tr>
<td>Vagus</td>
<td>X</td>
<td>Taste from supraglottic region, swallowing, soft palate elevation, midline uvula, talking, cough reflex, parasympathetics to thoracoabdominal viscera, monitoring aortic arch chemosensory and baroreceptors</td>
<td>Both</td>
<td>Brains</td>
</tr>
<tr>
<td>Accessory</td>
<td>XI</td>
<td>Head turning, shoulder shrugging (SCM, trapezius)</td>
<td>Motor</td>
<td>Matter</td>
</tr>
<tr>
<td>Hypoglossal</td>
<td>XII</td>
<td>Tongue movement</td>
<td>Motor</td>
<td>Most</td>
</tr>
</tbody>
</table>

### Vagal nuclei

<table>
<thead>
<tr>
<th>NUCLEUS</th>
<th>FUNCTION</th>
<th>CRANIAL NERVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus Solitarius</td>
<td>Visceral Sensory information (eg, taste, baroreceptors, gut distention)</td>
<td>VII, IX, X</td>
</tr>
<tr>
<td>Nucleus Ambigus</td>
<td>Motor innervation of pharynx, larynx, upper esophagus (eg, swallowing, palate elevation)</td>
<td>IX, X, XI (cranial portion)</td>
</tr>
<tr>
<td>Dorsal motor nucleus</td>
<td>Sends autonomic (parasympathetic) fibers to heart, lungs, upper GI</td>
<td>X</td>
</tr>
</tbody>
</table>

### Cranial nerve reflexes

<table>
<thead>
<tr>
<th>REFLEX</th>
<th>AFFERENT</th>
<th>EFFERENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal</td>
<td>V&lt;sub&gt;1&lt;/sub&gt; ophthalmic (nasociliary branch)</td>
<td>Bilateral VII (temporal branch: orbicularis oculi)</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>V&lt;sub&gt;1&lt;/sub&gt; (loss of reflex does not preclude emotional tears)</td>
<td>VII</td>
</tr>
<tr>
<td>Jaw jerk</td>
<td>V&lt;sub&gt;1&lt;/sub&gt; (sensory—muscle spindle from masseter)</td>
<td>V&lt;sub&gt;3&lt;/sub&gt; (motor—masseter)</td>
</tr>
<tr>
<td>Pupillary</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Gag</td>
<td>IX</td>
<td>X</td>
</tr>
</tbody>
</table>
Mastication muscles

3 muscles close jaw: Masseter, Temporalis, Medial pterygoid. 1 opens: Lateral pterygoid. All are innervated by trigeminal nerve (V3).

M’s Munch.

Lateral Lowers (when speaking of pterygoids with respect to jaw motion).

“It takes more muscle to keep your mouth shut.”

Spinal nerves

There are 31 pairs of spinal nerves in total: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal. Nerves C1–C7 exit above the corresponding vertebra. C8 spinal nerve exits below C7 and above T1. All other nerves exit below (eg, C3 exits above the 3rd cervical vertebra; L2 exits below the 2nd lumbar vertebra).

Vertebral disc herniation—nucleus pulposus (soft central disc) herniates through annulus fibrosus (outer ring); usually occurs posterolaterally at L4–L5 or L5–S1. Nerve usually affected is below the level of herniation (eg, L3–L4 disc spares L3 nerve and involves L4 nerve). Compression of S1 nerve root → absent ankle reflex.

Spinal cord—lower extent

In adults, spinal cord ends at lower border of L1–L2 vertebrae. Subarachnoid space (which contains the CSF) extends to lower border of S2 vertebra. Lumbar puncture is usually performed between L3–L4 or L4–L5 (level of cauda equina).

Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To keep the cord alive, keep the spinal needle between L3 and L5.
Spinal cord and associated tracts

Legs (Lumbosacral) are Lateral in Lateral corticospinal, spinothalamic tracts.

Dorsal columns are organized as you are, with hands at sides. “Arms outside, legs inside.”

Central canal

Dorsal column

Posterior horn

Anterior white commissure

Lateral corticospinal tract

Anterior horn

Anterior spinthalamic tract

ASCENDING

Dorsal column (pressure, vibration, fine touch, proprioception)

• Fasciculus gracilis (Lower body, legs)
• Fasciculus cuneatus (Upper body, arms)

DESCENDING

Lateral corticospinal tract (voluntary motor)

• Sacral
• Cervical

Anterior corticospinal tract (voluntary motor)

White matter

Anterior horn

Gray matter

Intermediate horn (sympathetic) (T1 - L2/L3)

Lateral spinothalamic tract (pain, temperature)

• Sacral
• Cervical

Anterior spinthalamic tract (crude touch, pressure)
### Spinal tract anatomy and functions

Ascending tracts synapse and then cross.

<table>
<thead>
<tr>
<th>Tract</th>
<th>Function</th>
<th>1st-order Neuron</th>
<th>Synapse 1</th>
<th>2nd-order Neuron</th>
<th>Synapse 2 + Projections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dorsal column</strong></td>
<td>Pressure, vibration, fine touch, proprioception</td>
<td>Sensory nerve ending → bypass pseudounipolar cell body in dorsal root ganglion → enter spinal cord → ascend ipsilaterally in dorsal columns</td>
<td>Nucleus gracilis, nucleus cuneatus (ipsilateral medulla)</td>
<td>Decussates in medulla → ascends contraterally as the medial lemniscus</td>
<td>VPL (thalamus) → sensory cortex</td>
</tr>
<tr>
<td><strong>Spinothalamic tract</strong></td>
<td>Lateral: pain, temperature</td>
<td>Sensory nerve ending (A(\delta) and C fibers) → bypass pseudounipolar cell body in dorsal root ganglion → enter spinal cord</td>
<td>Ipsilateral gray matter (spinal cord)</td>
<td>Decussates in spinal cord as the anterior white commissure → ascends contraterally</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anterior: crude touch, pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Descending tract</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lateral corticospinal tract</strong></td>
<td>Voluntary movement of contralateral limbs</td>
<td>UMN: cell body in 1° motor cortex → descends ipsilaterally (through posterior limb of internal capsule), most fibers decussate at caudal medulla (pyramidal decussation) → descends contraterally</td>
<td>Cell body of anterior horn (spinal cord)</td>
<td>LMN: leaves spinal cord</td>
<td>NMJ → muscle fibers</td>
</tr>
</tbody>
</table>
Clinical reflexes

Reflexes count up in order (main nerve root bolded):
- **Achilles reflex** = S1, S2 ("buckle my shoe")
- **Patellar reflex** = L3, L4 ("kick the door")
- **Biceps and brachioradialis reflexes** = C5, C6 ("pick up sticks")
- **Triceps reflex** = C7, C8 ("lay them straight")

Additional reflexes:
- **Cremasteric reflex** = L1, L2 ("testicles move")
- **Anal wink reflex** = S3, S4 ("winks galore")

Primitive reflexes

CNS reflexes that are present in a healthy infant, but are absent in a neurologically intact adult. Normally disappear within 1st year of life. These “primitive” reflexes are inhibited by a mature/developing frontal lobe. They may reemerge in adults following frontal lobe lesions → loss of inhibition of these reflexes.

- **Moro reflex**
  - "Hang on for life" reflex—abduct/extend arms when startled, and then draw together

- **Rooting reflex**
  - Movement of head toward one side if cheek or mouth is stroked (nipple seeking)

- **Sucking reflex**
  - Sucking response when roof of mouth is touched

- **Palmar reflex**
  - Curling of fingers if palm is stroked

- **Plantar reflex**
  - Dorsiflexion of large toe and fanning of other toes with plantar stimulation

- **Galant reflex**
  - Stroking along one side of the spine while newborn is in ventral suspension (face down) causes lateral flexion of lower body toward stimulated side

Landmark dermatomes

<table>
<thead>
<tr>
<th>DERMATOME</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>Posterior half of skull</td>
</tr>
<tr>
<td>C3</td>
<td>High turtle neck shirt; Diaphragm and gallbladder pain referred to right shoulder via phrenic nerve; C3, 4, 5 keeps the diaphragm alive</td>
</tr>
<tr>
<td>C4</td>
<td>Low-collar shirt</td>
</tr>
<tr>
<td>C6</td>
<td>Includes thumbs; <strong>Thumbs up</strong> sign on left hand looks like a 6</td>
</tr>
<tr>
<td>T4</td>
<td>At the <strong>nipple</strong>; T4 at the teat <strong>pore</strong></td>
</tr>
<tr>
<td>T7</td>
<td>At the xiphoid process</td>
</tr>
<tr>
<td>T10</td>
<td>At the umbilicus (belly button); Important point of referred pain in early appendicitis</td>
</tr>
<tr>
<td>L1</td>
<td>At the Inguinal <strong>Ligament</strong></td>
</tr>
<tr>
<td>L4</td>
<td>Includes the kneecaps; Down on <strong>ALL 4s</strong></td>
</tr>
<tr>
<td>S2, S3, S4</td>
<td>Sensation of penile and anal zones; S2, 3, 4 keep the penis off the floor</td>
</tr>
</tbody>
</table>
# Common brain lesions

<table>
<thead>
<tr>
<th>AREA OF LESION</th>
<th>CONSEQUENCE</th>
<th>EXAMPLES/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes.</td>
<td></td>
</tr>
<tr>
<td>Frontal eye fields</td>
<td>Eyes look toward (destructive) side of lesion. In seizures (irritative), eyes look away from side of the lesion.</td>
<td></td>
</tr>
<tr>
<td>Paramedian pontine reticular formation</td>
<td>Eyes look away from side of lesion.</td>
<td>Ipsilateral gaze palsy (inability to look toward side of lesion).</td>
</tr>
<tr>
<td>Medial longitudinal fasciculus</td>
<td>Internuclear ophthalmoplegia (impaired adduction of ipsilateral eye; nystagmus of contralateral eye with abduction).</td>
<td>Multiple sclerosis.</td>
</tr>
<tr>
<td>Dominant parietal cortex</td>
<td>Agraphia, acalculia, finger agnosia, left-right disorientation.</td>
<td>Gerstmann syndrome.</td>
</tr>
<tr>
<td>Nondominant parietal cortex</td>
<td>Agnosia of the contralateral side of the world.</td>
<td>Hemispatial neglect syndrome.</td>
</tr>
<tr>
<td>Hippocampus (bilateral)</td>
<td>Anterograde amnesia—inability to make new memories.</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>May result in tremor at rest, chorea, athetosis.</td>
<td>Parkinson disease, Huntington disease.</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>Contralateral hemiballismus.</td>
<td></td>
</tr>
<tr>
<td>Mammillary bodies (bilateral)</td>
<td>Wernicke-Korsakoff syndrome—Confusion, Ataxia, Nystagmus, Ophthalmpoplegia, memory loss (anterograde and retrograde amnesia), confabulation, personality changes.</td>
<td>Wernicke problems come in a CAN O' beer.</td>
</tr>
<tr>
<td>Amygdala (bilateral)</td>
<td>Klüver-Bucy syndrome—disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality).</td>
<td>HSV-1 encephalitis.</td>
</tr>
<tr>
<td>Reticular activating system (midbrain)</td>
<td>Reduced levels of arousal and wakefulness (eg, coma).</td>
<td></td>
</tr>
<tr>
<td>Cerebellar hemisphere</td>
<td>Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion.</td>
<td>Cerebellar hemispheres are laterally located—affect lateral limbs.</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>Decorticate (flexor) posturing—lesion above red nucleus, presents with flexion of upper extremities and extension of lower extremities. Decerebrate (extensor) posturing—lesion at or below red nucleus, presents with extension of upper and lower extremities.</td>
<td>Worse prognosis with decerebrate posturing.</td>
</tr>
</tbody>
</table>
**Ischemic brain disease/stroke**

Irreversible damage begins after 5 minutes of hypoxia. Most vulnerable: hippocampus, neocortex, cerebellum (Purkinje cells), watershed areas. Irreversible neuronal injury. **Hippocampus is most vulnerable** to ischemic hypoxia (“vulnerable hippoc”).

Stroke imaging: noncontrast CT to exclude hemorrhage (before tPA can be given). CT detects ischemic changes in 6–24 hr. Diffusion-weighted MRI can detect ischemia within 3–30 min.

<table>
<thead>
<tr>
<th>TIME SINCE ISCHEMIC EVENT</th>
<th>12–24 HOURS</th>
<th>24–72 HOURS</th>
<th>3–5 DAYS</th>
<th>1–2 WEEKS</th>
<th>&gt; 2 WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histologic features</strong></td>
<td>Eosinophilic cytoplasm + pyknotic nuclei (red neurons)</td>
<td>Necrosis + neutrophils</td>
<td>Macrophages (microglia)</td>
<td>Reactive gliosis (astrocytes) + vascular proliferation</td>
<td>Glial scar</td>
</tr>
</tbody>
</table>

**Ischemic stroke**

Acute blockage of vessels → disruption of blood flow and subsequent ischemia → liquefactive necrosis.

3 types:
- **Thrombotic**—due to a clot forming directly at site of infarction (commonly the MCA), usually over an atherosclerotic plaque.
- **Embolic**—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation, carotid artery stenosis, DVT with patent foramen ovale.
- **Hypoxic**—due to hypoperfusion or hypoxemia. Common during cardiovascular surgeries, tends to affect watershed areas.

Treatment: tPA (if within 3–4.5 hr of onset and no hemorrhage/risk of hemorrhage). Reduce risk with medical therapy (eg, aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; and treat conditions that ↑ risk (eg, atrial fibrillation, carotid artery stenosis).

**Transient ischemic attack**

Brief, reversible episode of focal neurologic dysfunction without acute infarction ( MRI), with the majority resolving in < 15 minutes; deficits due to focal ischemia.

**Neonatal intraventricular hemorrhage**

Bleeding into ventricles (arrow in A shows blood in right intraventricular blood, extending into periventricular white matter). Increased risk in premature and low-birth-weight infants. Originates in germinal matrix, a highly vascularized layer within the subventricular zone. Due to reduced glial fiber support and impaired autoregulation of BP in premature infants. Can present with altered level of consciousness, bulging fontanelle, hypotension, seizures, coma.
Intracranial hemorrhage

**Epidural hematoma**

Rupture of middle meningeal artery (branch of maxillary artery), often 2º to skull fracture (circle in A) involving the pterion (thinnest area of the lateral skull). Lucid interval. Scalp hematoma (arrows in A) and rapid intracranial expansion (arrows in B) under systemic arterial pressure → transtentorial herniation, CN III palsy. CT shows biconvex (lentiform), hyperdense blood collection **not crossing suture lines**.

**Subdural hematoma**

Rupture of bridging veins. Can be acute (traumatic, high-energy impact → hyperdense on CT) or chronic (associated with mild trauma, cerebral atrophy, elderly, alcoholism → hypodense on CT). Also seen in shaken babies. Predisposing factors: brain atrophy, trauma. Crescent-shaped hemorrhage (red arrows in C and D) that crosses suture lines. Can cause midline shift (yellow arrow in C), findings of “acute on chronic” hemorrhage (blue arrows in D).

**Subarachnoid hemorrhage**

Bleeding due to trauma, or rupture of an aneurysm (such as a saccular aneurysm E) or arteriovenous malformation. Rapid time course. Patients complain of “worst headache of my life.” Bloody or yellow (xanthochromic) spinal tap. Vasospasm can occur due to blood breakdown or rebleed 3–10 days after hemorrhage → ischemic infarct; nimodipine used to prevent/reduce vasospasm. ↑ risk of developing communicating and/or obstructive hydrocephalus.

**Intraparenchymal hemorrhage**

Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vasculitis, neoplasm. May be 2º to reperfusion injury in ischemic stroke. Hypertensive hemorrhages (Charcot-Bouchard microaneurysm) most often occur in putamen of basal ganglia (lenticulostriate vessels G), followed by thalamus, pons, and cerebellum H.
## Effects of Strokes

<table>
<thead>
<tr>
<th>ARTERY</th>
<th>AREA OF LESION</th>
<th>SYMPTOMS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior circulation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>Motor and sensory cortices—upper limb</td>
<td>Contralateral paralysis and sensory loss—face and upper limb.</td>
<td>Wernicke aphasia is associated with right superior quadrant visual field defect due to temporal lobe involvement.</td>
</tr>
<tr>
<td></td>
<td>and face.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporal lobe (Wernicke area);</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>frontal lobe (Broca area).</td>
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</tr>
<tr>
<td>Lenticulostriate artery</td>
<td>Striatum, internal capsule.</td>
<td>Contralateral paralysis. Absence of cortical signs (eg, neglect, aphasia, visual field loss).</td>
<td>Common location of lacunar infarcts, due to hyaline arteriosclerosis $^{2}$ to unmanaged hypertension.</td>
</tr>
<tr>
<td><strong>Posterior circulation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior spinal artery</td>
<td>Lateral corticospinal tract.</td>
<td>Contralateral paralysis—upper and lower limbs.</td>
<td>Medial medullary syndrome—caused by infarct of paramedian branches of ASA and/or vertebral arteries.</td>
</tr>
<tr>
<td></td>
<td>Medial lemniscus.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Caudal medulla—hypoglossal nerve.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior inferior</td>
<td>Lateral medulla: Nucleus ambiguus</td>
<td>Dysphagia, hoarseness, gag reflex, hiccups</td>
<td>Lateral medullary (Wallenberg) syndrome. Nucleus ambiguus effects are specific to PICA lesions.</td>
</tr>
<tr>
<td>cerebellar artery</td>
<td>(CN IX, X, XI)</td>
<td></td>
<td>“Don’t pick a (PICA) horse (hoarseness) that can’t eat (dysphagia).” “Facial droop means AICA’s pooped.” Also supplies inferior cerebellar peduncle (part of cerebellum).</td>
</tr>
<tr>
<td></td>
<td>Vestibular nuclei</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lateral spinothalamic tract, spinal</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>trigeminal nucleus</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Sympathetic fibers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inferior cerebellar peduncle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior inferior</td>
<td>Lateral pons: Facial nucleus</td>
<td>Paralysis of face (LMN lesion vs UMN lesion in cortical stroke),</td>
<td>Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions. “Facial droop means AICA’s pooped.” Also supplies middle and inferior cerebellar peduncles (part of cerebellum).</td>
</tr>
<tr>
<td>cerebellar artery</td>
<td></td>
<td>↓ lacrimation, ↓ salvation, ↓ taste from anterior 2/3 of tongue</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting, vertigo, nystagmus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ pain and temperature sensation from contralateral body, ipsilateral</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>face</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral Horner syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral ataxia, dysmetria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral sensorineural deafness, vertigo</td>
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</tbody>
</table>
Effects of strokes (continued)

<table>
<thead>
<tr>
<th>ARTERY</th>
<th>AREA OF LESION</th>
<th>SYMPTOMS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilar artery</td>
<td>Pons, medulla, lower midbrain</td>
<td>RAS spared, therefore preserved consciousness</td>
<td>Locked-in syndrome (locked in the basement)</td>
</tr>
<tr>
<td></td>
<td>Corticospinal and corticobulbar tracts</td>
<td>Quadriplegia; loss of voluntary facial, mouth, and tongue movements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ocular cranial nerve nuclei, paramedian pontine reticular formation</td>
<td>Loss of horizontal, but not vertical, eye movements</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>Occipital lobe D.</td>
<td>Contralateral hemianopia with macular sparing; alexia without agraphia (dominant hemisphere).</td>
<td></td>
</tr>
</tbody>
</table>

Central post-stroke pain syndrome

Neuropathic pain due to thalamic lesions. Initial paresthesias followed in weeks to months by allodynia (ordinarily painless stimuli cause pain) and dysesthesia on the contralateral side. Occurs in 10% of stroke patients.

Diffuse axonal injury

Caused by traumatic shearing forces during rapid acceleration and/or deceleration of the brain (eg, motor vehicle accident). Usually results in devastating neurologic injury, often causing coma or persistent vegetative state. Shows multiple lesions (punctate hemorrhages) involving the white matter tracts.
Aphasia

Aphasia—higher-order language deficit (inability to understand/produce/use language appropriately); caused by pathology in dominant cerebral hemisphere (usually left).

Dysarthria—motor inability to speak (movement deficit).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SPEECH FLUENCY</th>
<th>COMPREHENSION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition impaired</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Broca (expressive) | Nonfluent       | Intact        | **Broca = Broken Boca (boca = mouth in Spanish).**
Broca area in inferior frontal gyrus of frontal lobe. Patient appears frustrated, insight intact. |
| Wernicke (receptive)| Fluent          | Impaired      | **Wernicke is Wordy but makes no sense. Patients do not have insight.**
Wernicke area in superior temporal gyrus of temporal lobe. |
| Conduction         | Fluent          | Intact        | Can be caused by damage to arcuate fasciculus.                           |
| Global             | Nonfluent       | Impaired      | Arcuate fasciculus; Broca and Wernicke areas affected (all areas).      |

Repetition intact

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SPEECH FLUENCY</th>
<th>COMPREHENSION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcortical motor</td>
<td>Nonfluent</td>
<td>Intact</td>
<td>Affects frontal lobe around Broca area, but Broca area is spared.</td>
</tr>
<tr>
<td>Transcortical sensory</td>
<td>Fluent</td>
<td>Impaired</td>
<td>Affects temporal lobe around Wernicke area, but Wernicke area is spared.</td>
</tr>
<tr>
<td>Transcortical, mixed</td>
<td>Nonfluent</td>
<td>Impaired</td>
<td>Broca and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.</td>
</tr>
</tbody>
</table>

Aneurysms

Abnormal dilation of an artery due to weakening of vessel wall.

Saccular aneurysm

Also known as berry aneurysm. Occurs at bifurcations in the circle of Willis. Most common site is junction of ACom and ACA. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race (risk in African-Americans).

Usually clinically silent until rupture (most common complication) → subarachnoid hemorrhage ("worst headache of my life" or "thunderclap headache") → focal neurologic deficits. Can also cause symptoms via direct compression of surrounding structures by growing aneurysm.

- ACom—compression → bitemporal hemianopia (compression of optic chiasm); visual acuity deficits; rupture → ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
- MCA—rupture → ischemia in MCA distribution → contralateral upper extremity and lower facial hemiparesis, sensory deficits.
- PCom—compression → ipsilateral CN III palsy → mydriasis ("blown pupil"); may also see ptosis, “down and out” eye.

Charcot-Bouchard microaneurysm

Common, associated with chronic hypertension; affects small vessels (eg, lenticulostriate arteries in basal ganglia, thalamus) and can cause lacunar strokes. Not visible on angiography.
### Seizures

**Characterized by synchronized, high-frequency neuronal firing. Variety of forms.**

**Partial (focal) seizures**
Affect single area of the brain. Most commonly originate in medial temporal lobe. Types:
- **Simple partial** (consciousness intact)—motor, sensory, autonomic, psychic
- **Complex partial** (impaired consciousness, automatisms)

**Generalized seizures**
Diffuse. Types:
- **Absence** (petit mal)—3 Hz spike-and-wave discharges, no postictal confusion, blank stare
- **Myoclonic**—quick, repetitive jerks
- **Tonic-clonic** (grand mal)—alternating stiffening and movement
- **Tonic**—stiffening
- **Atonic**—“drop” seizures (falls to floor); commonly mistaken for fainting

**Epilepsy**—a disorder of recurrent seizures (febrile seizures are not epilepsy).

**Status epilepticus**—continuous (≥ 5 min) or recurring seizures that may result in brain injury.

**Causes of seizures by age:**
- **Children**—genetic, infection (febrile), trauma, congenital, metabolic
- **Adults**—tumor, trauma, stroke, infection
- **Elderly**—stroke, tumor, trauma, metabolic, infection
**Headaches**

Pain due to irritation of structures such as the dura, cranial nerves, or extracranial structures. More common in females, except cluster headaches.

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>LOCALIZATION</th>
<th>DURATION</th>
<th>DESCRIPTION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cluster</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unilateral</td>
<td>15 min–3 hr; repetitive</td>
<td>Excruciating periorbital pain (“suicide headache”) with lacrimation and rhinorrhea. May present with Horner syndrome. More common in males.</td>
<td>Acute: sumatriptan, 100% O&lt;sub&gt;2&lt;/sub&gt; Prophylaxis: verapamil</td>
</tr>
<tr>
<td><strong>Tension</strong></td>
<td>Bilateral</td>
<td>&gt; 30 min (typically 4–6 hr); constant</td>
<td>Steady, “band-like” pain. No photophobia or phonophobia. No aura.</td>
<td>Analgesics, NSAIDs, acetaminophen; amitriptyline for chronic pain</td>
</tr>
<tr>
<td><strong>Migraine</strong></td>
<td>Unilateral</td>
<td>4–72 hr</td>
<td>Pulsating pain with nausea, photophobia, or phonophobia. May have “aura.” Due to irritation of CN V, meninges, or blood vessels (release of substance P, calcitonin gene-related peptide, vasoactive peptides).</td>
<td>Acute: NSAIDs, triptans, dihydroergotamine Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, amitriptyline, topiramate, valproate. POUND–Pulsatile, One-day duration, Unilateral, Nausea, Disabling</td>
</tr>
</tbody>
</table>

Other causes of headache include subarachnoid hemorrhage (“worst headache of my life”), meningitis, hydrocephalus, neoplasia, giant cell (temporal) arteritis.

<sup>a</sup>Compare with trigeminal neuralgia, which produces repetitive, unilateral, shooting pain in the distribution of CN V. Triggered by chewing, talking, touching certain parts of the face. Lasts (typically) for seconds to minutes, but episodes often increase in intensity and frequency over time. First-line therapy: carbamazepine.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Presentation</th>
<th>Characteristic Lesion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>Restlessness and intense urge to move</td>
<td></td>
<td>Can be seen with neuroleptic use or as a side-effect of Parkinson treatment.</td>
</tr>
<tr>
<td>Asterixis</td>
<td>Extension of wrists causes “flapping” motion</td>
<td></td>
<td>Associated with hepatic encephalopathy, Wilson disease, and other metabolic derangements.</td>
</tr>
<tr>
<td>Athetosis</td>
<td>Slow, snake-like, writhing movements; especially seen in the fingers</td>
<td>Basal ganglia</td>
<td></td>
</tr>
<tr>
<td>Chorea</td>
<td>Sudden, jerky, purposeless movements</td>
<td>Basal ganglia</td>
<td><em>Chorea</em> = dancing. Seen in Huntington disease and in acute rheumatic fever (Sydenham chorea).</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Sustained, involuntary muscle contractions</td>
<td></td>
<td>Writer’s cramp, blepharospasm, torticollis.</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>High-frequency tremor with sustained posture (eg, outstretched arms), worsened with movement or when anxious</td>
<td></td>
<td>Often familial. Patients often self-medicate with alcohol, which ↑ tremor amplitude. Treatment: nonselective β-blockers (eg, propranolol), primidone.</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>Sudden, wild flailing of 1 arm +/- ipsilateral leg</td>
<td>Contralateral subthalamic nucleus (eg, lacunar stroke)</td>
<td>Pronounce “Half-of-body ballistic.” Contralateral lesion.</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>Slow, zigzag motion when pointing/extending toward a target</td>
<td>Cerebellar dysfunction</td>
<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Sudden, brief, uncontrolled muscle contraction</td>
<td></td>
<td>Jerks; hiccups; common in metabolic abnormalities such as renal and liver failure.</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>Uncontrolled movement of distal appendages (most noticeable in hands); tremor alleviated by intentional movement</td>
<td>Substantia nigra (<em>Parkinson disease</em>)</td>
<td>Occurs at rest; “pill-rolling tremor” of Parkinson disease. When you park your car, it is at rest.</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>Worse at rest/nighttime. Relieved by movement</td>
<td></td>
<td>Associated with iron deficiency, CKD. Treat with dopamine agonists (pramipexole, ropinirole).</td>
</tr>
</tbody>
</table>
# Neurodegenerative Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Histologic/Gross Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parkinson Disease</strong></td>
<td>Tremor (pill-rolling tremor at rest), Rigidity (cogwheel), Akinesia (or bradykinesia), Postural instability, Shuffling gait</td>
<td>Loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta. Lewy bodies: composed of α-synuclein (intracellular eosinophilic inclusions).</td>
</tr>
<tr>
<td><strong>Huntington Disease</strong></td>
<td>Autosomal dominant trinucleotide (CAG) n repeat expansion in the huntingtin (HTT) gene on chromosome 4 (4 letters). Symptoms manifest between ages 20 and 50: chorea, athetosis, aggression, depression, dementia (sometimes initially mistaken for substance abuse). Anticipation results from expansion of CAG repeats. Caudate loses ACh and GABA.</td>
<td>Atrophy of caudate and putamen with ex vacuo ventriculomegaly. ↑ dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity.</td>
</tr>
<tr>
<td><strong>Alzheimer Disease</strong></td>
<td>Most common cause of dementia in elderly. Down syndrome patients have ↑ risk of developing Alzheimer disease, as APP is located on chromosome 21. ↓ ACh. Associated with the following altered proteins: ApoE-2: ↑ risk of sporadic form ApoE-4: ↑ risk of sporadic form APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset</td>
<td>Widespread cortical atrophy (normal cortex; cortex in Alzheimer disease), especially hippocampus (arrows in and ). Narrowing of gyri and widening of sulci. Senile plaques in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy → intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP). Neurofibrillary tangles: intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree of dementia.</td>
</tr>
<tr>
<td><strong>Frontotemporal Dementia</strong></td>
<td>Also known as Pick disease. Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia). May have associated movement disorders (eg, parkinsonism).</td>
<td>Frontotemporal lobe degeneration. Inclusions of hyperphosphorylated tau (round Pick bodies or ubiquitinated TDP-43).</td>
</tr>
<tr>
<td><strong>Lewy Body Dementia</strong></td>
<td>Visual hallucinations (&quot;haLewycinations&quot;), dementia with fluctuating cognition/alertness, REM sleep behavior disorder, and parkinsonism. Called Lewy body dementia if cognitive and motor symptom onset &lt; 1 year apart, otherwise considered dementia 2° to Parkinson disease.</td>
<td>Intracellular Lewy bodies primarily in cortex.</td>
</tr>
</tbody>
</table>
Neurodegenerative disorders (continued)

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DESCRIPTION</th>
<th>HISTOLOGIC/GROSS FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular dementia</td>
<td>Result of multiple arterial infarcts and/or chronic ischemia. Step-wise</td>
<td>MRI or CT shows multiple cortical and/or subcortical infarcts.</td>
</tr>
<tr>
<td></td>
<td>decline in cognitive ability with late-onset memory impairment. 2nd most</td>
<td></td>
</tr>
<tr>
<td></td>
<td>common cause of dementia in elderly.</td>
<td></td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Rapidly progressive (weeks to months) dementia with myoclonus (“startle</td>
<td>Spongiform cortex.</td>
</tr>
</tbody>
</table>
|                              | myoclonus”) and ataxia. Commonly see periodic sharp waves on EEG and ↑    | Prions (PrP\(_c\) \rightarrow PrP\(_\beta\) sheet [\(\beta\)-pleated sheet resistant to proteases])
|                              | 14-3-3 protein in CSF.                                                      |                                                                                           |

**Idiopathic intracranial hypertension**

Also known as pseudotumor cerebri. ↑ ICP with no apparent cause on imaging (eg, hydrocephalus, obstruction of CSF outflow). Risk factors include female gender, Tetracyclines, Obesity, vitamin A excess, Danazol (female TOAD).

Findings: headache, tinnitus, diplopia (usually from CN VI palsy), no change in mental status. Impaired optic nerve axoplasmic flow → papilledema. Visual field testing shows enlarged blind spot and peripheral constriction. Lumbar puncture reveals ↑ opening pressure and provides temporary headache relief.

Treatment: weight loss, acetazolamide, invasive procedures for refractory cases (eg, CSF shunt placement, optic nerve sheath fenestration surgery for visual loss).
**Hydrocephalus**

<table>
<thead>
<tr>
<th>Communicating hydrocephalus</th>
<th>↑ CSF volume → ventricular dilation +/- ↑ ICP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicating hydrocephalus</td>
<td>↑ CSF absorption by arachnoid granulations (eg, arachnoid scarring post-meningitis) → ↑ ICP, papilledema, herniation.</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>Affects the elderly; idiopathic; CSF pressure elevated only episodically; does not result in increased subarachnoid space volume. Expansion of ventricles A distorts the fibers of the corona radiata → triad of <strong>urinary incontinence</strong>, <strong>gait apraxia</strong> (magnetic gait), and <strong>cognitive dysfunction</strong> (sometimes reversible). “Wet, wobbly, and wacky.” Symptoms potentially reversible with CSF shunt placement.</td>
</tr>
</tbody>
</table>

**Noncommunicating (obstructive)**

| Noncommunicating hydrocephalus | Caused by structural blockage of CSF circulation within ventricular system (eg, stenosis of aqueduct of Sylvius; colloid cyst blocking foramen of Monro; tumor [3]). |

**Hydrocephalus mimics**

| Ex vacuo ventriculomegaly | Appearance of ↑ CSF on imaging C, but is actually due to ↓ brain tissue and neuronal atrophy (eg, Alzheimer disease, advanced HIV, Pick disease, Huntington disease). ICP is normal; NPH triad is not seen. |
Multiple sclerosis

Autoimmune inflammation and demyelination of CNS (brain and spinal cord) with subsequent axonal damage. Can present with:
- Acute optic neuritis (painful unilateral visual loss associated with Marcus Gunn pupil)
- Brain stem/cerebellar syndromes (eg, diplopia, ataxia, scanning speech, intention tremor, nystagmus/INO (bilateral > unilateral)
- Pyramidal tract weakness
- Spinal cord syndromes (eg, electric shock-like sensation along spine on neck flexion [Lhermitte phenomenon], neurogenic bladder, paraparesis, sensory manifestations affecting the trunk or one or more extremity)

Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). Relapsing and remitting is most common clinical course. Most often affects women in their 20s and 30s; more common in Caucasians living farther from equator.

**FINDINGS**

† IgG level and myelin basic protein in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques (areas of oligodendrocyte loss and reactive gliosis). Multiple white matter lesions disseminated in space and time.

**TREATMENT**

Stop relapses and halt/slow progression with disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABA<sub>B</sub> receptor agonists), pain (TCAs, anticonvulsants).
Other demyelinating and dysmyelinating disorders

**Osmotic demyelination syndrome**
Also known as central pontine myelinolysis. Massive axonal demyelination in pontine white matter due to rapid osmotic changes, most commonly iatrogenic correction of hyponatremia but also rapid shifts of other osmolytes (eg, glucose). Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause “locked-in syndrome.”
Correcting serum Na⁺ too fast:
- “From low to high, your pons will die” (osmotic demyelination syndrome).
- “From high to low, your brains will blow” (cerebral edema/herniation).

**Acute inflammatory demyelinating polyradiculopathy**
Most common subtype of Guillain-Barré syndrome. Autoimmune condition associated with infections (eg, Campylobacter jejuni, viruses [eg, Zika]) that destroys Schwann cells by inflammation and demyelination of peripheral nerves (including cranial nerves III-XII) and motor fibers likely due to molecular mimicry, inoculations, and stress, but no definitive link to pathogens. Results in symmetric ascending muscle weakness/paralysis and depressed/absent DTRs beginning in lower extremities. Facial paralysis (usually bilateral) and respiratory failure are common. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive; majority recover completely after weeks to months. ↑ CSF protein with normal cell count (albumino-cytologic dissociation). Respiratory support is critical until recovery. Disease-modifying treatment: plasmapheresis, IV immunoglobulins. No role for steroids.

**Acute disseminated (postinfectious) encephalomyelitis**
Multifocal inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.

**Charcot-Marie-Tooth disease**
Also known as hereditary motor and sensory neuropathy. Group of progressive hereditary nerve disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant inheritance pattern and associated with foot deformities (eg, pes cavus, hammer toe), lower extremity weakness (eg, foot drop), and sensory deficits. Most common type, CMT1A, is caused by PMP22 gene duplication.

**Progressive multifocal leukoencephalopathy**
Demyelination of CNS due to destruction of oligodendrocytes (2° to reactivation of latent JC virus infection). Seen in 2–4% of patients with AIDS. Rapidly progressive, usually fatal. Predominantly involves parietal and occipital areas; visual symptoms are common. ↑ risk associated with natalizumab, rituximab.

**Other disorders**
Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy.
Neurocutaneous disorders

**Sturge-Weber syndrome**
Also known as encephalotrigeminal angiomatosis. Congenital, noninherited (sporadic), developmental anomaly of neural crest derivatives due to somatic mosaicism for an activating mutation in one copy of the GNAQ gene. Affects small (capillary-sized) blood vessels → port-wine stain of the face (nevus flammeus, a non-neoplastic “birthmark” in CN V1/V2 distribution); ipsilateral leptomeningeal angiomatoma → seizures/epilepsy; intellectual disability; and episcleral hemangioma → IOP → early-onset glaucoma.

STURGE-Weber: Sporadic, port-wine stain; Tram track calcifications (opposing gyri); Unilateral; Retardation (intellectual disability); Glaucoma, GNAQ gene; Epilepsy.

**Tuberous sclerosis**
TSC1 mutation on chromosome 9 or TSC2 mutation on chromosome 16. Tumor suppressor genes. Autosomal dominant, variable expression. HAMARTOMAS: Hamartomas in CNS and skin; Angiofibromas; Mitral regurgitation; Ash-leaf spots; cardiac Rhabdomyoma;
(Tuberous sclerosis); autosomal dominant; Mental retardation (intellectual disability); renal Angiomyolipoma; Seizures, Shagreen patches. 1 incidence of subependymal giant cell astrocytomas and ungual fibromas.

**Neurofibromatosis type I**
Also known as von Recklinghausen disease. Mutation in NF1 tumor suppressor gene on chromosome 17 (17 letters in “von Recklinghausen”), which normally codes for neurofibromin, a negative regulator of RAS. Autosomal dominant, 100% penetrance. Café-au-lait spots, cutaneous neurofibromas, optic gliomas, pheochromocytomas, Lisch nodules (pigmented iris hamartomas).

**Neurofibromatosis type II**
Mutation in NF2 tumor suppressor gene on chromosome 22. Autosomal dominant. Findings: bilateral acoustic schwannomas, juvenile cataracts, meningiomas, and ependymomas. NF2 affects 2 ears, 2 eyes, and 2 parts of the brain.

**von Hippel-Lindau disease**
Deletion of VHL gene on chromosome 3p (VHL = 3 letters). Autosomal dominant. pVHL ubiquitinates hypoxia-inducible factor 1α. Characterized by development of numerous tumors, both benign and malignant. HARP: Hemangioblastomas (high vascularity with hyperchromatic nuclei) in retina, brain stem, cerebellum, spine; Angiomatosis (eg, cavernous hemangiomas in skin, mucosa, organs); bilateral Renal cell carcinomas; Pheochromocytomas.
**Adult primary brain tumors**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Description</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glioblastoma multiforme</strong></td>
<td>Grade IV astrocytoma. Common, highly malignant 1° brain tumor with ~ 1-year median survival. Found in cerebral hemispheres. Can cross corpus callosum (&quot;butterfly glioma&quot;).</td>
<td>Astrocyte origin, GFAP ⊕. “Pseudopalisading” pleomorphic tumor cells border central areas of necrosis, hemorrhage, and/or microvascular proliferation.</td>
</tr>
<tr>
<td><strong>Meningioma</strong></td>
<td>Common, typically benign. Females &gt; males. Most often occurs near surfaces of brain and in parasagittal region. Extra-axial (external to brain parenchyma) and may have a dural attachment (&quot;tail&quot;). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery.</td>
<td>Arachnoid cell origin. Spindle cells concentrically arranged in a whorled pattern; psammoma bodies (laminated calcifications).</td>
</tr>
<tr>
<td><strong>Hemangioblastoma</strong></td>
<td>Most often cerebellar. Associated with von Hippel-Lindau syndrome when found with retinal angiomatas. Can produce erythropoietin → 2° polycythemia.</td>
<td>Blood vessel origin. Closely arranged, thin-walled capillaries with minimal intervening parenchyma.</td>
</tr>
<tr>
<td><strong>Pituitary adenoma</strong></td>
<td>Adenoma may be nonfunctioning (silent) or hyperfunctioning (hormone producing). Most commonly from lactotrophs (prolactinoma) → hyperprolactinemia; less commonly adenoma of somatotrophs (GH) → acromegaly/gigantism; corticotrophs (ACTH) → Cushing disease. Rarely, adenoma of thyrotrophs (TSH) and gonadotroph (FSH, LH). Nonfunctional tumors present with mass effect (bitemporal hemianopia, hypopituitarism, headache). Bitemporal hemianopia due to pressure on optic chiasm (shows normal visual field above, patient’s perspective below). Sequelae include hyper- or hypopituitarism, which may be caused by pituitary apoplexy.</td>
<td>Hyperplasia of only one type of endocrine cells found in pituitary (ie, lactotroph, gonadotroph, somatotroph, corticotroph). Prolactinoma in women classically presents as galactorrhea, amenorrhea, and bone density due to suppression of estrogen. Prolactinoma in men classically presents as low libido and infertility. Treatment: dopamine agonists (eg, bromocriptine, cabergoline), transsphenoidal resection.</td>
</tr>
<tr>
<td><strong>Schwannoma</strong></td>
<td>Classically at the cerebellopontine angle involving both CNs VII and VIII, but can be along any peripheral nerve. Often localized to CN VIII in internal acoustic meatus → vestibular schwannoma. Bilateral vestibular schwannomas found in NF-2. Resection or stereotactic radiosurgery.</td>
<td>Schwann cell origin. Dense, hypercellular areas containing spindle cells alternating with hypocellular, myxoid areas.</td>
</tr>
</tbody>
</table>
Adult primary brain tumors (continued)
### Childhood primary brain tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Description</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>Most commonly found in 4th ventricle. Can cause hydrocephalus. Poor prognosis.</td>
<td>Ependymal cell origin. Characteristic perivascular pseudorosettes. Rod-shaped blepharoplasts (basal ciliary bodies) found near the nucleus.</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Most common childhood supratentorial tumor. May be confused with pituitary adenoma (both cause bitemporal hemianopia).</td>
<td>Derived from remnants of Rathke pouch (ectoderm). Calcification is common. Cholesterol crystals found in “motor oil”-like fluid within tumor.</td>
</tr>
<tr>
<td>Pinealoma</td>
<td>Tumor of pineal gland. Can cause Parinaud syndrome (compression of tectum → vertical gaze palsy); obstructive hydrocephalus (compression of cerebral aqueduct); precocious puberty in males (β-hCG production).</td>
<td>Similar to germ cell tumors (eg, testicular seminoma).</td>
</tr>
</tbody>
</table>

![Image of various brain tumors and histological sections](image-url)
Herniation syndromes

1. Cingulate (subfalcine) herniation under falx cerebri
   Can compress anterior cerebral artery.

2. Transtentorial (central/downward) herniation
   Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal.

3. Unical herniation
   Uncus = medial temporal lobe. Herniation compresses ipsilateral CN III and contralateral crus cerebri against Kernohan notch (causes contralateral CN III palsy and/or ipsilateral hemiparesis, i.e., a false localizing sign).

4. Cerebellar tonsillar herniation into the foramen magnum
   Coma and death result when these herniations compress the brain stem.

Motor neuron signs

<table>
<thead>
<tr>
<th>Sign</th>
<th>UMN lesion</th>
<th>LMN lesion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>+</td>
<td>+</td>
<td>Lower motor neuron = everything lowered (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes).</td>
</tr>
<tr>
<td>Atrophy</td>
<td>−</td>
<td>+</td>
<td>Upper motor neuron = everything up (tone, DTRs, toes).</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>↑</td>
<td>↓</td>
<td>Fasciculations = muscle twitching. Positive Babinski is normal in infants.</td>
</tr>
<tr>
<td>Reflexes</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Tone</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Babinski</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Spastic paresis</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Flaccid paralysis</td>
<td>−</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Clasp knife spasticity</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>
### Spinal cord lesions

<table>
<thead>
<tr>
<th>AREA AFFECTED</th>
<th>DISEASE</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Spinal muscular atrophy</strong></td>
<td>Congenital degeneration of anterior horns of spinal cord. LMN lesions only, symmetric weakness. “Floppy baby” with marked hypotonia (Flaccid paralysis) and tongue Fasciculations. Autosomal recessive inheritance of mutation in SMN1. SMA type 1 is called <em>Werdnig-Hoffmann disease</em>.</td>
</tr>
<tr>
<td></td>
<td><strong>Amyotrophic lateral sclerosis</strong></td>
<td>Combined UMN (corticobulbar/corticospinal) and LMN (medullary and spinal cord) degeneration. No sensory or bowel/bladder deficits. Can be caused by defect in superoxide dismutase 1. LMN deficits due to anterior horn cell involvement (eg, dysarthria, dysphagia, asymmetric limb weakness, fasciculations, atrophy) and UMN deficits (pseudobulbar palsy, eg, dysarthria, dysphagia, emotional lability, spastic gait, clonus). Fatal. Commonly known as Lou Gehrig disease. Treatment: riluzole.</td>
</tr>
<tr>
<td></td>
<td><strong>Complete occlusion of anterior spinal artery</strong></td>
<td>Spares dorsal columns and Lissauer tract; mid-thoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below T8. Can be caused by aortic aneurysm repair. Presents with UMN deficit below the lesion (corticospinal tract), LMN deficit at the level of the lesion (anterior horn), and loss of pain and temperature sensation below the lesion (spinothalamic tract).</td>
</tr>
<tr>
<td></td>
<td><strong>Tabes dorsalis</strong></td>
<td>Caused by 3° syphilis. Results from degeneration (demyelination) of dorsal columns and roots → progressive sensory ataxia (impaired proprioception → poor coordination). Romberg sign and absent DTRs. Associated with Charcot joints, shooting pain, Argyll Robertson pupils.</td>
</tr>
<tr>
<td></td>
<td><strong>Syringomyelia</strong></td>
<td>Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral symmetrical loss of pain and temperature sensation in cape-like distribution. Seen with Chiari I malformation. Can affect other tracts.</td>
</tr>
<tr>
<td></td>
<td><strong>Vitamin B₁₂ deficiency</strong></td>
<td>Subacute combined degeneration (SCD)—demyelination of Spinocerebellar tracts, lateral Corticospinal tracts, and Dorsal columns. Ataxic gait, paresthesia, impaired position/vibration sense.</td>
</tr>
<tr>
<td></td>
<td><strong>Cauda equina syndrome</strong></td>
<td>Compression of spinal roots L₂ and below, often due to intervertebral disc herniation or tumor. Unilateral radicular pain, absent knee and ankle reflex, loss of bladder and anal sphincter control, saddle anesthesia. Treatment: emergent surgery and steroids.</td>
</tr>
</tbody>
</table>
Poliomyelitis
Caused by poliovirus (fecal-oral transmission). Replicates in oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death).
Signs of LMN lesion: asymmetric weakness, hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Respiratory muscle involvement leads to respiratory failure. Signs of infection: malaise, headache, fever, nausea, etc.
CSF shows ↑ WBCs (lymphocytic pleocytosis) and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

Brown-Séquard syndrome
Hemisection of spinal cord. Findings:
1. Ipsilateral loss of all sensation at level of lesion
2. Ipsilateral LMN signs (eg, flaccid paralysis) at level of lesion
3. Ipsilateral UMN signs below level of lesion (due to corticospinal tract damage)
4. Ipsilateral loss of proprioception, vibration, light (2-point discrimination) touch, and tactile sense below level of lesion (due to dorsal column damage).
5. Contralateral loss of pain, temperature, and crude (nonadiscriminative) touch below level of lesion (due to spinothalamic tract damage).
If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.

Friedreich ataxia
Autosomal recessive trinucleotide repeat disorder (GAA)n on chromosome 9 in gene that encodes frataxin (iron binding protein). Leads to impairment in mitochondrial functioning. Degeneration of lateral corticospinal tract (spastic paralysis), spinocerebellar tract (ataxia), dorsal columns (vibratory sense, proprioception), and dorsal root ganglia (loss of DTRs). Staggering gait, frequent falling, nystagmus, dysarthria, pes cavus, hammer toes, diabetes mellitus, hypertrophic cardiomyopathy (cause of death). Presents in childhood with kyphoscoliosis A B.

Friedreich is Fratastic (frataxin): he’s your favorite frat brother, always staggering and falling but has a sweet, big heart.
Ataxic GAAit.
Common cranial nerve lesions

**CN V motor lesion** Jaw deviates *toward* side of lesion due to unopposed force from the opposite pterygoid muscle.

**CN X lesion** Uvula deviates *away* from side of lesion. Weak side collapses and uvula points away.

**CN XI lesion** Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius). The left SCM contracts to help turn the head to the right.

**CN XII lesion** LMN lesion. Tongue deviates *toward* side of lesion (“lick your wounds”) due to weakened tongue muscles on affected side.

Facial nerve lesions

**Bell palsy** is the most common cause of peripheral facial palsy. Usually develops after HSV reactivation. Treatment: corticosteroids ± acyclovir. Most patients gradually recover function, but aberrant regeneration can occur. Other causes of peripheral facial palsy include Lyme disease, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors (eg, parotid gland), diabetes mellitus.

<table>
<thead>
<tr>
<th>Upper motor neuron lesion</th>
<th>Lower motor neuron lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LESION LOCATION</strong></td>
<td>Motor cortex, connection from motor cortex to facial nucleus in pons</td>
</tr>
<tr>
<td><strong>AFFECTED SIDE</strong></td>
<td>Contralateral</td>
</tr>
<tr>
<td><strong>MUSCLES INVOLVED</strong></td>
<td>Lower muscles of facial expression</td>
</tr>
<tr>
<td><strong>FOREHEAD INVOLVED?</strong></td>
<td>Spared, due to bilateral UMN innervation</td>
</tr>
<tr>
<td><strong>OTHER SYMPTOMS</strong></td>
<td>None</td>
</tr>
</tbody>
</table>
Auditory physiology

Outer ear
Visible portion of ear (pinna), includes auditory canal and tympanic membrane. Transfers sound waves via vibration of tympanic membrane.

Middle ear
Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from tympanic membrane to inner ear.

Inner ear
Snail-shaped, fluid-filled cochlea. Contains basilar membrane that vibrates 2° to sound waves. Vibration transduced via specialized hair cells ➔ auditory nerve signaling ➔ brain stem. Each frequency leads to vibration at specific location on basilar membrane (tonotopy):
- Low frequency heard at apex near helicotrema (wide and flexible).
- High frequency heard best at base of cochlea (thin and rigid).

Diagnosing hearing loss

<table>
<thead>
<tr>
<th>Condutive hearing loss</th>
<th>Weber Test</th>
<th>Rinne Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizes to affected ear</td>
<td>Abnormal (bone &gt; air)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensorineural hearing loss</th>
<th>Weber Test</th>
<th>Rinne Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizes to unaffected ear</td>
<td>Normal (air &gt; bone)</td>
<td></td>
</tr>
</tbody>
</table>

Types of hearing loss

Noise-induced hearing loss
Damage to stereociliated cells in organ of Corti. Loss of high-frequency hearing first. Sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.

Presbycusis
Aging-related progressive bilateral/symmetric sensorineural hearing loss (often of higher frequencies) due to destruction of hair cells at the cochlear base (preserved low-frequency hearing at apex).

Cholesteatoma
Overgrowth of desquamated keratin debris within the middle ear space (arrows); may erode ossicles, mastoid air cells ➔ conductive hearing loss. Often presents with painless otorrhea.
Vertigo

Sensation of spinning while actually stationary. Subtype of “dizziness,” but distinct from “lightheadedness.”

Peripheral vertigo

More common. Inner ear etiology (eg, semicircular canal debris, vestibular nerve infection, Ménière disease [triad: sensorineural hearing loss, vertigo, tinnitus], benign paroxysmal positional vertigo [BPPV]). Treatment: antihistamines, anticholinergics, antiemetics (symptomatic relief); low-salt diet ± diuretics (Ménière disease); Epley maneuver (BPPV).

Central vertigo

Brain stem or cerebellar lesion (eg, stroke affecting vestibular nuclei or posterior fossa tumor). Findings: directional or purely vertical nystagmus, skew deviation, diplopia, dysmetria. Focal neurologic findings.

Conjunctivitis

Inflammation of the conjunctiva → red eye. Allergic—itchy eyes, bilateral. Bacterial—pus; treat with antibiotics. Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node; self-resolving.
Refractive errors

Common cause of impaired vision, correctable with glasses.

Hyperopia

Also known as “farsightedness.” Eye too short for refractive power of cornea and lens → light focused behind retina. Correct with convex (converging) lenses.

Myopia

Also known as “nearsightedness.” Eye too long for refractive power of cornea and lens → light focused in front of retina. Correct with concave (diverging) lens.

Astigmatism

Abnormal curvature of cornea → different refractive power at different axes. Correct with cylindrical lens.

Presbyopia

Aging-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity, changes in lens curvature, ↓ strength of the ciliary muscle. Patients often need “reading glasses” (magnifiers).

Cataract

Painless, often bilateral, opacification of lens → often resulting in glare and ↓ vision, especially at night. Acquired risk factors: ↑ age, smoking, excessive alcohol use, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection. Congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), ToRCHeS infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.

Aqueous humor pathway

Trabecular outflow (90%) 
Drainage through trabecular meshwork → canal of Schlemm → episcleral vasculature (↑ with M3 agonists)

Uveoscleral outflow (10%) 
Drainage into uvea and sclera (↑ with prostaglandin agonists)
Glaucoma
Optic disc atrophy with characteristic cupping (thinning of outer rim of optic nerve head B versus normal A), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss if untreated. Treatment is through pharmacologic or surgical lowering of IOP.

Open-angle glaucoma
Associated with ↑ age, African-American race, family history. Painless, more common in US. Primary—cause unclear. Secondary—blocked trabecular meshwork from WBCs (eg, uveitis), RBCs (eg, vitreous hemorrhage), retinal elements (eg, retinal detachment).

Closed- or narrow-angle glaucoma
Primary—enlargement or anterior movement of lens against central iris (pupil margin) → obstruction of normal aqueous flow through pupil → fluid builds up behind iris, pushing peripheral iris against cornea C and impeding flow through trabecular meshwork. Secondary—hypoxia from retinal disease (eg, diabetes mellitus, vein occlusion) induces vasoproliferation in iris that contracts angle. Chronic closure—often asymptomatic with damage to optic nerve and peripheral vision. Acute closure—true ophthalmic emergency. ↑ IOP pushes iris forward → angle closes abruptly. Very painful, red eye D, sudden vision loss, halos around lights, frontal headache, fixed and mid-dilated pupil. Mydriatic agents contraindicated.

Uveitis
Inflammation of uvea; specific name based on location within affected eye. Anterior uveitis: iritis; posterior uveitis: choroiditis and/or retinitis. May have hypopyon (accumulation of pus in anterior chamber A) or conjunctival redness. Associated with systemic inflammatory disorders (eg, sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions).

Age-related macular degeneration
Degeneration of macula (central area of retina). Causes distortion (metamorphopsia) and eventual loss of central vision (scotomas).
- **Dry (nonexudative, > 80%)**—Deposition of yellowish extracellular material in between Bruch membrane and retinal pigment epithelium (“Drusen”) A with gradual ↓ in vision. Prevent progression with multivitamin and antioxidant supplements.
- **Wet (exudative, 10–15%)**—rapid loss of vision due to bleeding 2° to choroidal neovascularization. Treat with anti-VEGF (vascular endothelial growth factor) injections (eg, bevacizumab, ranibizumab).
Diabetic retinopathy

Retinal damage due to chronic hyperglycemia. Two types:
* Nonproliferative—damaged capillaries leak blood → lipids and fluid seep into retina → hemorrhages (arrows in A) and macular edema. Treatment: blood sugar control.
* Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina. Treatment: peripheral retinal photocoagulation, surgery, anti-VEGF.

Hypertensive retinopathy

Retinal damage due to chronic uncontrolled HTN.
Flame-shaped retinal hemorrhages, arteriovenous nicking, microaneurysms, macular star (exudate, red arrow in A), cotton-wool spots (blue arrow in A). Presence of papilledema requires immediate lowering of BP.
Associated with ↑ risk of stroke, CAD, kidney disease.

Retinal vein occlusion

Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis.
Retinal hemorrhage and venous engorgement (“blood and thunder appearance”; arrows in A), edema in affected area.

Retinal detachment

Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) → degeneration of photoreceptors → vision loss. May be 2° to retinal breaks, diabetic traction, inflammatory effusions. Visualized on fundoscopy as crinkling of retinal tissue A and changes in vessel direction.
Breaks more common in patients with high myopia and/or history of head trauma. Often preceded by posterior vitreous detachment (“flashes” and “floaters”) and eventual monocular loss of vision like a “curtain drawn down.” Surgical emergency.
Central retinal artery occlusion

Acute, painless monocular vision loss. Retina cloudy with attenuated vessels and “cherry-red” spot at fovea (center of macula). Evaluate for embolic source (eg, carotid artery atherosclerosis, cardiac vegetations, patent foramen ovale).

Retinitis pigmentosa

Inherited retinal degeneration. Painless, progressive vision loss beginning with night blindness (rods affected first). Bone spicule-shaped deposits around macula.

Retinitis

Retinal edema and necrosis (arrows) leading to scar. Often viral (CMV, HSV, VZV), but can be bacterial or parasitic. May be associated with immunosuppression.

Papilledema

Optic disc swelling (usually bilateral) due to ↑ ICP (eg, 2° to mass effect). Enlarged blind spot and elevated optic disc with blurred margins.
**Pupillary control**

### Miosis
Constriction, parasympathetic:
- 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
- 2nd neuron: short ciliary nerves to sphincter pupillae muscles

Short ciliary nerves **shorten** the pupil diameter.

### Pupillary light reflex
Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines in image) in midbrain that activates bilateral Edinger-Westphal nuclei; pupils constrict bilaterally (direct and consensual reflex).
Result: illumination of 1 eye results in bilateral pupillary constriction.

---

**Mydriasis**
Dilation, sympathetic:
- 1st neuron: hypothalamus to ciliospinal center of Budge (C8–T2)
- 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels)
- 3rd neuron: plexus along internal carotid, through cavernous sinus; enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractors) and sweat glands of forehead and face.
Long ciliary nerves make the pupil diameter **longer**.

---

**Marcus Gunn pupil**
When the light shines into a normal eye, constriction of the ipsilateral (direct reflex) and contralateral eye (consensual reflex) is observed. When the light is then swung to the affected eye, both pupils dilate instead of constrict due to impaired conduction of light signal along the injured optic nerve.
Horner syndrome

Sympathetic denervation of face:
- Ppiosis (slight drooping of eyelid: superior tarsal muscle)
- Anhidrosis (absence of sweating) and flushing of affected side of face
- Myosis (pupil constriction)

Associated with lesions along the sympathetic chain:
- 1st neuron: pontine hemorrhage, lateral medullary syndrome, spinal cord lesion above T1 (eg, Brown-Séquard syndrome, late-stage syringomyelia)
- 2nd neuron (stellate ganglion): Pancoast tumor
- 3rd neuron: carotid dissection (painful)

PAM is horny (Horner).

Ocular motility

To test each muscle, ask patient to move his/her eye in the path diagrammed to the right, from neutral position toward the muscle being tested.

CN VI innervates the Lateral Rectus.
CN IV innervates the Superior Oblique.
CN III innervates the Rest.
The “chemical formula” LR₆SO₃R₃.
The strongest action of the superior oblique is depression when the eye is adducted. The further the eye is abducted, the more the superior oblique acts to intort the eye toward the nose.

Obliques go Opposite (left SO and IO tested with patient looking right).
IOU: IO tested looking Up.
CN III, IV, VI palsies

**CN III damage**

CN III has both motor (central) and parasympathetic (peripheral) components. Common causes include:

- Ischemia → pupil sparing
- Uncal herniation → coma
- PCA aneurysm → sudden-onset headache
- Cavernous sinus thrombosis → proptosis, involvement of CNs IV, V₁/V₂, VI
- Midbrain stroke → contralateral hemiplegia

Motor output to extraocular muscles—affected primarily by vascular disease (eg, diabetes mellitus: glucose → sorbitol) due to ↓ diffusion of oxygen and nutrients to the interior fibers from compromised vasculature that resides on outside of nerve. Signs: ptosis, “down and out” gaze.

Parasympathetic output—fibers on the periphery are first affected by compression (eg, PCom aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, “blown pupil” often with “down-and-out” gaze.

**CN IV damage**

Eye moves upward, particularly with contralateral gaze B (→ going down stairs, head may tilt in the opposite direction to compensate).

Can’t see the floor with CN IV damage.

**CN VI damage**

Affected eye unable to abduct and is displaced medially in primary position of gaze C.
Visual field defects

1. Right anopia
2. Bitemporal hemianopia (pituitary lesion, chiasm)
3. Left homonymous hemianopia
4. Left upper quadrantanopia (right temporal lesion, MCA)
5. Left lower quadrantanopia (right parietal lesion, MCA)
6. Left hemianopia with macular sparing (PCA infarct)
7. Central scotoma (eg, macular degeneration)

Meyer Loop—Lower retina; Loops around inferior horn of Lateral ventricle.
Dorsal optic radiation—superior retina; takes shortest path via internal capsule.

Cavernous sinus

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.
CNs III, IV, V_1, VI, and V_2 plus postganglionic sympathetic pupillary fibers en route to orbit all pass through cavernous sinus. Cavernous portion of internal carotid artery is also here.
Cavernous sinus syndrome—presents with variable ophthalmoplegia, ↓ corneal sensation, Horner syndrome and occasional decreased maxillary sensation. 2° to pituitary tumor mass effect, carotid-cavernous fistula, or cavernous sinus thrombosis related to infection. CN VI is most susceptible to injury.
**Internuclear ophthalmoplegia**

Medial longitudinal fasciculus (MLF): pair of tracts that allows for crosstalk between CN VI and CN III nuclei. Coordinates both eyes to move in same horizontal direction. Highly myelinated (must communicate quickly so eyes move at same time). Lesions may be unilateral or bilateral (latter classically seen in multiple sclerosis).

Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to contract. Abducting eye gets nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

MLF in MS.

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus. Directional term (eg, right INO, left INO) refers to which eye is paralyzed.

INO = Ipsilateral adduction failure, Nystagmus Opposite.
## Epilepsy drugs

<table>
<thead>
<tr>
<th></th>
<th>GENERALIZED</th>
<th>MECHANISM</th>
<th>SIDE EFFECTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td><strong>↑ GABA&lt;sub&gt;x&lt;/sub&gt; action</strong></td>
<td>Sedation, tolerance, dependence, respiratory depression</td>
<td>Also for eclampsia seizures (1st line is MgSO&lt;sub&gt;4&lt;/sub&gt;)</td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>✓</td>
<td>Blocks Na&lt;sup&gt;+&lt;/sup&gt; channels</td>
<td>Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis (cleft lip/palate, spina bifida), induction of cytochrome P-450, SIADH, Stevens-Johnson syndrome</td>
<td>1st line for trigeminal neuralgia</td>
</tr>
<tr>
<td><strong>Ethosuximide</strong></td>
<td>✓</td>
<td>Blocks thalamic T-type Ca&lt;sup&gt;2+&lt;/sup&gt; channels</td>
<td>EF&lt;sub&gt;GHIJ&lt;/sub&gt;—Ethosuximide causes Fatigue, GI distress, Headache, Itching (and urticaria), and Stevens-Johnson syndrome</td>
<td>Sucks to have Silent (absence) Seizures</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>✓</td>
<td>Primarily inhibits high-voltage-activated Ca&lt;sup&gt;2+&lt;/sup&gt; channels; designed as GABA analog</td>
<td>Sedation, ataxia</td>
<td>Also used for peripheral neuropathy, postherpetic neuralgia</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>✓</td>
<td>Blocks voltage-gated Na&lt;sup&gt;+&lt;/sup&gt; channels, inhibits the release of glutamate</td>
<td>Stevens-Johnson syndrome (must be titrated slowly)</td>
<td></td>
</tr>
<tr>
<td><strong>Levetiracetam</strong></td>
<td>✓</td>
<td>Unknown; may modulate GABA and glutamate release</td>
<td>Neuropsychiatric symptoms (eg, personality change), fatigue, drowsiness, headache</td>
<td></td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td>✓</td>
<td><strong>↑ GABA&lt;sub&gt;x&lt;/sub&gt; action</strong></td>
<td>Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression</td>
<td>1st line in neonates (&quot;phenobarbital&quot;)</td>
</tr>
<tr>
<td><strong>Phenytoin, fosphenytoin</strong></td>
<td>✓</td>
<td>Blocks Na&lt;sup&gt;+&lt;/sup&gt; channels, zero-order kinetics</td>
<td>PHENYTOIN: P450 induction, Hirsutism, Enlarged gums, Nystagmus, Yellow-brown skin, Teratogenicity (fetal hydantoin syndrome), Osteopenia, Inhibited folate absorption, Neuropathy. Rare adverse reactions including Stevens-Johnson syndrome, DRESS syndrome, SLE-like syndrome. Toxicity leads to diplopia, ataxia, sedation.</td>
<td></td>
</tr>
<tr>
<td><strong>Tiagabine</strong></td>
<td>✓</td>
<td><strong>↑ GABA</strong> by inhibiting reuptake</td>
<td>Permanent visual loss (black box warning)</td>
<td></td>
</tr>
<tr>
<td><strong>Topiramate</strong></td>
<td>✓</td>
<td>Blocks Na&lt;sup&gt;+&lt;/sup&gt; channels, <strong>↑ GABA</strong> action</td>
<td>Sedation, mental dulling, word-finding difficulty, kidney stones, weight loss, glaucoma</td>
<td>Also used for migraine prevention</td>
</tr>
<tr>
<td><strong>Valproic acid</strong></td>
<td>✓</td>
<td>**↑ Na&lt;sup&gt;+&lt;/sup&gt; channel inactivation, <strong>↑ GABA concentration</strong> by inhibiting GABA transaminase</td>
<td>GI distress, rare but fatal hepatotoxicity (measure LFTs), pancreatitis, neural tube defects, tremor, weight gain, contraindicated in pregnancy</td>
<td>Also used for myoclonic seizures, bipolar disorder, migraine prophylaxis</td>
</tr>
<tr>
<td><strong>Vigabatrin</strong></td>
<td>✓</td>
<td><strong>↑ GABA. Irreversible GABA transaminase inhibitor</strong></td>
<td>Permanent visual loss (black box warning)</td>
<td></td>
</tr>
</tbody>
</table>

* = Common use, ** = 1st line for acute, *** = 1st line for recurrent seizure prophylaxis.
### Barbiturates
Phenobarbital, pentobarbital, thiopental, secobarbital.

**Mechanism**
Facilitate GABA$_A$ action by ↑ duration of Cl$^-$ channel opening, thus ↑ neuron firing (barbiturates ↑ duration).

**Clinical Use**
Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).

**Adverse Effects**
Respiratory and cardiovascular depression (can be fatal); CNS depression (can be exacerbated by alcohol use); dependence; drug interactions (induces cytochrome P-450). Overdose treatment is supportive (assist respiration and maintain BP). Contraindicated in porphyria.

### Benzodiazepines
Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

**Mechanism**
Facilitate GABA$_A$ action by ↑ frequency of Cl$^-$ channel opening. ↓ REM sleep. Most have long half-lives and active metabolites (exceptions [ATOM]: Alprazolam, Triazolam, Oxazepam, and Midazolam are short acting → higher addictive potential).

**Clinical Use**
Anxiety, spasticity, status epilepticus (lorazepam, diazepam, midazolam), eclampsia, detoxification (especially alcohol withdrawal–DTIs), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia).

**Adverse Effects**
Dependence, additive CNS depression effects with alcohol. Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). Can precipitate seizures by causing acute benzodiazepine withdrawal.

### Nonbenzodiazepine Hypnotics
Zolpidem, Zaleplon, eszopiclone. “These ZZZs put you to sleep.”

**Mechanism**
Act via the BZ$_1$ subtype of the GABA receptor. Effects reversed by flumazenil. Sleep cycle less affected as compared with benzodiazepine hypnotics.

**Clinical Use**
Insomnia.

**Adverse Effects**
Ataxia, headaches, confusion. Short duration because of rapid metabolism by liver enzymes. Unlike older sedative-hypnotics, cause only modest day-after psychomotor depression and few amnestic effects. ↓ dependence risk than benzodiazepines.
### Suvorexant

**MECHANISM**
Orexin (hypocretin) receptor antagonist.

**CLINICAL USE**
Insomnia.

**ADVERSE EFFECTS**

### Ramelteon

**MECHANISM**
Melatonin receptor agonist, binds MT1 and MT2 in suprachiasmatic nucleus.

**CLINICAL USE**
Insomnia.

**ADVERSE EFFECTS**
Dizziness, nausea, fatigue, headache. No dependence (not a controlled substance).

### Triptans

**MECHANISM**
5-HT1B/1D agonists. Inhibit trigeminal nerve activation; prevent vasoactive peptide release; induce vasoconstriction.

**CLINICAL USE**
Acute migraine, cluster headache attacks.

**ADVERSE EFFECTS**
Coronary vasospasm (contraindicated in patients with CAD or Prinzmetal angina), mild paresthesia, serotonin syndrome (in combination with other 5-HT agonists).
Parkinson disease drugs

Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity. 
Bromocriptine, Amantadine, Levodopa (with carbidopa), Selegline (and COMT inhibitors), Antimuscarinics (BALSA).

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine agonists</td>
<td>Ergot—Bromocriptine. Non-ergot (preferred)—pramipexole, ropinirole; toxicity includes impulse control disorder (eg, gambling), postural hypotension, hallucinations/confusion.</td>
</tr>
<tr>
<td>↑ dopamine availability</td>
<td>Amantadine (↑ dopamine release and ↓ dopamine reuptake); toxicity = ataxia, livedo reticularis.</td>
</tr>
</tbody>
</table>
| ↑ L-DOPA availability | Agents prevent peripheral (pre-BBB) L-DOPA degradation → ↑ L-DOPA entering CNS → ↑ central L-DOPA available for conversion to dopamine.  
  - Levodopa (L-DOPA)/carbidopa—carbidopa blocks peripheral conversion of L-DOPA to dopamine by inhibiting DOPA decarboxylase. Also reduces side effects of peripheral L-DOPA conversion into dopamine (eg, nausea, vomiting).  
  - Entacapone prevents peripheral L-DOPA degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT. Used in conjunction with levodopa. |
| Prevent dopamine breakdown | Agents act centrally (post-BBB) to inhibit breakdown of dopamine.  
  - Selegiline, rasagiline—block conversion of dopamine into DOPAC by selectively inhibiting MAO-B.  
  - Entacapone—blocks conversion of dopamine to 3-methoxytyramine (3-MT) by inhibiting central COMT. |
| Curb excess cholinergic activity | Benztropine, trihexyphenidyl (Antimuscarinic; improves tremor and rigidity but has little effect on bradykinesia in Parkinson disease). Park your Mercedes-Benz. |
**Levodopa/carbidopa**

**MECHANISM**
- ↑ level of dopamine in brain. Unlike dopamine, L-DOPA can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with L-DOPA to ↑ the bioavailability of L-DOPA in the brain and to limit peripheral side effects.

**CLINICAL USE**
- Parkinson disease.

**ADVERSE EFFECTS**
- Nausea, hallucinations, postural hypotension from ↑ peripheral formation of catecholamines. Long-term use can lead to dyskinesia following administration (“on-off” phenomenon), akinesia between doses.

---

**Selegiline, rasagiline**

**MECHANISM**
- Selectively inhibit MAO-B (metabolize dopamine) → ↑ dopamine availability.

**CLINICAL USE**
- Adjunctive agent to L-DOPA in treatment of Parkinson disease.

**ADVERSE EFFECTS**
- May enhance adverse effects of L-DOPA.

---

**Tetrabenzine, reserpine**

**MECHANISM**
- Inhibit vesicular monoamine transporter (VMAT) dopamine → ↓ vesicle packaging and release.

**CLINICAL USE**
- Huntington chorea, tardive dyskinesia

---

**Riluzole**

**MECHANISM**
- ↓ neuron glutamate excitotoxicity

**CLINICAL USE**
- ALS, ↑ survival

- For Lou Gehrig disease, give riluzole.

---

**Alzheimer disease drugs**

**Memantine**

**MECHANISM**
- NMDA receptor antagonist; helps prevent excitotoxicity (mediated by Ca²⁺).

**ADVERSE EFFECTS**
- Dizziness, confusion, hallucinations.

**Donepezil, rivastigmine, galantamine**

**MECHANISM**
- AChE inhibitors.

**ADVERSE EFFECTS**
- Nausea, dizziness, insomnia.

**Dona Riva dances at the gala.**

---

**Anesthetics—general principles**

- CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported. Drugs with ↓ solubility in blood = rapid induction and recovery times.

- Drugs with ↑ solubility in lipids = ↑ potency = \( \frac{1}{MAC} \)

**MAC** = Minimal Alveolar Concentration (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (eg, skin incision).

Examples: nitrous oxide (N₂O) has ↓ blood and lipid solubility, and thus fast induction and low potency. Halothane, propofol, and thiopental, in contrast, have ↑ lipid and blood solubility, and thus high potency and slow induction.
**Inhaled anesthetics**

**Mechanism**
Mechanism unknown.

**Effects**
Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand).

**Adverse Effects**
Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane, epileptogenic), expansion of trapped gas in a body cavity (N₂O).

**Malignant hyperthermia**—rare, life-threatening condition in which inhaled anesthetics or succinylcholine induce fever and severe muscle contractions. Susceptibility is often inherited as autosomal dominant with variable penetrance. Mutations in voltage-sensitive ryanodine receptor (RYR1 gene) cause ↑ Ca²⁺ release from sarcoplasmic reticulum. Treatment: dantrolene (a ryanodine receptor antagonist).

---

**Intravenous anesthetics**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Anesthesia Use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Facilitate GABA&lt;sub&gt;A&lt;/sub&gt; (benzodiazepine).</td>
<td>Procedural sedation (eg, endoscopy), anesthesia induction.</td>
<td>May cause severe postoperative respiratory depression, ↓ BP, anterograde amnesia.</td>
</tr>
<tr>
<td>Propofol</td>
<td>Potentiates GABA&lt;sub&gt;A&lt;/sub&gt;.</td>
<td>Rapid anesthesia induction, short procedures, ICU sedation.</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA receptor antagonist.</td>
<td>Dissociative anesthesia. Sympathomimetic.</td>
<td>↑ cerebral blood flow. Emergence reaction possible with disorientation, hallucination, vivid dreams.</td>
</tr>
</tbody>
</table>

**Local anesthetics**

**Mechanism**
Block Na<sup>+</sup> channels by binding to specific receptors on inner portion of channel. Most effective in rapidly firing neurons. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form.

Can be given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding, ↑ anesthesia by ↓ systemic concentration.

In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively → need more anesthetic.

Order of nerve blockade: small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination such that small myelinated fibers > small unmyelinated fibers > large myelinated fibers > large unmyelinated fibers.

Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure.

**Clinical Use**
Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides.

**Adverse Effects**
CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine).
Neuromuscular blocking drugs

Muscle paralysis in surgery or mechanical ventilation. Selective for Nm nicotinic receptors at neuromuscular junction but not autonomic Nn receptors.

Depolarizing neuromuscular blocking drugs

Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction.

Reversal of blockage:
- Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors.
- Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—may be reversed with cholinesterase inhibitors.

Complications include hypercalcemia, hyperkalemia, malignant hyperthermia.

Nondepolarizing neuromuscular blocking drugs

Atracurium, cisatracurium, pancuronium, rocuronium, tubocurarine, vecuronium—competitive with ACh for receptors.

Reversal of blockade—neostigmine (must be given with atropine or glycopyrrolate to prevent muscarinic effects such as bradycardia), edrophonium, and other cholinesterase inhibitors.

Dantrolene

**MECHANISM**
Prevents release of Ca$^{2+}$ from the sarcoplasmic reticulum of skeletal muscle by binding to the ryanodine receptor.

**CLINICAL USE**
Malignant hyperthermia (a toxicity of inhaled anesthetics and succinylcholine) and neuroleptic malignant syndrome (a toxicity of antipsychotic drugs).

Baclofen

**MECHANISM**
Skeletal muscle relaxant. GABAB receptor agonist in spinal cord.

**CLINICAL USE**
Muscle spasticity, dystonia, multiple sclerosis.

Cyclobenzaprine

**MECHANISM**
Skeletal muscle relaxant. Acts within CNS.

**CLINICAL USE**
Muscle spasms.

**ADVERSE EFFECTS**
Anticholinergic side effects. Sedation.

Opioid analgesics

**MECHANISM**
Act as agonists at opioid receptors (µ = β-endorphin, δ = enkephalin, κ = dynorphin) to modulate synaptic transmission—close presynaptic Ca$^{2+}$ channel, open postsynaptic K$^+$ channels → ↓ synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P.

**EFFICACY**
Full agonist: morphine, heroin, meperidine, methadone, codeine.
Partial agonist: buprenorphine.
Mixed agonist/antagonist: nalbuphine, pentazocine.
Antagonist: naloxone, naltrexone, methylnaltrexone.

**CLINICAL USE**
Moderate to severe or refractory pain, cough suppression (dextromethorphan), diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for heroin addicts (methadone, buprenorphine + naloxone).

**ADVERSE EFFECTS**
Nausea, vomiting, pruritus, addiction, respiratory depression, constipation, sphincter of Oddi spasm, miosis (except meperidine → mydriasis), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone (opioid receptor antagonist) and relapse prevention with naltrexone once detoxified.
### Pentazocine

**MECHANISM**
κ-opioid receptor agonist and μ-opioid receptor weak antagonist or partial agonist.

**CLINICAL USE**
Analgesia for moderate to severe pain.

**ADVERSE EFFECTS**
Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (due to competition for opioid receptors).

### Butorphanol

**MECHANISM**
κ-opioid receptor agonist and μ-opioid receptor partial agonist.

**CLINICAL USE**
Severe pain (eg, migraine, labor). Causes less respiratory depression than full opioid agonists.

**ADVERSE EFFECTS**
Use with full opioid agonist can precipitate withdrawal. Not easily reversed with naloxone.

### Tramadol

**MECHANISM**
Very weak opioid agonist; also inhibits 5-HT receptors.

**CLINICAL USE**
Chronic pain.

**ADVERSE EFFECTS**
Similar to opioids. Decreases seizure threshold. Serotonin syndrome.

### Glaucoma drugs

‡ IOP via ‡ amount of aqueous humor (inhibit synthesis/secretion or ‡ drainage). **BAD** humor may not be **Politically Correct**.

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>EXAMPLES</th>
<th>MECHANISM</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>Timolol, betaxolol, carteolol</td>
<td>‡ aqueous humor synthesis</td>
<td>No pupillary or vision changes</td>
</tr>
</tbody>
</table>
| α-agonists       | Epinephrine (α₁), apraclonidine, brimonidine (α₂) | ‡ aqueous humor synthesis via vasoconstriction (epinephrine)  
‡ aqueous humor synthesis (apraclonidine, brimonidine) | Mydriasis (α₁); do not use in closed-angle glaucoma
Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus |
| Diuretics        | Acetazolamide        | ‡ aqueous humor synthesis via inhibition of carbonic anhydrase | No pupillary or vision changes                                                  |
| Prostaglandins   | Bimatoprost, latanoprost (PGF₂α) | ‡ outflow of aqueous humor via resistance of flow through uveoscleral pathway | Darkens color of iris (browning), eyelash growth                               |
| Cholinomimetics (M₃) | Direct: pilocarpine, carbachol  
Indirect: physostigmine, echothiophate | ‡ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork  
Use pilocarpine in acute angle closure glaucoma—very effective at opening meshwork into canal of Schlemm | Miosis (contraction of pupillary sphincter muscles) and cyclospasm (contraction of ciliary muscle) |
“Words of comfort, skillfully administered, are the oldest therapy known to man.”
—Louis Nizer

“All men should strive to learn before they die what they are running from, and to, and why.”
—James Thurber

“Man wishes to be happy even when he so lives as to make happiness impossible.”
—St. Augustine

“It’s no use going back to yesterday, because I was a different person then.”
—Lewis Carroll, Alice in Wonderland

This chapter encompasses overlapping areas in psychiatry, psychology, sociology, and psychopharmacology. High-yield topics include schizophrenia, mood disorders, eating disorders, personality disorders, psychosomatic/somatoform disorders, and antipsychotic agents. Know the DSM-5 criteria for diagnosing common psychiatric disorders.
### Classical conditioning
Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food). Usually deals with involuntary responses. Pavlov’s classical experiments with dogs—ringing the bell provoked salivation.

### Operant conditioning
Learning in which a particular action is elicited because it produces a punishment or reward. Usually deals with voluntary responses.

- **Reinforcement**
  - Target behavior (response) is followed by desired reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement).

- **Extinction**
  - Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.

- **Punishment**
  - Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior (Skinner’s operant conditioning quadrant).

- **Increase behavior**
  - Add a stimulus
  - Positive reinforcement
  - Negative reinforcement

- **Decrease behavior**
  - Remove a stimulus
  - Positive punishment
  - Negative punishment

### Transference and countertransference

- **Transference**
  - Patient projects feelings about formative or other important persons onto physician (e.g., psychiatrist is seen as parent).

- **Countertransference**
  - Doctor projects feelings about formative or other important persons onto patient (e.g., patient reminds physician of younger sibling).

### Ego defenses
Mental processes (unconscious or conscious) used to resolve conflict and prevent undesirable feelings (e.g., anxiety, depression).

<table>
<thead>
<tr>
<th>IMMATURE DEFENSES</th>
<th>DESCRIPTION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acting out</td>
<td>Expressing unacceptable feelings and thoughts through actions.</td>
<td>A young boy throws a temper tantrum when he does not get the toy he wants.</td>
</tr>
<tr>
<td>Denial</td>
<td>Avoiding the awareness of some painful reality.</td>
<td>A patient with cancer plans a full-time work schedule despite being warned of significant fatigue during chemotherapy.</td>
</tr>
<tr>
<td>Displacement</td>
<td>Redirection of emotions or impulses to a neutral person or object (vs projection).</td>
<td>A teacher is yelled at by the principal. Instead of confronting the principal directly, the teacher goes home and criticizes her husband’s dinner selection.</td>
</tr>
<tr>
<td>Dissociation</td>
<td>Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress. Patient has incomplete or no memory of traumatic event.</td>
<td>A victim of sexual abuse suddenly appears numb and detached when she is exposed to her abuser.</td>
</tr>
</tbody>
</table>
# Ego defenses (continued)

<table>
<thead>
<tr>
<th>IMMATURE DEFENSES</th>
<th>DESCRIPTION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixation</td>
<td>Partially remaining at a more childish level of development (vs regression).</td>
<td>A surgeon throws a tantrum in the operating room because the last case ran very late.</td>
</tr>
<tr>
<td>Idealization</td>
<td>Expressing extremely positive thoughts of self and others while ignoring negative thoughts.</td>
<td>A patient boasts about his physician and his accomplishments while ignoring any flaws.</td>
</tr>
<tr>
<td>Identification</td>
<td>Largely unconscious assumption of the characteristics, qualities, or traits of another person or group.</td>
<td>A resident starts putting his stethoscope in his pocket like his favorite attending, instead of wearing it around his neck like before.</td>
</tr>
<tr>
<td>Intellectualization</td>
<td>Using facts and logic to emotionally distance oneself from a stressful situation.</td>
<td>In a therapy session, patient diagnosed with cancer focuses only on rates of survival.</td>
</tr>
<tr>
<td>Isolation (of affect)</td>
<td>Separating feelings from ideas and events.</td>
<td>Describing murder in graphic detail with no emotional response.</td>
</tr>
<tr>
<td>Passive aggression</td>
<td>Demonstrating hostile feelings in a nonconfrontational manner; showing indirect opposition.</td>
<td>Disgruntled employee is repeatedly late to work, but won’t admit it is a way to get back at the manager.</td>
</tr>
<tr>
<td>Projection</td>
<td>Attributing an unacceptable internal impulse to an external source (vs displacement).</td>
<td>A man who wants to cheat on his wife accuses his wife of being unfaithful.</td>
</tr>
<tr>
<td>Rationalization</td>
<td>Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.</td>
<td>After getting fired, claiming that the job was not important anyway.</td>
</tr>
<tr>
<td>Reaction formation</td>
<td>Replacing a warded-off idea or feeling with an (unconsciously derived) emphasis on its opposite (vs sublimation).</td>
<td>A patient with lustful thoughts enters a monastery.</td>
</tr>
<tr>
<td>Regression</td>
<td><strong>Involuntarily</strong> turning back the maturational clock and going back to earlier modes of dealing with the world (vs fixation).</td>
<td>Seen in children under stress such as illness, punishment, or birth of a new sibling (eg, bedwetting in a previously toilet-trained child).</td>
</tr>
<tr>
<td>Repression</td>
<td>Involuntarily withholding an idea or feeling from conscious awareness (vs suppression).</td>
<td>A 20-year-old does not remember going to counseling during his parents’ divorce 10 years earlier.</td>
</tr>
<tr>
<td>Splitting</td>
<td>Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Commonly seen in borderline personality disorder.</td>
<td>A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MATURE DEFENSES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublimation</td>
<td>Replacing an unacceptable wish with a course of action that is similar to the wish but socially acceptable (vs reaction formation).</td>
</tr>
<tr>
<td></td>
<td>Teenager’s aggressive urges toward his parents’ high expectations are channeled into excelling in sports.</td>
</tr>
<tr>
<td>Altruism</td>
<td>Alleviating negative feelings via unsolicited generosity, which provides gratification (vs reaction formation).</td>
</tr>
<tr>
<td></td>
<td>Mafia boss makes large donation to charity.</td>
</tr>
<tr>
<td>Suppression</td>
<td><strong>Intentionally</strong> withholding an idea or feeling from conscious awareness (vs repression); temporary.</td>
</tr>
<tr>
<td></td>
<td>Choosing to not worry about the big game until it is time to play.</td>
</tr>
<tr>
<td>Humor</td>
<td>Appreciating the amusing nature of an anxiety-provoking or adverse situation.</td>
</tr>
<tr>
<td></td>
<td>Nervous medical student jokes about the boards.</td>
</tr>
</tbody>
</table>

**Mature adults wear a SASH.**
### Infant deprivation effects

Long-term deprivation of affection results in:
- Failure to thrive
- Poor language/socialization skills
- Lack of basic trust
- Reactive attachment disorder (infant withdrawn/unresponsive to comfort)
- Disinhibited social engagement (infant indiscriminately attaches to strangers)

Deprivation for > 6 months can lead to irreversible changes.
Severe deprivation can result in infant death.

### Child abuse

<table>
<thead>
<tr>
<th>Physical abuse</th>
<th>Sexual abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVIDENCE</strong></td>
<td>Fractures (eg, ribs, long bone spiral, multiple in different stages of healing), bruises (eg, trunk, ear, neck, in pattern of implement), burns (eg, cigarette, buttocks/thighs), subdural hematomas/retinal hemorrhages (“shaken baby syndrome”). During exam, children often avoid eye contact. Red flags include history inconsistent with degree or type of injury (eg, 2-month-old rolling out of bed or falling down stairs), delayed medical care, caregiver story changes with retelling.</td>
</tr>
<tr>
<td><strong>ABUSER</strong></td>
<td>Usually biological mother.</td>
</tr>
<tr>
<td><strong>EPIDEMIOLOGY</strong></td>
<td>40% of deaths related to child abuse or neglect occur in children &lt; 1 year old.</td>
</tr>
</tbody>
</table>

### Child neglect

Failure to provide a child with adequate food, shelter, supervision, education, and/or affection. Most common form of child maltreatment. Evidence: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive.
As with child abuse, suspected child neglect must be reported to local child protective services.

### Vulnerable child syndrome

Parents perceive the child as especially susceptible to illness or injury. Usually follows a serious illness or life-threatening event. Can result in missed school or overuse of medical services.
### Childhood and early-onset disorders

**Attention-deficit hyperactivity disorder**
- Onset before age 12. At least 6 months of limited attention span and/or poor impulse control.
- Characterized by hyperactivity, impulsivity, and/or inattention in multiple settings (school, home, places of worship, etc).
- Normal intelligence, but commonly coexists with difficulties in school. Often persists into adulthood.
- Treatment: stimulants (eg, methylphenidate) +/- cognitive behavioral therapy (CBT); alternatives include atomoxetine, guanfacine, clonidine.

**Autism spectrum disorder**
- Characterized by poor social interactions, social communication deficits, repetitive/ritualized behaviors, restricted interests.
- Must present in early childhood.
- May be accompanied by intellectual disability; rarely accompanied by unusual abilities (savants).
- More common in boys.
- Associated with ↑ head/brain size.

**Conduct disorder**
- Repetitive and pervasive behavior violating the basic rights of others or societal norms (eg, aggression to people and animals, destruction of property, theft).
- After age 18, often reclassified as antisocial personality disorder.
- Treatment for both: psychotherapy such as CBT.

**Disruptive mood dysregulation disorder**
- Onset before age 10. Severe and recurrent temper outbursts out of proportion to situation.
- Child is constantly angry and irritable between outbursts.
- Treatment: stimulants, antipsychotics, CBT.

**Oppositional defiant disorder**
- Enduring pattern of hostile, defiant behavior toward authority figures in the absence of serious violations of social norms.
- Treatment: psychotherapy such as CBT.

**Separation anxiety disorder**
- Overwhelming fear of separation from home or attachment figure lasting ≥ 4 weeks.
- Can be normal behavior up to age 3–4.
- May lead to factitious physical complaints to avoid school.
- Treatment: CBT, play therapy, family therapy.

**Tourette syndrome**
- Onset before age 18. Characterized by sudden, rapid, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for > 1 year.
- Coprolalia (involuntary obscene speech) found in only 40% of patients.
- Associated with OCD and ADHD.
- Treatment: psychoeducation, behavioral therapy.
- For intractable and distressing tics, high-potency antipsychotics (eg, haloperidol, fluphenazine), tetrabenazine, α₂-agonists (eg, guanfacine, clonidine), or atypical antipsychotics may be used.

### Orientation
- Patient’s ability to know who he or she is, where he or she is, and the date and time.
- Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies, hypoxia.

| Orientation | Patient’s ability to know who he or she is, where he or she is, and the date and time. | Order of loss: time → place → person. | Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies, hypoxia. |
Amnesias

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrograde amnesia</strong></td>
<td>Inability to remember things that occurred <strong>before</strong> a CNS insult.</td>
</tr>
<tr>
<td><strong>Anterograde amnesia</strong></td>
<td>Inability to remember things that occurred <strong>after</strong> a CNS insult (<strong>acquisition of new memory</strong>).</td>
</tr>
<tr>
<td><strong>Korsakoff syndrome</strong></td>
<td>Amnesia (<strong>anterograde &gt; retrograde</strong>) caused by vitamin B₁ deficiency and associated destruction of mammillary bodies. Seen in alcoholics as a late neuropsychiatric manifestation of Wernicke encephalopathy. Confabulations are characteristic.</td>
</tr>
</tbody>
</table>

Dissociative disorders

| Syndrome                      | Description                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------|                                                                                                                                                                                                                                                                                                                                 |
| **Depersonalization/derealization disorder** | Persistent feelings of detachment or estrangement from one’s own body, thoughts, perceptions, and actions (depersonalization) or one’s environment (derealization). Intact reality testing (vs psychosis).                                                                                                                                                                                                       |
| **Dissociative amnesia**      | Inability to recall important personal information, usually subsequent to severe trauma or stress.                                                                                                                                                                                                                                                                                                                                 |
| **Dissociative identity disorder** | Formerly known as multiple personality disorder. Presence of 2 or more distinct identities or personality states. More common in women. Associated with history of sexual abuse, PTSD, depression, substance abuse, borderline personality, somatoform conditions. May be accompanied by **dissociative fugue** (abrupt travel or wandering associated with traumatic circumstances).                                                          |

Delirium

“Waxing and waning” level of consciousness with acute onset; rapid ↓ in attention span and level of arousal. Characterized by disorganized thinking, hallucinations (often visual), illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction, agitation. Usually 2° to other illness (e.g., CNS disease, infection, trauma, substance abuse/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention).

Most common presentation of altered mental status in inpatient setting, especially in the intensive care unit and with prolonged hospital stays. EEG may show diffuse slowing. Treatment is aimed at identifying and addressing underlying condition. Use antipsychotics acutely as needed. Avoid benzodiazepines.

Delirium = changes in sensorium. May be caused by medications (e.g., anticholinergics), especially in the elderly. **Reversible.**
### Psychosis
Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thought/speech. Can occur in patients with medical illness, psychiatric illness, or both.

<table>
<thead>
<tr>
<th>Delusions</th>
<th>Unique, false, fixed, idiosyncratic beliefs that persist despite the facts and are not typical of a patient's culture or religion (eg, thinking aliens are communicating with you). Types include erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorganized thought</td>
<td>Speech may be incoherent (&quot;word salad&quot;), tangential, or detailed (&quot;loose associations&quot;).</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present). Contrast with illusions, misperceptions of real external stimuli. Types include:</td>
</tr>
<tr>
<td></td>
<td>* Visual—more commonly a feature of medical illness (eg, drug intoxication) than psychiatric illness.</td>
</tr>
<tr>
<td></td>
<td>* Auditory—more commonly a feature of psychiatric illness (eg, schizophrenia) than medical illness.</td>
</tr>
<tr>
<td></td>
<td>* Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors.</td>
</tr>
<tr>
<td></td>
<td>* Gustatory—rare, but seen in epilepsy.</td>
</tr>
<tr>
<td></td>
<td>* Tactile—common in alcohol withdrawal and stimulant use (eg, cocaine, amphetamines), delusional parasitosis, “cocaine crawlies.”</td>
</tr>
<tr>
<td></td>
<td>* Hypnagogic—occurs while going to sleep. Sometimes seen in narcolepsy.</td>
</tr>
<tr>
<td></td>
<td>* Hypnopompic—occurs while waking from sleep (&quot;pompous upon awakening&quot;). Sometimes seen in narcolepsy.</td>
</tr>
</tbody>
</table>
**Schizophrenia**

Chronic mental disorder with periods of psychosis, disturbed behavior and thought, and decline in functioning lasting ≥ 6 months (including prodrome and residual symptoms). Associated with ↑ dopaminergic activity, ↓ dendritic branching.

Diagnosis requires ≥ 2 of the following symptoms for ≥ 1 month, and at least 1 of these should include #1–3 (first 4 are “positive symptoms”):

1. Delusions
2. Hallucinations—often auditory
3. Disorganized speech
4. Disorganized or catatonic behavior
5. Negative symptoms (affective flattening, avolition, anhedonia, asociality, alogia)

**Brief psychotic disorder**—≥ 1 positive symptom(s) lasting < 1 month, usually stress related.

**Schizophreniform disorder**—≥ 2 symptoms, lasting 1–6 months.

**Schizoaffective disorder**—Meets criteria for schizophrenia in addition to major mood disorder (major depressive or bipolar). To differentiate from a major mood disorder with psychotic features, patient must have > 2 weeks of psychotic symptoms without major mood episode.

**Delusional disorder**

Fixed, persistent, false belief system lasting > 1 month. Functioning otherwise not impaired (eg, a woman who genuinely believes she is married to a celebrity when, in fact, she is not). Can be shared by individuals in close relationships (folie à deux).

**Mood disorder**

Characterized by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive, bipolar, dysthymic, and cyclothymic disorders. Episodic superimposed psychotic features (delusions, hallucinations, disorganized speech/behavior) may be present.

**Manic episode**

Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently ↑ activity or energy lasting ≥ 1 week. Often disturbing to patient and causes marked functional impairment and oftentimes hospitalization.

Diagnosis requires hospitalization or at least 3 of the following (manics DIG FAST):

- **Distractibility**
- **Impulsivity/Indiscretion**—seeks pleasure without regard to consequences (hedonistic)
- **Grandiosity**—inflated self-esteem
- **Flight of ideas**—racing thoughts
- ↑ goal-directed Activity/psychomotor Agitation
- ↓ need for Sleep
- Talkativeness or pressured speech

Frequent cannabis use is associated with psychosis/schizophrenia in teens.

Lifetime prevalence—1.5% (males > females, African Americans = Caucasians). Presents earlier in men (late teens to early 20s vs late 20s to early 30s in women). Patients at ↑ risk for suicide.

Ventriculomegaly on brain imaging.

Treatment: atypical antipsychotics (eg, risperidone) are first line.

Negative symptoms often persist after treatment, despite resolution of positive symptoms.
Hypomanic episode

Similar to a manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. No psychotic features. Lasts ≥ 4 consecutive days.

Bipolar disorder (manic depression)

Bipolar I defined by presence of at least 1 manic episode +/- a hypomanic or depressive episode (may be separated by any length of time).

Bipolar II defined by presence of a hypomanic and a depressive episode (no history of manic episodes).

Patient’s mood and functioning usually normalize between episodes. Use of antidepressants can destabilize mood. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine, lamotrigine), atypical antipsychotics.

Cyclothymic disorder—milder form of bipolar disorder lasting ≥ 2 years, fluctuating between mild depressive and hypomanic symptoms.

Major depressive disorder

Episodes characterized by at least 5 of the 9 diagnostic symptoms lasting ≥ 2 weeks (symptoms must include patient-reported depressed mood or anhedonia). Screen for history of manic episodes to rule out bipolar disorder.

Treatment: CBT and SSRIs are first line. SNRIs, mirtazapine, bupropion can also be considered. Electroconvulsive therapy (ECT) in treatment-resistant patients.

Persistent depressive disorder (dysthymia)—often milder, ≥ 2 depressive symptoms lasting ≥ 2 years, with no more than 2 months without depressive symptoms.

MDD with seasonal pattern—formerly known as seasonal affective disorder. Lasting ≥ 2 years with ≥ 2 major depressive episodes associated with seasonal pattern (usually winter) and absence of nonseasonal depressive episodes. Atypical symptoms common (eg, hypersomnia, hyperphagia, leaden paralysis).

Depression with atypical features

Characterized by mood reactivity (able to experience improved mood in response to positive events, albeit briefly), “reversed” vegetative symptoms (hypersomnia, hyperphagia), leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors are effective but not first line because of their risk profile.

Diagnostic symptoms (SIG E CAPS):

- Depressed mood
- Sleep disturbance
- Loss of Interest (anhedonia)
- Guilt or feelings of worthlessness
- Energy loss and fatigue
- Concentration problems
- Appetite/weight changes
- Psychomotor retardation or agitation
- Suicidal ideations

Patients with depression typically have the following changes in their sleep stages:

- ↓ slow-wave sleep
- ↓ REM latency
- ↑ REM early in sleep cycle
- ↑ total REM sleep
- Repeated nighttime awakenings
- Early-morning awakening (terminal insomnia)
Postpartum mood disturbances

Onset during pregnancy or within 4 weeks of delivery.

Maternal (postpartum) blues

50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 10 days. Treatment: supportive. Follow up to assess for possible postpartum depression.

Postpartum depression

10–15% incidence rate. Characterized by depressed affect, anxiety, and poor concentration for ≥ 2 weeks. Treatment: CBT and SSRIs are first line.

Postpartum psychosis

0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include history of bipolar or psychotic disorder, first pregnancy, family history, recent discontinuation of psychotropic medication. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.

Grief

The five stages of grief per the Kübler-Ross model are denial, anger, bargaining, depression, and acceptance (may occur in any order). Other normal grief symptoms include shock, guilt, sadness, anxiety, yearning, and somatic symptoms that usually occur in waves. Simple hallucinations of the deceased person are common (eg, hearing the deceased speaking). Any thoughts of dying are limited to joining the deceased (vs pathological grief). Duration varies widely; usually within 6–12 months.

Pathologic grief is persistent and causes functional impairment. Can meet criteria for major depressive episode.

Electroconvulsive therapy

Rapid-acting method to treat resistant or refractory depression, depression with psychotic symptoms, and acute suicidality. Induces grand mal seizure while patient anesthetized. Adverse effects include disorientation, temporary headache, partial anterograde/retrograde amnesia usually resolving in 6 months. No absolute contraindications. Safe in pregnant and elderly individuals.

Risk factors for suicide completion

Sex (male)
Age (young adult or elderly)
Depression
Previous attempt (highest risk factor)
Ethanol or drug use
Rational thinking loss (psychosis)
Sickness (medical illness)
Organized plan
No spouse or other social support
Stated future intent

SAD PERSONS are more likely to complete suicide.

Most common method in US is firearms; access to guns ↑ risk of suicide completion.

Women try more often; men complete more often.

Family history of completed suicide is another well-known risk factor.

Anxiety disorder

Inappropriate experience of fear/worry and its physical manifestations (anxiety) incongruent with the magnitude of the perceived stressor. Symptoms interfere with daily functioning and are not attributable to another mental disorder, medical condition, or substance abuse. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism. Treatment: CBT, SSRIs, SNRIs.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Panic disorder</strong></td>
<td>Recurrent unexpected panic attacks not associated with a known trigger. Periods of intense fear and discomfort peak in 10 minutes with at least 4 of the following: Palpitations, Paresthesias, dePersonalization or derealization, Abdominal distress or Nausea, Intense fear of dying, Intense fear of losing control or “going crazy,” Lightheadedness, Chest pain, Chills, Choking, Sweating, Shaking, Shortness of breath. Strong genetic component. ↑ risk of suicide. Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.</td>
</tr>
<tr>
<td><strong>Specific phobia</strong></td>
<td>Severe, persistent (≥ 6 months) fear or anxiety due to presence or anticipation of a specific object or situation. Person often recognizes fear is excessive. Can be treated with systematic desensitization.</td>
</tr>
<tr>
<td><strong>Social anxiety disorder</strong></td>
<td>— exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For performance type (eg, anxiety restricted to public speaking), use β-blockers or benzodiazepines as needed.</td>
</tr>
<tr>
<td><strong>Agoraphobia</strong></td>
<td>— irrational fear/anxiety while facing or anticipating ≥ 2 specific situations (eg, open/closed spaces, lines, crowds, public transport). If severe, patients may refuse to leave their homes. Associated with panic disorder. Treatment: CBT, SSRIs.</td>
</tr>
<tr>
<td><strong>Generalized anxiety disorder</strong></td>
<td>Anxiety lasting &gt; 6 months unrelated to a specific person, situation, or event. Associated with restlessness, irritability, sleep disturbance, fatigue, muscle tension, difficulty concentrating. Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line.</td>
</tr>
<tr>
<td><strong>Adjustment disorder</strong></td>
<td>— emotional symptoms (anxiety, depression) that occur within 3 months of an identifiable psychosocial stressor (eg, divorce, illness) lasting &lt; 6 months once the stressor has ended. If symptoms persist &gt; 6 months after stressor ends, it is GAD. Symptoms do not meet criteria for MDD. Treatment: CBT, SSRIs.</td>
</tr>
<tr>
<td><strong>Obsessive-compulsive disorder</strong></td>
<td>Recurring intrusive thoughts, feelings, or sensations (obsessions) that cause severe distress; relieved in part by the performance of repetitive actions (compulsions). Ego-dystonic: behavior inconsistent with one’s own beliefs and attitudes (vs obsessive-compulsive personality disorder, ego-syntonic). Associated with Tourette syndrome. Treatment: CBT, SSRIs, venlafaxine, and clomipramine are first line.</td>
</tr>
<tr>
<td><strong>Body dysmorphic disorder</strong></td>
<td>— preoccupation with minor or imagined defect in appearance → significant emotional distress or impaired functioning; patients often repeatedly seek cosmetic treatment. Treatment: CBT.</td>
</tr>
</tbody>
</table>
**Post-traumatic stress disorder**  
Experiencing a potentially life-threatening situation (eg, serious injury, rape, witnessing death) → persistent Hyperarousal, Avoidance of associated stimuli, intrusive Re-experiencing of the event (nightmares, flashbacks), changes in cognition or mood (fear, horror, Distress) (having PTSD is HARD). Disturbance lasts > 1 month with significant distress or impaired social-occupational functioning. Treatment: CBT, SSRIs, and venlafaxine are first line. Prazosin can reduce nightmares.

**Acute stress disorder**—lasts between 3 days and 1 month. Treatment: CBT; pharmacotherapy is usually not indicated.

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**Diagnostic criteria by symptom duration**

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**Personality**

**Personality trait**
An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and oneself.

**Personality disorder**
Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem (ego-syntonic). Usually presents by early adulthood.  
Three clusters: A, B, C; remember as Weird, Wild, and Worried, respectively, based on symptoms.
<table>
<thead>
<tr>
<th><strong>Cluster A personality disorders</strong></th>
<th>Odd or eccentric; inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia.</th>
<th>“Weird.” Cluster A: Accusatory, Aloof, Awkward.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paranoid</strong></td>
<td>Pervasive distrust (Accusatory) and suspiciousness of others and a profoundly cynical view of the world.</td>
<td></td>
</tr>
<tr>
<td><strong>Schizoid</strong></td>
<td>Voluntary social withdrawal (Aloof), limited emotional expression, content with social isolation (vs avoidant).</td>
<td>Pronounce schiz-type-al: odd-type thoughts.</td>
</tr>
<tr>
<td><strong>Schizotypal</strong></td>
<td>Eccentric appearance, odd beliefs or magical thinking, interpersonal Awkwardness.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cluster B personality disorders</strong></th>
<th>Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse.</th>
<th>“Wild.” Cluster B: Bad, Borderline, flamBoyant, must be the Best</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antisocial</strong></td>
<td>Disregard for and violation of rights of others with lack of remorse, criminality, impulsivity; males &gt; females; must be ≥ 18 years old and have history of conduct disorder before age 15. Conduct disorder if &lt; 18 years old.</td>
<td>Antisocial = sociopath. Bad.</td>
</tr>
<tr>
<td><strong>Borderline</strong></td>
<td>Unstable mood and interpersonal relationships, impulsivity, self-mutilation, suicidality, sense of emptiness; females &gt; males; splitting is a major defense mechanism.</td>
<td>Treatment: dialectical behavior therapy. Borderline.</td>
</tr>
<tr>
<td><strong>Histrionic</strong></td>
<td>Excessive emotionality and excitability, attention seeking, sexually provocative, overly concerned with appearance.</td>
<td>FlamBoyant.</td>
</tr>
<tr>
<td><strong>Narcissistic</strong></td>
<td>Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the “best” and reacts to criticism with rage.</td>
<td>Must be the Best.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cluster C personality disorders</strong></th>
<th>Anxious or fearful; genetic association with anxiety disorders.</th>
<th>“Worried.” Cluster C: Cowardly, obsessive-Compulsive, Clingy.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avoidant</strong></td>
<td>Hypersensitive to rejection, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs schizoid).</td>
<td>Cowardly.</td>
</tr>
<tr>
<td><strong>Obsessive-Compulsive</strong></td>
<td>Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one’s own beliefs and attitudes (vs OCD).</td>
<td></td>
</tr>
<tr>
<td><strong>Dependent</strong></td>
<td>Excessive need for support, low self-confidence. Patients often get stuck in abusive relationships.</td>
<td>Submissive and Clingy.</td>
</tr>
</tbody>
</table>
Malingering

Symptoms are **intentional**, motivation is **intentional**. Patient consciously fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific 2° (external) gain (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder).

Factitious disorders

Symptoms are **intentional**, motivation is **unconscious**. Patient consciously creates physical and/or psychological symptoms in order to assume “sick role” and to get medical attention and sympathy (1° [internal] gain).

- **Factitious disorder imposed on self**
  Also known as Munchausen syndrome. **Chronic** factitious disorder with predominantly physical signs and symptoms. Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures. More common in women and healthcare workers.

- **Factitious disorder imposed on another**
  Also known as Munchausen syndrome by proxy. Illness in a child or elderly patient is caused or fabricated by the caregiver. Motivation is to assume a sick role by proxy. Form of child/elder abuse.

Somatic symptom and related disorders

Symptoms are **unconscious**, motivation is **unconscious**. Category of disorders characterized by physical symptoms causing significant distress and impairment. Symptoms not intentionally produced or feigned. More common in women.

- **Somatic symptom disorder**
  Variety of bodily complaints (eg, pain, fatigue) lasting for months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness. Treatment: regular office visits with the same physician in combination with psychotherapy.

- **Conversion disorder**
  Also known as functional neurologic symptom disorder. Loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient may be aware of but indifferent toward symptoms (“la belle indifférence”); more common in females, adolescents, and young adults.

- **Illness anxiety disorder**
  Also known as hypochondriasis. Excessive preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal somatic symptoms.

Eating disorders

Most common in young females.

- **Anorexia nervosa**
  Intense fear of weight gain and distortion or overvaluation of body image leading to restriction of caloric intake and severe weight loss (BMI < 18.5 kg/m²). Restricting and binge/purge subtypes. Associated with ↓ bone density (often irreversible), amenorrhea (due to loss of pulsatile GnRH secretion), lanugo, anemia, electrolyte disturbances. Commonly coexists with depression. Psychotherapy and nutritional rehabilitation are first line; pharmacotherapy includes SSRIs for comorbid anxiety and/or depression.
  **Refeeding syndrome** — ↑ insulin → hypophosphatemia, hypokalemia, hypomagnesemia → cardiac complications, rhabdomyolysis, seizures. Can occur in significantly malnourished patients.

- **Bulimia nervosa**
  Binge eating with recurrent inappropriate compensatory behaviors (eg, self-induced vomiting, using laxatives or diuretics, fasting, excessive exercise) occurring weekly for at least 3 months and overvaluation of body image. Body weight often maintained within normal range. Associated with parotitis, enamel erosion, electrolyte disturbances (eg, hypokalemia, hypochloremia), metabolic alkalosis, dorsal hand calluses from induced vomiting (Russell sign). Treatment: psychotherapy, nutritional rehabilitation, antidepressants (eg, SSRIs). Bupropion is contraindicated due to seizure risk.

- **Binge eating disorder**
  Regular episodes of excessive, uncontrollable eating without inappropriate compensatory behaviors. ↑ risk of diabetes. Treatment: psychotherapy such as CBT is first line; SSRIs, lisdexamfetamine.
### Gender dysphoria

Persistent cross-gender identification that leads to persistent distress with sex assigned at birth.

**Transsexualism**—desire to live as the opposite sex, often through surgery or hormone treatment.

**Transvestism**—paraphilia, not gender dysphoria. Wearing clothes (eg, *vest*) of the opposite sex (cross-dressing).

### Sexual dysfunction

Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (dyspareunia, vaginismus).

Differential diagnosis includes:
- Drug side effects (eg, antihypertensives, antipsychotics, SSRIs, ethanol)
- Medical disorders (eg, depression, diabetes, STIs)
- Psychological or performance anxiety (eg, nighttime erections [nocturnal tumescence])

### Sleep terror disorder

Inconsolable periods of terror with screaming in the middle of the night; occurs during slow-wave/sleep (stage N3) sleep. Most common in children. Occurs during non-REM sleep (no memory of the arousal episode) as opposed to nightmares that occur during REM sleep (remembering a scary dream). Cause unknown, but triggers include emotional stress, fever, or lack of sleep. Usually self limited.

### Enuresis

Urinary incontinence ≥ 2 times/week for ≥ 3 months in person > 5 years old. First-line treatment: behavioral modification (eg, scheduled voids) and positive reinforcement. For refractory cases: bedwetting alarm, oral desmopressin (ADH analog; preferred over imipramine due to more favorable side effect profile).

### Narcolepsy

Disordered regulation of sleep-wake cycles characterized by excessive daytime sleepiness (despite feeling rested upon waking) and “sleep attacks” (rapid-onset, overwhelming sleepiness). Caused by hypocretin (orexin) production in lateral hypothalamus. Strong genetic component.

Also associated with:
- Hypnagogic (just before going to sleep) or hypnopompic (just before awakening; “pompous upon awakening”) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep (sleep paralysis).
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter) in some patients.

Treatment: good sleep hygiene (scheduled naps, regular sleep schedule), daytime stimulants (eg, amphetamines, modafinil) and nighttime sodium oxybate (GHB).
### Substance use disorder

Maladaptive pattern of substance use defined as 2 or more of the following signs in 1 year related specifically to substance use:
- Tolerance—need more to achieve same effect
- Withdrawal—manifesting as characteristic signs and symptoms
- Substance taken in larger amounts, or over longer time, than desired
- Persistent desire or unsuccessful attempts to cut down
- Significant energy spent obtaining, using, or recovering from substance
- Important social, occupational, or recreational activities reduced
- Continued use despite knowing substance causes physical and/or psychological problems
- Craving
- Recurrent use in physically dangerous situations
- Failure to fulfill major obligations at work, school, or home
- Social or interpersonal conflicts

### Stages of change in overcoming substance addiction

1. **Precontemplation**—not yet acknowledging that there is a problem
2. **Contemplation**—acknowledging that there is a problem, but not yet ready or willing to make a change
3. **Preparation/determination**—getting ready to change behaviors
4. **Action/willpower**—changing behaviors
5. **Maintenance**—maintaining the behavioral changes
6. **Relapse**—returning to old behaviors and abandoning new changes. Does not always happen.

### Psychiatric emergencies

<table>
<thead>
<tr>
<th>Cause</th>
<th>Manifestation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotonin syndrome</strong></td>
<td>Any drug that ↑ 5-HT. Psychiatric drugs: MAO inhibitors, SSRIs, SNRIs, TCAs, vilazodone, vortioxetine Nonpsychiatric drugs: tramadol, ondansetron, triptans, linezolid, MDMA, dextromethorphan, meperidine, St. John’s wort</td>
<td>3 A’s: ↑ Activity (neuromuscular) Autonomic stimulation Agitation Symptoms of neuromuscular hyperactivity include clonus, hyperreflexia, hypertonia, tremor, seizure Symptoms of autonomic stimulation include hyperthermia, diaphoresis, diarrhea Cyproheptadine (5-HT₂ receptor antagonist)</td>
</tr>
<tr>
<td><strong>Carcinoid syndrome</strong></td>
<td>Carcinoid tumor of GI tract, lung</td>
<td>Diarrhea, flushing, wheezing, right heart disease (if tumor is in the gut) Octreotide</td>
</tr>
<tr>
<td>Cause</td>
<td>Manifestation</td>
<td>Treatment</td>
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<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
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<tr>
<td><strong>Hypertensive crisis</strong></td>
<td>Eating tyramine-rich foods (e.g., aged cheeses, cured meats, wine) while taking MAO inhibitor</td>
<td>Hypertensive crisis (tyramine displaces other neurotransmitters [e.g., NE] in the synaptic cleft) → ↑ sympathetic stimulation</td>
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<tr>
<td></td>
<td></td>
<td>Phentolamine</td>
</tr>
<tr>
<td><strong>Neuroleptic malignant syndrome</strong></td>
<td>Antipsychotics + genetic predisposition</td>
<td>Malignant FEVER:</td>
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<tr>
<td></td>
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<td>Myoglobinuria</td>
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<td>Fever</td>
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<td></td>
<td>Encephalopathy</td>
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<td>Vitals unstable</td>
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<td>↑ Enzymes (e.g., ↑ CK)</td>
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<td></td>
<td>Rigidity of muscles (&quot;lead pipe&quot;)</td>
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<td>Dantrolene, dopamine agonist (e.g., bromocriptine), discontinue causative agent</td>
</tr>
<tr>
<td><strong>Malignant hyperthermia</strong></td>
<td>Inhaled anesthetics, succinylcholine + genetic predisposition</td>
<td>Fever, severe muscle contractions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dantrolene</td>
</tr>
<tr>
<td><strong>Delirium tremens</strong></td>
<td>Alcohol withdrawal; occurs 2–4 days after last drink</td>
<td>Altered mental status (e.g., hallucinations), autonomic hyperactivity, anxiety, seizures, tremors, psychomotor agitation, insomnia, nausea</td>
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<tr>
<td></td>
<td>Classically seen in hospital setting when inpatient cannot drink</td>
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<tr>
<td></td>
<td></td>
<td>Benzodiazepines (e.g., chlordiazepoxide, lorazepam, diazepam)</td>
</tr>
<tr>
<td><strong>Acute dystonia</strong></td>
<td>Typical antipsychotics, anticonvulsants (e.g., carbamazepine), metoclopramide</td>
<td>Sudden onset of muscle spasm, stiffness, ocular crisis that occurs within hours to days after medication use; can lead to laryngospasm requiring intubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benztropine or diphenhydramine</td>
</tr>
<tr>
<td><strong>Lithium toxicity</strong></td>
<td>Change in lithium dosage or health status (narrow therapeutic window), concurrent use of thiazides, ACE inhibitors, NSAIDs, or other nephrotoxic agents</td>
<td>Nausea, vomiting, slurred speech, hyperreflexia, seizures, ataxia, nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue lithium, hydrate aggressively with isotonic sodium chloride, consider hemodialysis</td>
</tr>
<tr>
<td><strong>Tricyclic antidepressant toxicity</strong></td>
<td>TCA overdose</td>
<td>Respiratory depression, hyperpyrexia, prolonged QT interval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tri-C’s:</td>
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<tr>
<td></td>
<td></td>
<td>Convulsions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coma</td>
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<tr>
<td></td>
<td></td>
<td>Cardiotoxicity (arrhythmia due to Na⁺ channel inhibition)</td>
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<tr>
<td></td>
<td></td>
<td>Supportive treatment, monitor ECG, NaHCO₃ (prevents arrhythmia), activated charcoal</td>
</tr>
</tbody>
</table>

*Carcinoid syndrome and malignant hyperthermia are not psychiatric emergencies, but are included for comparison with serotonin syndrome and neuroleptic malignant syndrome, respectively.*
### Psychoactive drug intoxication and withdrawal

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTOXICATION</th>
<th>WITHDRAWAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (GGT)—sensitive indicator of alcohol use. <strong>AST</strong> value is $2 \times ALT$ value (“toAST 2 ALcohol”).</td>
<td>Time from last drink: 3–36 hr: tremors, insomnia, GI upset, diaphoresis, mild agitation 6–48 hr: withdrawal seizures 12–48 hr: alcoholic hallucinosis (usually visual) 48–96 hr: delirium tremens (DTs) Treatment: benzodiazepines.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Low safety margin, marked respiratory depression. Treatment: symptom management (eg, assist respiration, BP).</td>
<td>Delirium, life-threatening cardiovascular collapse.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Greater safety margin. Ataxia, minor respiratory depression. Treatment: flumazenil (benzodiazepine receptor antagonist, but rarely used as it can precipitate seizures).</td>
<td>Sleep disturbance, depression, rebound anxiety, seizure.</td>
</tr>
<tr>
<td><strong>Stimulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>Impaired judgment, pupillary dilation, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death. Chronic use may lead to perforated nasal septum due to vasoconstriction and resulting ischemic necrosis. Treatment: α-blockers, benzodiazepines. β-blockers not recommended.</td>
<td>Non-specific: post-use “crash,” including depression, lethargy, appetite, sleep disturbance, vivid nightmares.</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Restlessness, diuresis, muscle twitching.</td>
<td>Headache, difficulty concentrating, flu-like symptoms.</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Restlessness.</td>
<td>Irritability, anxiety, restlessness, difficulty concentrating. Treatment: nicotine patch, gum, or lozenges; bupropion/varenicline.</td>
</tr>
</tbody>
</table>
Psychoactive drug intoxication and withdrawal (continued)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTOXICATION</th>
<th>WITHDRAWAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>Violence, impulsivity, psychomotor agitation, nystagmus, tachycardia, hypertension, analgesia, psychosis, delirium, seizures. Trauma is most common complication.</td>
<td></td>
</tr>
<tr>
<td>Lysergic acid diethylamide</td>
<td>Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, possible flashbacks.</td>
<td></td>
</tr>
<tr>
<td>Marijuana (cannabinoid)</td>
<td>Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, hallucinations. Pharmaceutical form is dronabinol: used as antiemetic (chemotherapy) and appetite stimulant (in AIDS).</td>
<td>Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite.</td>
</tr>
<tr>
<td>MDMA (ecstasy)</td>
<td>Hallucinogenic stimulant: euphoria, disinhibition, hyperactivity, distorted sensory and time perception, teeth clenching. Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome.</td>
<td>Depression, fatigue, change in appetite, difficulty concentrating, anxiety.</td>
</tr>
</tbody>
</table>

Alcoholism

Physiologic tolerance and dependence on alcohol with symptoms of withdrawal when intake is interrupted.
Complications: alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy.
Treatment: disulfiram (to condition the patient to abstain from alcohol use), acamprosate, naltrexone (reduces cravings), supportive care. Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family.

Wernicke-Korsakoff syndrome

Caused by vitamin B₁ deficiency. Triad of confusion, opthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff syndrome). Symptoms may be precipitated by giving dextrose before administering vitamin B₁ to a patient with thiamine deficiency. Associated with periventricular hemorrhage/necrosis of mammillary bodies. Treatment: IV vitamin B₁.
**Preferred medications for selected psychiatric conditions**

<table>
<thead>
<tr>
<th>PSYCHIATRIC CONDITION</th>
<th>PREFERRED DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Stimulants (methylphenidate, amphetamines)</td>
</tr>
<tr>
<td>Alcohol withdrawal</td>
<td>Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Lithium, valproic acid, carbamazepine, lamotrigine, atypical antipsychotics</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>SSRIs, SNRIs</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>SSRIs, venlafaxine, clomipramine</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>SSRIs, venlafaxine, benzodiazepines</td>
</tr>
<tr>
<td>PTSD</td>
<td>SSRIs, venlafaxine</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Social anxiety disorder</td>
<td>SSRIs, venlafaxine</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>Antipsychotics (eg, fluphenazine, risperidone), tetrabenazine</td>
</tr>
</tbody>
</table>

**Central nervous system stimulants**

- **Mechanism**: Elevation of catecholamines in the synaptic cleft, especially norepinephrine and dopamine.
- **Clinical use**: ADHD, narcolepsy.
- **Adverse effects**: Nervousness, agitation, anxiety, insomnia, anorexia, tachycardia, hypertension, weight loss, tics.
**Typical antipsychotics**  
| MECHANISM | Block dopamine D₂ receptor (↑ cAMP). |
| CLINICAL USE | Schizophrenia (1° positive symptoms), psychosis, bipolar disorder, delirium, Tourette syndrome, Huntington disease, OCD. |
| POTENCY | **High** potency: Trifluoperazine, Fluphenazine, Haloperidol (Try to Fly High)—more neurologic side effects (eg, extrapyramidal symptoms [EPS]).  
**Low** potency: Chlorpromazine, Thioridazine (Cheating Thieves are low)—more anticholinergic, antihistamine, α₁-blockade effects. |
| ADVERSE EFFECTS | Lipid soluble → stored in body fat → slow to be removed from body.  
Endocrine: dopamine receptor antagonism → hyperprolactinemia → galactorrhea, oligomenorrhea, gynecomastia.  
Metabolic: dyslipidemia, weight gain, hyperglycemia.  
Antimuscarinic: dry mouth, constipation.  
Antihistamine: sedation.  
α₁-blockade: orthostatic hypotension.  
Cardiac: QT prolongation.  
Ophthalmologic: Chlorpromazine—Corneal deposits; Thioridazine—Retinal deposits.  
Neuroleptic malignant syndrome.  
**EPS—ADAPT:**  
- Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyric crisis). Treatment: benztropine, diphenhydramine.  
- Days to months:  
  - Parkinsonism (bradykinesia). Treatment: benztropine, amantadine.  
- Months to years: Tardive dyskinesia (orofacial chorea). Treatment: switch to atypical antipsychotic (eg, clozapine), tetrabenazine, reserpine. |

**Atypical antipsychotics**  
| MECHANISM | Not completely understood. Most are D₂ antagonists; aripiprazole is D₂ partial agonist. Varied effects on 5-HT₂, dopamine, and α₁- and H₁-receptors. |
| CLINICAL USE | Schizophrenia—both positive and negative symptoms. Also used for bipolar disorder, OCD, anxiety disorder, depression, mania, Tourette syndrome. Use clozapine for treatment-resistant schizophrenia or schizoaffective disorder and for suicidality in schizophrenia. |
| ADVERSE EFFECTS | All—prolonged QT interval, fewer EPS and anticholinergic side effects than typical antipsychotics.  
“-pines”—metabolic syndrome (weight gain, diabetes, hyperlipidemia).  
Clozapine—agranulocytosis (monitor WBCs frequently) and seizures (dose related).  
Risperidone—hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia).  
Olanzapine, clozapine → Obesity  
Must watch bone marrow closely with clozapine. |
**Lithium**

**MECHANISM**
Not established; possibly related to inhibition of phosphoinositol cascade.

**CLINICAL USE**
Mood stabilizer for bipolar disorder; treats acute manic episodes and prevents relapse.

**ADVERSE EFFECTS**
Tremor, hypothyroidism, polyuria (causes nephrogenic diabetes insipidus), teratogenesis. Causes Ebstein anomaly in newborn if taken by pregnant mother. Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT with Na+. Thiazides (and other nephrotoxic agents) are implicated in lithium toxicity.

**LiTHIUM:**
- Low Thyroid (hypothyroidism)
- Heart (Ebstein anomaly)
- Insipidus (nephrogenic diabetes insipidus)
- Unwanted Movements (tremor)

**Buspirone**

**MECHANISM**
Stimulates 5-HT\textsubscript{1A} receptors.

**CLINICAL USE**
Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Takes 1–2 weeks to take effect. Does not interact with alcohol (vs barbiturates, benzodiazepines).

**I'm always anxious if the bus will be on time, so I take buspirone.**

**Antidepressants**
### Selective serotonin reuptake inhibitors

- **Mechanism:** SSRIs inhibit 5-HT reuptake.
- **Clinical Use:** Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.
- **Adverse Effects:** Fewer than TCAs. GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido).

### Serotonin-norepinephrine reuptake inhibitors

- **Mechanism:** SNRIs inhibit 5-HT and NE reuptake.
- **Clinical Use:** Depression, general anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD. Duloxetine is also indicated for fibromyalgia.
- **Adverse Effects:** ↑ BP, stimulant effects, sedation, nausea.

### Tricyclic antidepressants

- **Mechanism:** TCAs inhibit 5-HT and NE reuptake.
- **Clinical Use:** Major depression, OCD (clomipramine), peripheral neuropathy, chronic pain, migraine prophylaxis. Nocturnal enuresis (imipramine, although adverse effects may limit use).
- **Adverse Effects:** Sedation, α₁-blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth). 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval. Tri-C’s: Convulsions, Coma, Cardiotoxicity (arrhythmia due to Na⁺ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations in the elderly due to anticholinergic side effects (nortriptyline better tolerated in the elderly). Treatment: NaHCO₃ to prevent arrhythmia.

### Monoamine oxidase inhibitors

- **Mechanism:** Tranylcypromine, Phenelzine, Isoxcarboxazid, Selegiline (selective MAO-B inhibitor). (MAO Takes Pride In Shanghai).
- **Clinical Use:** Nonselective MAO inhibition ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).
- **Adverse Effects:** Atypical depression, anxiety. Parkinson disease (selegiline). CNS stimulation; hypertensive crisis, most notably with ingestion of tyramine. Contraindicated with SSRIs, TCAs, St. John’s wort, meperidine, dextromethorphan (to prevent serotonin syndrome). Wait 2 weeks after stopping MAO inhibitors before starting serotonergic drugs or stopping dietary restrictions.
### Atypical antidepressants

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Mechanism of Action</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion</strong></td>
<td>Inhibits NE and dopamine reuptake. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in anorexic/bulimic patients. Favorable sexual side effect profile.</td>
<td></td>
</tr>
<tr>
<td><strong>Mirtazapine</strong></td>
<td>α₂-antagonist (↑ release of NE and 5-HT), potent 5-HT₂ and 5-HT₃ receptor antagonist and H₁ antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in elderly or anorexic patients), dry mouth.</td>
<td></td>
</tr>
<tr>
<td><strong>Trazodone</strong></td>
<td>Primarily blocks 5-HT₂, α₁-adrenergic, and H₁ receptors; also weakly inhibits 5-HT reuptake. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Called traiZZZtobone due to sedative and male-specific side effects.</td>
<td></td>
</tr>
<tr>
<td><strong>Varenicline</strong></td>
<td>Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance, may depress mood. Varenicline helps nicotine cravings decline.</td>
<td></td>
</tr>
<tr>
<td><strong>Vilazodone</strong></td>
<td>Inhibits 5-HT reuptake; 5-HT₁A receptor partial agonist. Used for major depressive disorder. Toxicity: headache, diarrhea, nausea, ↑ weight, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.</td>
<td></td>
</tr>
<tr>
<td><strong>Vortioxetine</strong></td>
<td>Inhibits 5-HT reuptake; 5-HT₁A receptor agonist and 5-HT₃ receptor antagonist. Used for major depressive disorder. Toxicity: nausea, sexual dysfunction, sleep disturbances (abnormal dreams), anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.</td>
<td></td>
</tr>
</tbody>
</table>

### Opioid withdrawal and detoxification

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methadone</strong></td>
<td>Long-acting oral opiate used for heroin detoxification or long-term maintenance therapy.</td>
</tr>
<tr>
<td><strong>Buprenorphine + Naloxone</strong></td>
<td>Sublingual buprenorphine (partial agonist) is absorbed and used for maintenance therapy. Naloxone (antagonist, not orally bioavailable) is added to lower IV abuse potential.</td>
</tr>
<tr>
<td><strong>Naltrexone</strong></td>
<td>Long-acting opioid given IM or as nasal spray to treat acute overdose in unconscious individual. Also used for relapse prevention once detoxified. Use naltrexone for the long trex back to sobriety.</td>
</tr>
</tbody>
</table>
“But I know all about love already. I know precious little still about kidneys.”
—Aldous Huxley, Antic Hay

“This too shall pass. Just like a kidney stone.”
—Hunter Madsen

“I drink too much. The last time I gave a urine sample it had an olive in it.”
—Rodney Dangerfield

Being able to understand and apply renal physiology will be critical for the exam. Important topics include electrolyte disorders, acid-base derangements, glomerular disorders (including histopathology), kidney failure, urine casts, diuretics, ACE inhibitors, and AT-II receptor blockers. Renal anomalies linked to various congenital defects is also a high-yield association to think about when you encounter pediatric vignettes.
Kidney embryology

Pronephros—week 4; then degenerates.
Mesonephros—functions as interim kidney for 1st trimester; later contributes to male genital system.
Metanephros—permanent; first appears in 5th week of gestation; nephrogenesis continues through weeks 32–36 of gestation.
- Ureteric bud—derived from caudal end of mesonephric duct; gives rise to ureter, pelvices, calyces, collecting ducts; fully canalized by 10th week
- Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)
- Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney (eg, renal agenesis, multicystic dysplastic kidney)
Ureteropelvic junction—last to canalize → most common site of obstruction (can be detected on prenatal ultrasound as hydronephrosis).

Potter sequence (syndrome)

Oligohydramnios → compression of developing fetus → limb deformities, facial anomalies (eg, low-set ears and retrognathia, flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).
Causes include ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis, chronic placental insufficiency.

Babies who can’t “Pee” in utero develop Potter sequence.

POTTER sequence associated with:
Pulmonary hypoplasia
Oligohydramnios (trigger)
Twisted face
Twisted skin
Extremity defects
Renal failure (in utero)
Horseshoe kidney

Inferior poles of both kidneys fuse abnormally. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys function normally. Associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, chromosomal aneuploidy syndromes (eg, Turner syndrome; trisomies 13, 18, 21), and rarely renal cancer.

Congenital solitary functioning kidney

Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common. Often diagnosed prenatally via ultrasound.

Unilateral renal agenesis

Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter.

Multicystic dysplastic kidney

Ureteric bud fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Predominantly nonhereditary and usually unilateral; bilateral leads to Potter sequence.

Duplex collecting system

Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs.

Posterior urethral valves

Membrane remnant in the posterior urethra in males; its persistence can lead to urethral obstruction. Can be diagnosed prenatally by hydronephrosis and dilated or thick-walled bladder on ultrasound. Most common cause of bladder outlet obstruction in male infants.
Kidney anatomy and glomerular structure

Left kidney is taken during donor transplantation because it has a longer renal vein.

Afferent = Arriving,
Efferent = Exiting.

Renal blood flow: renal artery → segmental artery → interlobar artery → arcuate artery → interlobular artery → afferent arteriole → glomerulus → efferent arteriole → vasa recta/peritubular capillaries → venous outflow.

Course of ureters

Course of ureter
- arises from renal pelvis, travels under gonadal arteries → over common iliac artery → under uterine artery/vas deferens (retroperitoneal).
- Gynecologic procedures (e.g., ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.
- Muscle fibers within the intramural part of the ureter prevent urine reflux.
- 3 constrictions of ureter:
  - Ureteropelvic junction
  - Pelvic inlet
  - Ureterovesical junction

Water (ureters) flows over the iliacs and under the bridge (uterine artery or vas deferens).
Fluid compartments

Body mass: 70 kg

- Total body water (TBW) 60% of body mass = 42 kg = 42 L
- Non water mass (NWM) 40% of body mass = 28 kg

Extracellular fluid (ECF)

- Interstitial fluid = 75% ECF = 10.5 L = 10.5 kg
- Plasma = 20% ECF ≈ 3.5 L ≈ 3.5 kg

Intracellular fluid (ICF)

- RBC volume = ~2.8 L
- NWM = 40% ICF, mainly composed of K+, Mg2+, organic phosphates (eg, ATP)
- ECF = 20% ICF, mainly composed of Na+, Cl–, HCO3–, albumin

Normal HCT = 45%

Plasma volume can be measured by radiolabeling albumin.

Extracellular volume can be measured by inulin or mannitol.

Osmolality = 285–295 mOsm/kg H2O.

Glomerular filtration barrier

Responsible for filtration of plasma according to size and charge selectivity.

Composed of:
- Fenestrated capillary endothelium
- Basement membrane with type IV collagen chains and heparan sulfate
- Epithelial layer consisting of podocyte foot processes

Charge barrier—all 3 layers contain charged glycoproteins that prevent entry of charged molecules (eg, albumin).

Size barrier—fenestrated capillary endothelium (prevent entry of > 100 nm molecules/blood cells); podocyte foot processes interpose with basement membrane; slit diaphragm (prevent entry of molecules > 50–60 nm).
Renal clearance

\[ C_x = \frac{(U_xV)}{P_x} \]  
(volume of plasma from which the substance is completely cleared per unit time. 
If \( C_x < \text{GFR} \): net tubular reabsorption of X.  
If \( C_x > \text{GFR} \): net tubular secretion of X.  
If \( C_x = \text{GFR} \): no net secretion or reabsorption.

\[ C_x = \text{clearance of X (mL/min)}. \]
\[ U_x = \text{urine concentration of X (eg, mg/mL)}. \]
\[ P_x = \text{plasma concentration of X (eg, mg/mL)}. \]
\[ V = \text{urine flow rate (mL/min)}. \]

Glomerular filtration rate

Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

\[ \text{GFR} = \frac{U_{\text{inulin}} \times V}{P_{\text{inulin}}} = C_{\text{inulin}} \]
\[ = K_f \left( \left( P_{\text{GC}} - P_{\text{BS}} \right) - \left( \pi_{\text{GC}} - \pi_{\text{BS}} \right) \right) \]

(GC = glomerular capillary; BS = Bowman space; \( \pi_{\text{BS}} \) normally equals zero; \( K_f \) = filtration coefficient).

Normal GFR \( \approx 100 \text{ mL/min}. \)
Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by renal tubules.
Incremental reductions in GFR define the stages of chronic kidney disease.

Effective renal plasma flow

Effective renal plasma flow (eRPF) can be estimated using \( \text{para} \)-aminohippuric acid (PAH) clearance. Between filtration and secretion, there is nearly 100% excretion of all PAH that enters the kidney.

\[ \text{eRPF} = \frac{U_{\text{PAH}} \times V}{P_{\text{PAH}}} = C_{\text{PAH}}. \]

Renal blood flow (RBF) = RPF/(1 - Hct). Usually 20–25% of cardiac output.
Plasma volume = TBV \( \times (1 - \text{Hct}) \).
\( \text{eRPF} \) underestimates true renal plasma flow (RPF) slightly.
**Filtration**

Filtration fraction (FF) = GFR/RPF.
- Normal FF = 20%.
- Filtered load (mg/min) = GFR (mL/min) × plasma concentration (mg/mL).

GFR can be estimated with creatinine clearance.
RPF is best estimated with PAH clearance.
Prostaglandins Dilate Afferent arteriole (PDA)
Angiotensin II Constricts Efferent arteriole (ACE)

\[
\text{Net filtration pressure} = (P_{\text{GC}} + \pi_{\text{BS}}) - (P_{\text{BS}} + \pi_{\text{GC}})
\]

### Changes in glomerular dynamics

<table>
<thead>
<tr>
<th>Effect</th>
<th>GFR</th>
<th>RPF</th>
<th>FF (GFR/RPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afferent arteriole constriction</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Efferent arteriole constriction</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>↑ plasma protein concentration</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>↓ plasma protein concentration</td>
<td>↓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Constriction of ureter</td>
<td>↓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dehydration</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

Prostaglandins dilate afferent arteriole (↑RPF, ↑GFR, so no ΔFF)
Angiotensin II constricts efferent arteriole (↓RPF, ↓GFR, so ↑FF)
Calculation of reabsorption and secretion rate

Filtered load = \( \text{GFR} \times P_x \).
Excretion rate = \( V \times U_x \).
Reabsorption rate = filtered – excreted.
Secretion rate = excreted – filtered.
\( Fe_{Na} \) = fractional excretion of sodium.

\[
Fe_{Na} = \frac{\text{Na}^+ \text{excreted}}{\text{Na}^+ \text{filtered}} = \frac{V \times U_{Na}}{\text{GFR} \times P_{Na}} \text{ where } \text{GFR} = \frac{U_{Cr} \times V}{P_{Cr}} = \frac{P_{Cr} \times U_{Na}}{U_{Cr} \times P_{Na}}
\]

Glucose clearance

Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by \( \text{Na}^+ \)/glucose cotransport.
In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated (\( T_m \)).
Normal pregnancy is associated with \( \downarrow \text{GFR} \).
With \( \uparrow \) filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations → glucosuria at normal plasma glucose levels.
Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -flozin drugs) result in glucosuria at plasma concentrations < 200 mg/dL.

Glucosuria is an important clinical clue to diabetes mellitus.
Splay phenomenon—\( T_m \) for glucose is reached gradually rather than sharply due to the heterogeneity of nephrons (ie, different \( T_m \) points); represented by the portion of the titration curve between threshold and \( T_m \).

Glucose transport (mg/min)

Plasma glucose (mg/dl)
Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most HCO₃⁻, Na⁺, Cl⁻, PO₄³⁻, K⁺, H₂O, and uric acid. Isotonic absorption. Generates and secretes NH₃, which enables the kidney to secrete more H⁺.

PTH—inhibits Na⁺/PO₄³⁻ cotransport → PO₄³⁻ excretion. AT II—stimulates Na⁺/H⁺ exchange → Na⁺, H₂O, and HCO₃⁻ reabsorption (permitting contraction alkalosis). 65–80% Na⁺ reabsorbed.

Early DCT—reabsorbs Na⁺, Cl⁻. Impermeable to H₂O. Makes urine fully dilute (hypotonic).

Thin descending loop of Henle—passively reabsorbs H₂O via medullary hypertonicity (impermeable to Na⁺).

Concentrating segment. Makes urine hypertonic.


ADH—acts at V₂ receptor → insertion of aquaporin H₂O channels on apical side. 3–5% Na⁺ reabsorbed.
Renal tubular defects

The kidneys put out Fabulous Glittering LiquidS (from front to end of tube)

<table>
<thead>
<tr>
<th>Defects</th>
<th>Effects</th>
<th>Causes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi syndrome</td>
<td>Generalized reabsorption defect in PCT</td>
<td>May lead to metabolic acidosis (proximal RTA), hypophosphatemia, osteopenia</td>
<td>Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drugs (eg, ifosfamide, cisplatin, expired tetracyclines), lead poisoning</td>
</tr>
<tr>
<td>Bartter syndrome</td>
<td>Resorptive defect in thick ascending loop of Henle (affects Na+/K+/2Cl– cotransporter)</td>
<td>Metabolic alkalosis, hypokalemia, hypercalciumia</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Gitelman syndrome</td>
<td>Reabsorption defect of NaCl in DCT</td>
<td>Metabolic alkalosis, hypomagnesemia, hypokalemia, hypocalciuria</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Liddle syndrome</td>
<td>Gain of function mutation → ↑ activity of Na+ channel → ↑ Na+ reabsorption in collecting tubules</td>
<td>Metabolic alkalosis, hypokalemia, hypertension, ↓ aldosterone</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Syndrome of Apparent Mineralocorticoid Excess</td>
<td>In cells containing mineralocorticoid receptors, 11β-hydroxysteroid dehydrogenase converts cortisol (can activate these receptors) to cortisone (inactive on these receptors) Hereditary deficiency of 11β-hydroxysteroid dehydrogenase → excess cortisol → ↑ mineralocorticoid receptor activity</td>
<td>Metabolic alkalosis, hypokalemia, hypertension ↓ serum aldosterone level; cortisol tries to be the SAME as aldosterone</td>
<td>Autosomal recessive Can acquire disorder from glycyrhrhetic acid (present in licorice), which blocks activity of 11β-hydroxysteroid dehydrogenase</td>
</tr>
</tbody>
</table>
Relative concentrations along proximal convoluted tubules

\[ \frac{[\text{Tubular fluid}]}{[\text{Plasma}]} > 1 \]
when solute is reabsorbed less quickly than water or when solute is secreted

\[ \frac{[\text{Tubular fluid}]}{[\text{Plasma}]} = 1 \]
when solute and water are reabsorbed at the same rate

\[ \frac{[\text{Tubular fluid}]}{[\text{Plasma}]} < 1 \]
when solute is reabsorbed more quickly than water

Tubular inulin ↑ in concentration (but not amount) along the PCT as a result of water reabsorption. \( \text{Cl}^- \) reabsorption occurs at a slower rate than \( \text{Na}^+ \) in early PCT and then matches the rate of \( \text{Na}^+ \) reabsorption more distally. Thus, its relative concentration ↑ before it plateaus.
Renin

Secreted by JG cells in response to ↓ renal perfusion pressure (detected by renal baroreceptors in afferent arteriole), ↑ renal sympathetic discharge (β₁ effect), and ↑ NaCl delivery to macula densa cells.

ATII

Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects.

ANP, BNP

Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; may act as a “check” on renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP → ↑ GFR, ↓ renin. Dilates afferent arteriole, constricts efferent arteriole, promotes natriuresis.

ADH

Primarily regulates serum osmolality; also responds to low blood volume states. Stimulates reabsorption of water in collecting ducts. Also stimulates reabsorption of urea in collecting ducts to maintain corticopapillary osmotic gradient.

Aldosterone

Primarily regulates ECF volume and Na⁺ content; responds to low blood volume states. Responds to hyperkalemia by ↑ K⁺ excretion.
**Juxtaglomerular apparatus**

Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole) and the macula densa (NaCl sensor, located at distal end of loop of Henle). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone (β1). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → ↑ GFR.

JGA maintains GFR via renin-angiotensin-aldosterone system.

In addition to vasodilatory properties, β-blockers can decrease BP by inhibiting β1-receptors of the JGA → ↓ renin release.

---

**Kidney endocrine functions**

**Erythropoietin**

Released by interstitial cells in peritubular capillary bed in response to hypoxia.

Stimulates RBC proliferation in bone marrow. Erythropoietin often supplemented in chronic kidney disease.

**Calciferol (vitamin D)**

PCT cells convert 25-OH vitamin D3 to 1,25-(OH)2 vitamin D3 (calcitriol, active form).

25-OH D3 → 1α-hydroxylase → 1,25-(OH)2 D3

**Prostaglandins**

Paracrine secretion vasodilates the afferent arterioles to ↑ RBF.

NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute renal failure in low renal blood flow states.

**Dopamine**

Secreted by PCT cells, promotes natriuresis. At low doses, dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR. At higher doses, acts as vasoconstrictor.
Hormones acting on kidney

**Angiotensin II**
Synthesized in response to ↓ BP. Causes efferent arteriole constriction and ↑ GFR and ↑ FF but with compensatory Na+ reabsorption in proximal and distal nephron. Net effect: Na+ loss and volume loss.

**Parathyroid hormone**
Secreted in response to ↓ plasma Ca2+, ↑ plasma PO43–, or ↓ plasma 1,25-(OH)2D3. Causes ↑ Ca2+ reabsorption (DCT), ↓ PO43– reabsorption (PCT), and ↑ 1,25-(OH)2D3 production (↑ Ca2+ and PO43– absorption from gut via vitamin D).

**Atrial natriuretic peptide**
Secreted in response to ↑ atrial pressure. Causes ↑ GFR and ↑ Na+ filtration with no compensatory Na+ reabsorption and loss and volume loss.

**Aldosterone**
Secreted in response to ↓ blood volume (via ATII) and ↑ plasma [K+], causes ↑ Na+ reabsorption, ↑ K+ secretion, and ↑ H+ secretion.

**ADH (vasopressin)**
Secreted in response to ↑ plasma osmolality and ↓ blood volume. Binds to receptors on principal cells, causing number of aquaporins and ↑ H2O reabsorption.

**Potassium shifts**

<table>
<thead>
<tr>
<th>SHIFTS K+ INTO CELL (CAUSING HYPOKALEMIA)</th>
<th>SHIFTS K+ OUT OF CELL (CAUSING HYPERKALEMIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis (blocks Na+/K+ ATPase)</td>
<td>Hyperosmolarity</td>
</tr>
<tr>
<td>Hypo-osmolarity</td>
<td>Lysis of cells (eg, crush injury, rhabdomyolysis, tumor lysis syndrome)</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>Acidosis</td>
</tr>
<tr>
<td>β-adrenergic agonist (↑ Na+/K+ ATPase)</td>
<td>β-blocker</td>
</tr>
<tr>
<td>Insulin (↑ Na+/K+ ATPase)</td>
<td>High blood Sugar (insulin deficiency)</td>
</tr>
<tr>
<td>Insulin shifts K+ into cells</td>
<td>Succinylcholine (↑ risk in burns/muscle trauma)</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia? DO LAJSS</td>
</tr>
</tbody>
</table>
Electrolyte disturbances

<table>
<thead>
<tr>
<th>ELECTROLYTE</th>
<th>LOW SERUM CONCENTRATION</th>
<th>HIGH SERUM CONCENTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>Nausea and malaise, stupor, coma, seizures</td>
<td>Irritability, stupor, coma</td>
</tr>
<tr>
<td>K⁺</td>
<td>U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness</td>
<td>Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>Tetany, seizures, QT prolongation, twitching (Chvostek sign), spasm (Trousseau sign)</td>
<td>Stones (renal), bones (pain), groans (abdominal pain), thrones († urinary frequency), psychiatric overtones (anxiety, altered mental status)</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>Tetany, torsades de pointes, hypokalemia, hypocalcemia (when [Mg²⁺] &lt; 1.2 mg/dL)</td>
<td>↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia</td>
</tr>
<tr>
<td>PO₄³⁻</td>
<td>Bone loss, osteomalacia (adults), rickets (children)</td>
<td>Renal stones, metastatic calcifications, hypocalcemia</td>
</tr>
</tbody>
</table>

Features of renal disorders

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>BLOOD PRESSURE</th>
<th>PLASMA RENIN</th>
<th>ALDOSTERONE</th>
<th>SERUM Mg²⁺</th>
<th>URINE Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartter syndrome</td>
<td>—</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Gitelman syndrome</td>
<td>—</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Liddle syndrome, syndrome of apparent mineralocorticoid excess</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIADH</td>
<td>—/↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hyperaldosteronism (Conn syndrome)</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renin-secreting tumor</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑ ↓ = important differentiating feature.
### Acid-base physiology

<table>
<thead>
<tr>
<th>Condition</th>
<th>pH</th>
<th>Pco2</th>
<th>[HCO3⁻]</th>
<th>Compensatory Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Hyperventilation (immediate)</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Hypoventilation (immediate)</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑ renal [HCO3⁻] reabsorption (delayed)</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓ renal [HCO3⁻] reabsorption (delayed)</td>
</tr>
</tbody>
</table>

Key: ↓ = 1st disturbance; ↑ = compensatory response.

Henderson-Hasselbalch equation: \( \text{pH} = 6.1 + \log \left( \frac{\text{[HCO}_3^-]}{0.05 \text{Pco}_2} \right) \)

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured \( \text{Pco}_2 > \) predicted \( \text{Pco}_2 \) → concomitant respiratory acidosis; if measured \( \text{Pco}_2 < \) predicted \( \text{Pco}_2 \) → concomitant respiratory alkalosis:

\[ \text{Pco}_2 = 1.5 \text{[HCO}_3^-] + 8 \pm 2 \]

### Acidosis and Alkalosis

**Check arterial pH**

- **Acidemia** (pH < 7.35)
  - Pco₂ > 44 mm Hg
  - HCO₃⁻ < 20 mEq/L
  - Respiratory acidosis
  - Hypoventilation
    - Airway obstruction
    - Acute lung disease
    - Chronic lung disease
    - Opioids, sedatives
    - Weakening of respiratory muscles

- **Metabolic acidosis**
  - Check anion gap
    - \( \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) \)

- **Alkalemia** (pH > 7.45)
  - Pco₂ < 36 mm Hg
  - HCO₃⁻ > 28 mEq/L
  - Respiratory alkalosis
  - Hyperventilation
    - Anxiety/panic attack
    - Hypoxemia (e.g., high altitude)
    - Salicylates (early)
    - Tumor
    - Pulmonary embolism

- **Metabolic alkalosis**
  - H⁺ loss/HCO₃⁻ excess
    - Loop diuretics
    - Vomiting
    - Antacid use
    - Hyperaldosteronism

**↑ Anion gap**

- **Normal anion gap**
  - **MUDPILES:**
    - Methanol (formic acid)
    - Uremia
    - Diabetic ketoacidosis
    - Propylene glycol
    - Iron tablets or INH
    - Lactic acidosis
    - Ethylene glycol (oxalic acid)
    - Salicylates (late)

- **HARDASS:**
  - Hyperalimentation
  - Addison disease
  - Renal tubular acidosis
  - Diarrhea
  - Acetazolamide
  - Spironolactone
  - Saline infusion

**Check anion gap**

\[ \text{Anion gap} = \text{Na}^+ - (\text{CI}^- + \text{HCO}_3^-) \]

**Buffer line**

- **Respiratory acidosis**
  - Pco₂ = 40 mm Hg

- **Metabolic acidosis**
  - Pco₂ < 36 mm Hg

- **Mixed acidosis**
  - Pco₂ > 36 mm Hg

- **Metabolic alkalosis**
  - Pco₂ > 36 mm Hg

Plasma [HCO₃⁻] (meq/L)

- 5 to 22 meq/L

**pH**

- 6.9 to 7.9

**Plasma [HCO₃⁻] vs pH**

- 6.9 to 7.9
### Renal tubular acidosis

Disorder of the renal tubules that causes normal anion gap (hyperchloremic) metabolic acidosis.

<table>
<thead>
<tr>
<th>RTA Type</th>
<th>Defect</th>
<th>Urine PH</th>
<th>Serum K⁺</th>
<th>Causes</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distal renal tubular acidosis</strong>&lt;br&gt;(type 1)</td>
<td>Inability of α-intercalated cells to secrete H⁺ → no new HCO₃⁻ is generated → metabolic acidosis</td>
<td>&gt; 5.5</td>
<td>↓</td>
<td>Amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract, autoimmune diseases (eg, SLE)</td>
<td>↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover)</td>
</tr>
<tr>
<td><strong>Proximal renal tubular acidosis</strong>&lt;br&gt;(type 2)</td>
<td>Defect in PCT HCO₃⁻ reabsorption → ↑ excretion of HCO₃⁻ in urine → metabolic acidosis&lt;br&gt;Urine can be acidified by α-intercalated cells in collecting duct, but not enough to overcome the increased excretion of HCO₃⁻ → metabolic acidosis</td>
<td>&lt; 5.5</td>
<td>↓</td>
<td>Fanconi syndrome, multiple myeloma, carbonic anhydrase inhibitors</td>
<td>↑ risk for hypophosphatemic rickets (in Fanconi syndrome)</td>
</tr>
<tr>
<td><strong>Hyperkalemic tubular acidosis</strong>&lt;br&gt;(type 4)</td>
<td>Hypoaldosteronism or aldosterone resistance; hyperkalemia → ↑ NH₃ synthesis in PCT → ↓ NH₄⁺ excretion</td>
<td>&lt; 5.5 (or variable)</td>
<td>↑</td>
<td>↑ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARBs, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, K⁺-sparing diuretics, nephropathy due to obstruction, TMP-SMX)</td>
<td></td>
</tr>
</tbody>
</table>
# Casts in urine

Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin. Bladder cancer, kidney stones → hematuria, no casts.

<table>
<thead>
<tr>
<th>Cast Type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC casts</td>
<td>Glomerulonephritis, hypertensive emergency.</td>
</tr>
<tr>
<td>WBC casts</td>
<td>Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.</td>
</tr>
<tr>
<td>Fatty casts</td>
<td>Nephrotic syndrome. Associated with “Maltese cross” sign.</td>
</tr>
<tr>
<td>Granular casts</td>
<td>Acute tubular necrosis (ATN).</td>
</tr>
<tr>
<td>Waxy casts</td>
<td>End-stage renal disease/chronic renal failure.</td>
</tr>
<tr>
<td>Hyaline casts</td>
<td>Nonspecific, can be a normal finding, often seen in concentrated urine samples.</td>
</tr>
</tbody>
</table>

## Nomenclature of glomerular disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>&lt; 50% of glomeruli are involved</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>Diffuse</td>
<td>&gt; 50% of glomeruli are involved</td>
<td>Diffuse proliferative glomerulonephritis</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Hypercellular glomeruli</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Membranous</td>
<td>Thickening of glomerular basement membrane (GBM)</td>
<td>Membranous nephropathy</td>
</tr>
<tr>
<td>Primary glomerular disease</td>
<td>1° disease of the kidney specifically impacting the glomeruli</td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>Secondary glomerular disease</td>
<td>Systemic disease or disease of another organ system that also impacts the glomeruli</td>
<td>SLE, diabetic nephropathy</td>
</tr>
</tbody>
</table>
Glomerular diseases

Nephritic syndrome—due to GBM disruption. Hypertension, ↑ BUN and creatinine, oliguria, hematuria, RBC casts in urine. Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range.
- Acute poststreptococcal glomerulonephritis
- Rapidly progressive glomerulonephritis
- IgA nephropathy (Berger disease)
- Alport syndrome
- Membranoproliferative glomerulonephritis

Nephrotic syndrome—podocyte disruption → charge barrier impaired. Massive proteinuria (> 3.5 g/day) with hypoalbuminemia, hyperlipidemia, edema. May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process [eg, diabetes]).
- Focal segmental glomerulosclerosis (1° or 2°)
- Minimal change disease (1° or 2°)
- Membranous nephropathy (1° or 2°)
- Amyloidosis (2°)
- Diabetic glomerulonephropathy (2°)

Nephritic-nephrotic syndrome—severe nephritic syndrome with profound GBM damage that damages the glomerular filtration charge barrier → nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephrotic syndrome. Can occur with any form of nephritic syndrome, but is most commonly seen with:
- Diffuse proliferative glomerulonephritis
- Membranoproliferative glomerulonephritis

GRAMS OF PROTEIN EXCRETED PER DAY (g/day)

| 0.25 | 3.5 | > 3.5 |
### Renal Pathology

#### Nephrotic syndrome
Nephrotic syndrome—massive proteinuria (> 3.5 g/day) with hypoalbuminemia, resulting edema, hyperlipidemia. Frothy urine with fatty casts. Disruption of glomerular filtration charge barrier may be 1° (eg, direct sclerosis of podocytes) or 2° (systemic process [eg, diabetes] secondarily damages podocytes). Severe nephritic syndrome may present with nephrotic syndrome features (nephritic-nephrotic syndrome) if damage to GBM is severe enough to damage charge barrier. Associated with hypercoagulable state due to antithrombin (AT) III loss in urine and risk of infection (loss of immunoglobulins in urine and soft tissue compromise by edema).

#### Minimal change disease (lipoid nephrosis)
Most common cause of nephrotic syndrome in children. Often 1° (idiopathic) and may be triggered by recent infection, immunization, immune stimulus. Rarely, may be 2° to lymphoma (eg, cytokine-mediated damage). 1° disease has excellent response to corticosteroids.
- LM—Normal glomeruli (lipid may be seen in PCT cells)
- IF—
- EM—effacement of podocyte foot processes

#### Focal segmental glomerulosclerosis
Most common cause of nephrotic syndrome in African-Americans and Hispanics. Can be 1° (idiopathic) or 2° to other conditions (eg, HIV infection, sickle cell disease, heroin abuse, massive obesity, interferon treatment, or congenital malformations). 1° disease has inconsistent response to steroids. May progress to CKD.
- LM—Segmental sclerosis and hyalinosis
- IF—often ⊗ but may be ⊕ for nonspecific focal deposits of IgM, C3, C1
- EM—effacement of foot processes similar to minimal change disease

#### Membranous nephropathy
Also known as membranous glomerulonephritis. Can be 1° (eg, antibodies to phospholipase A<sub>2</sub> receptor) or 2° to drugs (eg, NSAIDs, penicillamine, gold), infections (eg, HBV, HCV, syphilis), SLE, or solid tumors. 1° disease has poor response to steroids. May progress to CKD.
- LM—Diffuse capillary and GBM thickening
- IF—granular due to IC deposition
- EM—“Spike and dome” appearance of subepithelial deposits

#### Amyloidosis
Kidney is the most commonly involved organ (systemic amyloidosis). Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid).
- LM—Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium

#### Diabetic glomerulonephropathy
Most common cause of ESRD in the United States. Hyperglycemia → nonenzymatic glycation of tissue proteins → mesangial expansion; GBM thickening and permeability. Hyperfiltration (glomerular HTN and ↑ GFR) → glomerular hypertrophy and glomerular scarring (glomerulosclerosis) leading to further progression of nephropathy.
- LM—Mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions, arrows in D)
Nephritic syndrome

Nephritic syndrome = Inflammatory process. When glomeruli are involved, leads to hematuria and RBC casts in urine. Associated with azotemia, oliguria, hypertension (due to salt retention), proteinuria, hypercellular/inflamed glomeruli on biopsy.

Acute poststreptococcal glomerulonephritis

Most frequently seen in children. ~ 2–4 weeks after group A streptococcal infection of pharynx or skin. Resolves spontaneously in most children; may progress to renal insufficiency in adults. Type III hypersensitivity reaction. Presents with peripheral and periorbital edema, colo-colored urine, HTN. + strep titersserologies, ↓ complement levels (C3) due to consumption.
- LM—glomeruli enlarged and hypercellular
- IF—("starry sky") granular appearance ("lumpy-bumpy") due to IgG, IgM, and C3 deposition along GBM and mesangium
- EM—subepithelial immune complex (IC) humps

Rapidly progressive (crescentic) glomerulonephritis

Poor prognosis, rapidly deteriorating renal function (days to weeks).
- LM—crescent moon shape. Crescents consist of fibrin and plasma proteins (eg, C3b) with glomerular parietal cells, monocytes, macrophages
- Linear IF due to antibodies to GBM and alveolar basement membrane: Goodpasture syndrome—hematuria/hemoptysis; type II hypersensitivity reaction; Treatment: plasmapheresis
- Negative IF/Pauci-immune (no Ig/C3 deposition): Granulomatosis with polyangiitis (Wegener)—PR3-ANCA/c-ANCA or Microscopic polyangiitis—MPO-ANCA/p-ANCA
- Granular IF—PSGN or DPGN

Diffuse proliferative glomerulonephritis

Often due to SLE (think “wire lupus”). DPGN and MPGN often present as nephrotic syndrome and nephritic syndrome concurrently.
- LM—"wire looping" of capillaries
- IF—granular. EM—sub endothelial and sometimes intramembranous IgG-based ICs often with C3 deposition

IgA nephropathy (Berger disease)

Episodic hematuria that occurs concurrently with respiratory or GI tract infections (IgA is secreted by mucosal linings). Renal pathology of IgA vasculitis (HSP).
- LM—mesangial proliferation
- IF—IgA-based IC deposits in mesangium; EM—mesangial IC deposition

Alport syndrome

Mutation in type IV collagen → thinning and splitting of glomerular basement membrane. Most commonly X-linked dominant. Eye problems (eg, retinopathy, lens dislocation), glomerulonephritis, sensorineural deafness; “can’t see, can’t pee, can’t hear a bee.”
- EM—“Basket-weave”

Membrano-proliferative glomerulonephritis

MPGN is a nephritic syndrome that often co-presents with nephrotic syndrome.
- Type I may be 2° to hepatitis B or C infection. May also be idiopathic.
  - Sub endothelial IC deposits with granular IF
- Type II is associated with C3 nephritic factor (IgG antibody that stabilizes C3 convertase → persistent complement activation → ↓ C3 levels).
  - Intramembranous deposits, also called dense deposit disease
- In both types, mesangial ingrowth → GBM splitting → “tram-track” appearance on H&E and PAS stains.
Kidney stones

Can lead to severe complications such as hydronephrosis, pyelonephritis. Obstructed stone presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake.

Most common kidney stone presentation: calcium oxalate stone in patient with hypercalciuria and normocalcemia.

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>PRECIPITATES WITH</th>
<th>X-RAY FINDINGS</th>
<th>CT FINDINGS</th>
<th>URINE CRYSTAL</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Calcium oxalate:</td>
<td>Radiopaque</td>
<td>Radiopaque</td>
<td>Shaped like</td>
<td>Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones. Hypocitraturia often associated with ↓ urine pH. Can result from ethylene glycol (antifreeze) ingestion, vitamin C abuse, hypocitraturia, malabsorption (eg, Crohn disease). Treatment: thiazides, citrate, low-sodium diet.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>envelope or dumbbell</td>
<td></td>
</tr>
<tr>
<td>Calcium phosphate: ↑ pH</td>
<td>Radiopaque</td>
<td>Radiopaque</td>
<td>Wedge-shaped</td>
<td></td>
<td>Treatment: low-sodium diet, thiazides.</td>
</tr>
<tr>
<td>Ammonium magnesium phosphate</td>
<td>↑ pH</td>
<td>Radiopaque</td>
<td>Radiopaque</td>
<td>Coffin lid</td>
<td>Also known as struvite; account for 15% of stones. Caused by infection with urease ⊕ bugs (eg, Proteus mirabilis, Staphylococcus saprophyticus, Klebsiella) that hydrolyze urea to ammonia → urine alkalinization. Commonly form staghorn calculi ⊕. Treatment: eradication of underlying infection, surgical removal of stone.</td>
</tr>
<tr>
<td>Uric acid</td>
<td>↓ pH</td>
<td>Radiolucent</td>
<td>Minimally visible</td>
<td>Rhomboid or rosettes</td>
<td>About 5% of all stones. Risk factors: ↓ urine volume, arid climates, acidic pH. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↑ cell turnover (eg, leukemia). Treatment: alkalinization of urine, allopurinol.</td>
</tr>
<tr>
<td>Cystine</td>
<td>↓ pH</td>
<td>Faintly radiopaque</td>
<td>Moderately radiopaque</td>
<td>Hexagonal</td>
<td>Hereditary (autosomal recessive) condition in which Cystine-reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of Ornithine, Lysine, Arginine (COLA). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test ⊕. “SIXtine” stones have SIX sides. Treatment: low sodium diet, alkalinization of urine, chelating agents if refractory.</td>
</tr>
</tbody>
</table>
Hydronephrosis

Distention/dilation of renal pelvis and calyces. Usually caused by urinary tract obstruction (eg, renal stones, severe BPH, congenital obstructions, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated if obstruction is bilateral or if patient has an obstructed solitary kidney. Leads to compression and possible atrophy of renal cortex and medulla.

Renal cell carcinoma

Polygonal clear cells filled with accumulated lipids and carbohydrate. Often golden-yellow due to lipid content. Originates from PCT → invades renal vein (may develop varicocele if left sided) → IVC → hematogenous spread → metastasis to lung and bone. Manisfets with hematuria, palpable masses, 2° polycythemia, flank pain, fever, weight loss. Treatment: surgery/ablation for localized disease. Immunotherapy (eg, aldesleukin) or targeted therapy for metastatic disease, rarely curative. Resistant to chemotherapy and radiation therapy.

Renal oncocyoma

Benign epithelial cell tumor arising from collecting ducts (arrows in point to well-circumscribed mass with central scar). Large cosinophilic cells with abundant mitochondria without perinuclear clearing (vs chromophobe renal cell carcinoma). Presents with painless hematuria, flank pain, abdominal mass. Often resected to exclude malignancy (eg, renal cell carcinoma).
Nephroblastoma (Wilms tumor)

Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Presents with large, palpable, unilateral flank mass and/or hematuria. “Loss of function” mutations of tumor suppressor genes WT1 or WT2 on chromosome 11. May be a part of several syndromes:

- **WAGR complex**: Wilms tumor, Aniridia (absence of iris), Genitourinary malformations, mental retardation/intellectual disability (WT1 deletion)
- **Denys–Drash syndrome**: Wilms tumor, Diffuse mesangial sclerosis (early-onset nephrotic syndrome), Dysgenesis of gonads (male pseudohermaphroditism), WT1 mutation
- **Beckwith-Wiedemann syndrome**: Wilms tumor, macroglossia, organomegaly, hemihyperplasia (WT2 mutation)

Transitional cell carcinoma

Also known as urothelial carcinoma. Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder). Can be suggested by painless hematuria (no casts). Associated with problems in your Pee SAC: Phenacetin, Smoking, Aniline dyes, and Cyclophosphamide.

Squamous cell carcinoma of the bladder

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma. Risk factors include Schistosoma haematobium infection (Middle East), chronic cystitis, smoking, chronic nephrolithiasis. Presents with painless hematuria.

Urinary incontinence

**Stress incontinence**

Outlet incompetence (urethral hypermobility or intrinsic sphincteric deficiency) → leak with ↑ intra-abdominal pressure (eg, sneezing, lifting). ↑ risk with obesity, vaginal delivery, prostate surgery. ⚫ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver). Treatment: pelvic floor muscle strengthening (Kegel) exercises, weight loss, pessaries.

**Urgency incontinence**

Overactive bladder (detrusor instability) → leak with urge to void immediately. Associated with UTI. Treatment: Kegel exercises, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin).

**Mixed incontinence**

Features of both stress and urgency incontinence.

**Overflow incontinence**

Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling. Associated with polyuria (eg, diabetes), bladder outlet obstruction (eg, BPH), neurogenic bladder (eg, MS). ↑ post-void residual (urinary retention) on catheterization or ultrasound. Treatment: catheterization, relieve obstruction (eg, α-blockers for BPH).
Urinary tract infection (acute bacterial cystitis)

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (eg, high fever, chills) are usually absent. Risk factors include female gender (short urethra), sexual intercourse (“honeymoon cystitis”), indwelling catheter, diabetes mellitus, impaired bladder emptying. Causes:

* *E. coli* (most common).
* *Staphylococcus saprophyticus*—seen in sexually active young women (*E. coli* is still more common in this group).
* *Klebsiella*.
* *Proteus mirabilis*—urine has ammonia scent.

Lab findings: ⊕ leukocyte esterase, ⊕ nitrites (indicate gram ⊝ organisms). Sterile pyuria and ⊝ urine cultures suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

Pyelonephritis

**Acute pyelonephritis**

Neutrophils infiltrate renal interstitium. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills. Causes include ascending UTI (*E. coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/− WBC casts. CT would show striated parenchymal enhancement. Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy. Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis. Treatment: antibiotics.

**Chronic pyelonephritis**

The result of recurrent episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones. Coarse, asymmetric corticomedullary scarring, blunted calyx. Tubules can contain eosinophilic casts resembling thyroid tissue (thyroidization of kidney).

*Xanthogranulomatous pyelonephritis*—rare; grossly orange nodules that can mimic tumor nodules; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages. Associated with *Proteus* infection.
Acute kidney injury

Formerly known as acute renal failure. Acute kidney injury is defined as an abrupt decline in renal function as measured by ↑ creatinine and ↑ BUN or by oliguria/anuria.

Prerenal azotemia

Due to ↓ RBF (eg, hypotension) → ↓ GFR. Na+/H₂O and urea retained by kidney in an attempt to conserve volume → ↑ BUN/creatinine ratio (urea is reabsorbed, creatinine is not) and ↓ FE₅Na.

Intrinsic renal failure

Most commonly due to acute tubular necrosis (from ischemia or toxins); less commonly due to acute glomerulonephritis (eg, RPGN, hemolytic uremic syndrome) or acute interstitial nephritis. In ATN, patchy necrosis → debris obstructing tubule and fluid backflow across necrotic tubule → ↓ GFR. Urine has epithelial/granular casts. Urea reabsorption is impaired → ↑ BUN/creatinine ratio and ↓ FE₅Na.

Postrenal azotemia

Due to outflow obstruction (stones, BPH, neoplasia, congenital anomalies). Develops only with bilateral obstruction or in a solitary kidney.

<table>
<thead>
<tr>
<th></th>
<th>Prerenal</th>
<th>Intrinsic renal</th>
<th>Postrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine osmolality</td>
<td>&gt; 500</td>
<td>&lt; 350</td>
<td>&lt; 350</td>
</tr>
<tr>
<td>(mOsm/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Na⁺ (mEq/L)</td>
<td>&lt; 20</td>
<td>&gt; 40</td>
<td>Varies</td>
</tr>
<tr>
<td>FE₅Na</td>
<td>&lt; 1%</td>
<td>&gt; 2%</td>
<td>Varies</td>
</tr>
<tr>
<td>Serum BUN/Cr</td>
<td>&gt; 20</td>
<td>&lt; 15</td>
<td>Varies</td>
</tr>
</tbody>
</table>

Consequences of renal failure

Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.

Consequences (MAD HUNGER):

- Metabolic Acidosis
- Dyslipidemia (especially ↑ triglycerides)
- Hyperkalemia
- Uremia—clinical syndrome marked by:
  - Nausea and anorexia
  - Pericarditis
  - Asterixis
  - Encephalopathy
  - Platelet dysfunction
- Na⁺/H₂O retention (HF, pulmonary edema, hypertension)
- Growth retardation and developmental delay
- Erythropoietin failure (anemia)
- Renal osteodystrophy

Renal osteodystrophy

Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic renal disease → 2° hyperparathyroidism. High serum phosphate can bind with Ca²⁺ → tissue deposits → ↓ serum Ca²⁺; ↓ 1,25-(OH)₂D₃ → ↓ intestinal Ca²⁺ absorption. Causes subperiosteal thinning of bones.

2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).
Acute interstitial nephritis (tubulointerstitial nephritis)

Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, penicillin derivatives, proton pump inhibitors, sulfonamides, rifampin, NSAIDs). Less commonly may be 2° to other processes such as systemic infections (eg, *Mycoplasma*) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis). Associated with fever, rash, hematuria, pyuria, and costovertebral angle tenderness, but can be asymptomatic. Remember these P’s:
- Pee (diuretics)
- Pain-free (NSAIDs)
- Penicillins and cephalosporins
- Proton pump inhibitors
- Rifampin

Acute tubular necrosis

Most common cause of acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. ≤ FE Na.

Key finding: granular (“muddy brown”) casts.

3 stages:
1. Inciting event
2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia
3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia and renal wasting of other electrolytes and minerals

Can be caused by ischemic or nephrotoxic injury:
- Ischemic—2° to ↓ renal blood flow (eg, hypotension, shock, sepsis, hemorrhage, HF). Results in death of tubular cells that may slough into tubular lumen (PCT and thick ascending limb are highly susceptible to injury).
- Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin, ethylene glycol), crush injury (myoglobinuria), hemoglobinuria. Proximal tubules are particularly susceptible to injury.

Diffuse cortical necrosis

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC. Associated with obstetric catastrophes (eg, abruptio placentae), septic shock.

Renal papillary necrosis

Sloughing of necrotic renal papillae → gross hematuria and proteinuria. May be triggered by recent infection or immune stimulus. Associated with sickle cell disease or trait, acute pyelonephritis, NSAIDs, diabetes mellitus.

SAAD papa with papillary necrosis:
- Sickle cell disease or trait
- Acute pyelonephritis
- Analgesics (NSAIDs)
- Diabetes mellitus
Renal cyst disorders

<table>
<thead>
<tr>
<th>Type of Kidney Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>Numerous cysts in cortex and medulla causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure in ~50% of individuals. Mutation in PKD1 (85% of cases, chromosome 16) or PKD2 (15% of cases, chromosome 4). Death from complications of chronic kidney disease or hypertension (caused by renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis. Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.</td>
</tr>
<tr>
<td>Autosomal recessive polycystic kidney disease</td>
<td>Cystic dilation of collecting ducts. Often presents in infancy. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.</td>
</tr>
<tr>
<td>Autosomal dominant tubulointerstitial kidney disease</td>
<td>Also known as medullary cystic kidney disease. Inherited disease causing tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis.</td>
</tr>
<tr>
<td>Simple vs complex renal cysts</td>
<td>Simple cysts are filled with ultrafiltrate (anechoic on ultrasound). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic. Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to risk of renal cell carcinoma.</td>
</tr>
</tbody>
</table>

![Image of cysts](image1.png)
Diuretics site of action

- **Mannitol**
- **Acetazolamide**
- **Loop diuretics**
- **Thiazide**
- **K+ sparing diuretics**

1. **Glomerulus**
   - Afferent
   - Efferent
   - **HCO3−/Na+**
   - **H2O**

2. **Proximal convoluted tubule**
   - Sugars
   - Amino acids
   - Na+

3. **Descending limb, loop of Henle** (permeable to water)
   - Ca2+
   - Mg2+
   - Na+
   - Cl−

4. **Ascending limb, loop of Henle** (permeable to salts)
   - Na+
   - HCO3−
   - Ca2+

5. **Collecting duct**
   - K+
   - K+ (sodium and potassium)
   - Na+

---

**Cortex**

**Medulla**

1. **Sugars**
2. **Amino acids**
3. **Na+**
4. **K+**
5. **H+**
### Mannitol

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Drug overdose, elevated intracranial/intraocular pressure.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Pulmonary edema, dehydration, hypo- or hypernatremia. Contraindicated in anuria, HF.</td>
</tr>
</tbody>
</table>

### Acetazolamide

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Carbonic anhydrase inhibitor. Causes self-limited NaHCO₃ diuresis and ↑ total body HCO₃⁻ stores.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Glaucoma, metabolic alkalosis, altitude sickness, pseudotumor cerebri. Alkalizes urine.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Proximal renal tubular acidosis, paresthesias, NH₃ toxicity, sulfa allergy, hypokalemia. Promotes calcium phosphate stone formation (insoluble at high pH).</td>
</tr>
</tbody>
</table>

“ACID”azolamide causes ACIDosis.

### Loop diuretics

#### Furosemide, bumetanide, torsemide

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Sulfonamide loop diuretics. Inhibit cotransport system (Na⁺/K⁺/2Cl⁻) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Stimulate PGE release (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. ↑ Ca²⁺ excretion. Loops Lose Ca²⁺.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Ototoxicity, Hypokalemia, Hypomagnesemia, Dehydration, Allergy (sulfa), metabolic Alkalosis, Nephritis (interstitial), Gout.</td>
</tr>
</tbody>
</table>

“OHH DAANG!”

#### Ethacrynic acid

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Nonsulfonamide inhibitor of cotransport system (Na⁺/K⁺/2Cl⁻) of thick ascending limb of loop of Henle.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Diuresis in patients allergic to sulfa drugs.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Similar to furosemide, but more ototoxic.</td>
</tr>
</tbody>
</table>

Loop earrings hurt your ears.
### Thiazide diuretics

**Hydrochlorothiazide, chlorthalidone, metolazone.**

**MECHANISM**

Inhibit NaCl reabsorption in early DCT → ↓ diluting capacity of nephron. ↓ Ca²⁺ excretion.

**CLINICAL USE**

Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.

**ADVERSE EFFECTS**

Hypokalemic metabolic alkalosis, hyperGlycemia, hyperLipidemia, hyperUricemia, hyperCalcemia. Sulf allergy.

### Potassium-sparing diuretics

**Spironolactone, Eplerenone, Amiloride, Triamterene.**

**MECHANISM**

Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride act at the same part of the tubule by blocking Na⁺ channels in the cortical collecting tubule.

**CLINICAL USE**

Hyperaldosteronism, K⁺ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen.

**ADVERSE EFFECTS**

Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).

### Diuretics: electrolyte changes

| Urine NaCl | ↑ with all diuretics (strength varies based on potency of diuretic effect). Serum NaCl may decrease as a result. |
| Urine K⁺ | ↑ especially with loop and thiazide diuretics. Serum K⁺ may decrease as a result. |
| Blood pH | ↓ (acidemia): carbonic anhydrase inhibitors: ↓ HCO₃⁻ reabsorption. K⁺ sparing: aldosterone blockade prevents K⁺ secretion and H⁺ secretion. Additionally, hyperkalemia leads to K⁺ entering all cells (via H⁺/K⁺ exchanger) in exchange for H⁺ exiting cells. ↑ (alkalemia): loop diuretics and thiazides cause alkalemia through several mechanisms: * Volume contraction → ↑ AT II → ↑ Na⁺/H⁺ exchange in PCT → ↑ HCO₃⁻ reabsorption (“contraction alkalosis”) * K⁺ loss leads to K⁺ exiting all cells (via H⁺/K⁺ exchanger) in exchange for H⁺ entering cells * In low K⁺ state, H⁺ (rather than K⁺) is exchanged for Na⁺ in cortical collecting tubule → alkalosis and “paradoxical aciduria” |
| Urine Ca²⁺ | ↑ with loop diuretics: ↓ paracellular Ca²⁺ reabsorption → hypocalcemia. ↓ with thiazides: enhanced Ca²⁺ reabsorption. |
### Angiotensin-converting enzyme inhibitors

| MECHANISM | Captopril, enalapril, lisinopril, ramipril. Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator. |
| CLINICAL USE | Hypertension, HF (↑ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension. |
| ADVERSE EFFECTS | Cough, Angioedema (both due to ↑ bradykinin; contraindicated in C1 esterase inhibitor deficiency), Teratogen (fetal renal malformations), ↑ Creatinine (↓ GFR), Hyperkalemia, and Hypotension. Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR → renal failure. |

### Angiotensin II receptor blockers

| Losartan, candesartan, valsartan. Selectively block binding of angiotensin II to AT$_1$ receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin. |
| CLINICAL USE | Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema). |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension; teratogen. |

### Aliskiren

| Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. |
| CLINICAL USE | Hypertension. |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension, angioedema. Relatively contraindicated in patients already taking ACE inhibitors or ARBs and contraindicated in pregnancy. |
"Artificial insemination is when the farmer does it to the cow instead of the bull."
— Student essay

"Whoever called it necking was a poor judge of anatomy."
— Groucho Marx

"See, the problem is that God gives men a brain and a penis, and only enough blood to run one at a time."
— Robin Williams

"I think you can say that life is a system in which proteins and nucleic acids interact in ways that allow the structure to grow and reproduce. It’s that growth and reproduction, the ability to make more of yourself, that’s important."
— Andrew H. Knoll

The reproductive system can be intimidating at first but is manageable once you organize the concepts into the pregnancy, endocrinologic, embryologic, and oncologic aspects of reproduction. Study the endocrine and reproductive chapters together, because mastery of the hypothalamic-pituitary-gonadal axis is key to answering questions on ovulation, menstruation, disorders of sexual development, contraception, and many pathologies.

Embryology is a nuanced subject that covers multiple organ systems. Approaching it from a clinical perspective will allow for better understanding. For instance, make the connection between the presentation of DiGeorge syndrome and the 3rd/4th branchial pouch, and between the Müllerian/Wolffian systems and disorders of sexual development.

As for oncology, don’t worry about remembering screening or treatment guidelines. It is more important to know how these cancers present (eg, hormonal derangements, signs, and symptoms), their histologic pathology, and their underlying risk factors. In addition, some of the testicular and ovarian cancers have distinct patterns of hCG, AFP, LH, or FSH derangement that make good clues in exam questions.
Important genes of embryogenesis

**Sonic hedgehog gene**
Produced at base of limbs in zone of polarizing activity. Involved in patterning along anteroposterior axis and CNS development; mutation can cause holoprosencephaly.

**Wnt-7 gene**
Produced at apical ectodermal ridge (thickened ectoderm at distal end of each developing limb). Necessary for proper organization along dorsal-ventral axis.

**Fibroblast growth factor (FGF) gene**
Produced at apical ectodermal ridge. Stimulates mitosis of underlying mesoderm, providing for lengthening of limbs. “Look at that Fetus, Growing Fingers.”

**Homeobox (Hox) genes**
Involved in segmental organization of embryo in a craniocaudal direction. Code for transcription factors. Hox mutations → appendages in wrong locations.

Early fetal development

**Early embryonic development**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within week 1</td>
<td>hCG secretion begins around the time of implantation of blastocyst.</td>
</tr>
<tr>
<td>Within week 2</td>
<td>Bilaminar disc (epiblast, hypoblast).</td>
</tr>
<tr>
<td>Within week 3</td>
<td>Gastrulation forms trilaminar embryonic disc. Cells from epiblast invaginate → primitive streak → endoderm, mesoderm, ectoderm. Notochord arises from midline mesoderm; overlying ectoderm becomes neural plate.</td>
</tr>
<tr>
<td>Week 4</td>
<td>Heart begins to beat. Upper and lower limb buds begin to form.</td>
</tr>
<tr>
<td>Week 6</td>
<td>Fetal cardiac activity visible by transvaginal ultrasound.</td>
</tr>
<tr>
<td>Week 8</td>
<td>Fetal movements start.</td>
</tr>
<tr>
<td>Week 10</td>
<td>Genitalia have male/female characteristics.</td>
</tr>
</tbody>
</table>
### Embryologic derivatives

<table>
<thead>
<tr>
<th>Ectoderm</th>
<th>External/outer layer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface ectoderm</strong></td>
<td>Epidermis; adenohypophysis (from Rathke pouch); lens of eye; epithelial linings of oral cavity, sensory organs of ear, and olfactory epithelium; anal canal below the pectinate line; parotid, sweat, mammary glands.</td>
</tr>
<tr>
<td><strong>Neural tube</strong></td>
<td>Brain (neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland), retina, spinal cord.</td>
</tr>
<tr>
<td><strong>Neural crest</strong></td>
<td>Melanocytes, Myenteric (Auerbach) plexus, Odontoblasts, Endocardial cushions, Laryngeal cartilage, Parafollicular (C) cells of the thyroid, PNS (dorsal root ganglia, cranial nerves, autonomic ganglia), Adrenal medulla and all ganglia, Spiral membrane (aorticopulmonary septum), Schwann cells, pia and arachnoid, bones of skull.</td>
</tr>
<tr>
<td><strong>Mesoderm</strong></td>
<td>Muscle, bone, connective tissue, serous linings of body cavities (eg, peritoneum, pericardium, pleura), spleen (derived from foregut mesentery), cardiovascular structures, lymphatics, blood, wall of gut tube, upper vagina, kidneys, adrenal cortex, dermis, testes, ovaries. Notochord induces ectoderm to form neuroectoderm (neural plate); its only postnatal derivative is the nucleus pulposus of the intervertebral disc.</td>
</tr>
<tr>
<td><strong>Endoderm</strong></td>
<td>Gut tube epithelium (including anal canal above the pectinate line), most of urethra and lower vagina (derived from urogenital sinus), luminal epithelial derivatives (eg, lungs, liver, gallbladder, pancreas, eustachian tube, thymus, parathyroid, thyroid follicular cells).</td>
</tr>
</tbody>
</table>

### Types of errors in morphogenesis

<table>
<thead>
<tr>
<th>Agenesis</th>
<th>Absent organ due to absent primordial tissue.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplasia</td>
<td>Absent organ despite presence of primordial tissue.</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>Incomplete organ development; primordial tissue present.</td>
</tr>
<tr>
<td>Disruption</td>
<td>2nd breakdown of previously normal tissue or structure (eg, amniotic band syndrome).</td>
</tr>
<tr>
<td>Deformation</td>
<td>Extrinsic disruption; occurs after embryonic period.</td>
</tr>
<tr>
<td>Malformation</td>
<td>Intrinsic disruption; occurs during embryonic period (weeks 3–8).</td>
</tr>
<tr>
<td>Sequence</td>
<td>Abnormalities result from a single 1st embryologic event (eg, oligohydramnios → Potter sequence).</td>
</tr>
</tbody>
</table>
### Teratogens

Most susceptible in 3rd–8th weeks (embryonic period—organogenesis) of pregnancy. Before week 3, “all-or-none” effects. After week 8, growth and function affected.

<table>
<thead>
<tr>
<th>Teratogen</th>
<th>Effects on Fetus</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Renal damage</td>
<td></td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Absence of digits, multiple anomalies</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity</td>
<td>A mean guy hit the baby in the ear.</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>Neural tube defects, cardiac defects, cleft palate, skeletal abnormalities (eg, phalanx/nail hypoplasia, facial dysmorphism)</td>
<td>High-dose folate supplementation recommended. Most commonly valproate, carbamazepine, phenytoin, phenobarbital.</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>Vaginal clear cell adenocarcinoma, congenital Mullerian anomalies</td>
<td></td>
</tr>
<tr>
<td>Folate antagonists</td>
<td>Neural tube defects</td>
<td>Includes trimethoprim, methotrexate, antiepileptic drugs.</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Multiple severe birth defects</td>
<td>Contraception mandatory. IsoTERATinoin.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Ebstein anomaly (apical displacement of tricuspid valve)</td>
<td></td>
</tr>
<tr>
<td>Methimazole</td>
<td>Aplasia cutis congenita</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Discolored teeth, inhibited bone growth</td>
<td>“Teethracyclines.”</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Limb defects (phocomelia, micromelia—“flipper” limbs)</td>
<td>Limb defects with “tha-limb-domide.”</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Bone deformities, fetal hemorrhage, abortion, ophthalmologic abnormalities</td>
<td>Do not wage warfar on the baby; keep it heppy with heparin (does not cross placenta).</td>
</tr>
</tbody>
</table>

| Substance abuse | |
| Alcohol | Common cause of birth defects and intellectual disability; fetal alcohol syndrome |
| Cocaine | Low birth weight, preterm birth, IUGR, placental abruption | Cocaine → vasoconstriction. |
| Smoking (nicotine, CO) | Low birth weight (leading cause in developed countries), preterm labor, placental problems, IUGR, SIDS, ADHD | Nicotine → vasoconstriction. CO → impaired O₂ delivery. |

| Other | |
| Iodine (lack or excess) | Congenital goiter or hypothyroidism (cretinism) |
| Maternal diabetes | Caudal regression syndrome (anal atresia to sirenomelia), congenital heart defects (eg, VSD, transposition of the great vessels), neural tube defects, macrosomia, neonatal hypoglycemia, polycythemia |
| Methylmercury | Neurotoxicity | Highest in swordfish, shark, tilefish, king mackerel. |
| Vitamin A excess | Extremely high risk for spontaneous abortions and birth defects (cleft palate, cardiac) | |
| X-rays | Microcephaly, intellectual disability | Minimized by lead shielding. |
Fetal alcohol syndrome

Leading cause of intellectual disability in the US. Newborns of alcohol-consuming mothers have an incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities (e.g., smooth philtrum, thin vermillion border [upper lip], small palpebral fissures), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly in most severe form. Mechanism is failure of cell migration.

Neonatal abstinence syndrome

Complex disorder involving CNS, ANS, and GI systems. Secondary to maternal opiate use/abuse. Risk factors for maternal substance abuse during pregnancy include poor mental health, poor prenatal care, low SES, lack of family support, HCV. Universal screening for substance abuse is recommended in all pregnant patients. Newborns may present with uncoordinated sucking reflexes, irritability, high-pitched crying, tremors, tachypnea, sneezing, diarrhea, and possibly seizures.
Twinning

Dizygotic ("fraternal") twins arise from 2 eggs that are separately fertilized by 2 different sperm (always 2 zygotes) and will have 2 separate amniotic sacs and 2 separate placentas (chorions). Monozygotic ("identical") twins arise from 1 fertilized egg (1 egg + 1 sperm) that splits in early pregnancy. The timing of cleavage determines chorionicity (number of chorions) and amnionicity (number of amnions) (SCAB):

- Cleavage 0–4 days: Separate chorion and amnion
- Cleavage 4–8 days: shared Chorion
- Cleavage 8–12 days: shared Amnion
- Cleavage 13+ days: shared Body (conjoined)

<table>
<thead>
<tr>
<th>Dizygotic (fraternal) [-2h]</th>
<th>No twinning</th>
<th>Monozygotic (identical) [-1h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 eggs, 2 sperm</td>
<td>1 egg, 1 sperm</td>
<td>Dichorionic diamniotic (25%)</td>
</tr>
<tr>
<td>0–4 days</td>
<td>Cleavage</td>
<td>Monochorionic diamniotic (75%)</td>
</tr>
<tr>
<td>2-cell stage</td>
<td>Cleavage</td>
<td>Monochorionic monoamniotic (rare)</td>
</tr>
<tr>
<td>Monula</td>
<td>Cleavage</td>
<td>Monochorionic monamniotic (conjoined—rare)</td>
</tr>
<tr>
<td>Blastocyst</td>
<td>Cleavage or axis duplication</td>
<td></td>
</tr>
</tbody>
</table>
**Placenta**

1st site of nutrient and gas exchange between mother and fetus.

### Fetal component

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotrophoblast</td>
<td>Inner layer of chorionic villi. Cytotrophoblast makes cells.</td>
</tr>
<tr>
<td>Syncytiotrophoblast</td>
<td>Outer layer of chorionic villi; synthesizes and secretes hormones, e.g., hCG (structurally similar to LH; stimulates corpus luteum to secrete progesterone during first trimester). Syncytiotrophoblast synthesizes hormones. Lacks MHC-I expression → ↓ chance of attack by maternal immune system.</td>
</tr>
</tbody>
</table>

### Maternal component

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decidua basalis</td>
<td>Derived from endometrium. Maternal blood in lacunae.</td>
</tr>
</tbody>
</table>
**Umbilical cord**

Umbilical arteries (2)—return deoxygenated blood from fetal internal iliac arteries to placenta. Umbilical vein (1)—supplies oxygenated blood from placenta to fetus; drains into IVC via liver or via ductus venosus.

Single umbilical artery (2-vessel cord) is associated with congenital and chromosomal anomalies. Umbilical arteries and vein are derived from allantois.

**Urachus**

In the 3rd week the yolk sac forms the allantois, which extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus. Failure of urachus to involute can lead to anomalies that may increase risk of infection and/or malignancy (eg, adenocarcinoma) if not treated.

Obliterated urachus is represented by the median umbilical ligament after birth, which is covered by median umbilical fold of the peritoneum.

- **Patent urachus**
  - Total failure of urachus to obliterate → urine discharge from umbilicus.

- **Urachal cyst**
  - Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Cyst can become infected and present as painful mass below umbilicus.

- **Vesicourachal diverticulum**
  - Slight failure of urachus to obliterate → outpouching of bladder.

**Vitelline duct**

7th week—obliteration of vitelline duct (omphalomesenteric duct), which connects yolk sac to midgut lumen.

- **Vitelline fistula**
  - Vitelline duct fails to close → meconium discharge from umbilicus.

- **Meckel diverticulum**
  - Partial closure of vitelline duct, with patent portion attached to ileum (true diverticulum). May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain.
Aortic arch derivatives

1st
- Part of maxillary artery (branch of external carotid).
- 1st arch is maximal.

2nd
- Stapedial artery and hyoid artery.
- Second = Stapedial.

3rd
- Common Carotid artery and proximal part of internal Carotid artery.
- C is 3rd letter of alphabet.

4th
- On left, aortic arch; on right, proximal part of right subclavian artery.
- 4th arch (4 limbs) = systemic.

6th
- Proximal part of pulmonary arteries and (on left only) ductus arteriosus.
- 6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).

Branchial apparatus

Composed of branchial clefts, arches, pouches.
- Branchial clefts—derived from ectoderm. Also called branchial grooves.
- Branchial arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage).
- Branchial pouches—derived from endoderm.

Branchial cleft derivatives

1st cleft develops into external auditory meatus.
2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.
Persistent cervical sinus → branchial cleft cyst within lateral neck, anterior to sternocleidomastoid muscle.
### Branchial arch derivatives

<table>
<thead>
<tr>
<th>ARCH</th>
<th>CARTILAGE</th>
<th>MUSCLES</th>
<th>NERVES*</th>
<th>ABNORMALITIES/COMMENTS</th>
</tr>
</thead>
</table>
| 1st branchial arch | Maxillary process  
→ Maxilla, zygomatic bone  
Mandibular process  
→ Meckel cartilage  
→ Mandible, Malleus and incus, sphenomandibular ligament | Muscles of Mastication  
(temporals, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, anterior ⅔ of tongue, tensor veli palatini | CN V₃ chew | Pierre Robin sequence—micrognathia, glossoptosis, cleft palate, airway obstruction  
Treacher Collins syndrome—neural crest dysfunction  
→ mandibular hypoplasia, facial abnormalities |
| 2nd branchial arch | Reichert cartilage:  
Stapes, Styloid process, lesser horn of hyoid, Stylohyoid ligament | Muscles of facial expression,  
Stapedius, Stylohyoid, platysma, posterior belly of digastric | CN VII (facial expression) smile | |
| 3rd branchial arch | Greater horn of hyoid | Stylopharyngeus (think of stylopharyngeus innervated by glosso pharyngeal nerve) | CN IX (stylopharyngeus) swallow stylishly | |
| 4th–6th branchial arches | Arytenoids, Cricoid, Corniculate, Cuneiform, Thyroid (used to sing and ACCCT) | 4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini  
6th arch: all intrinsic muscles of larynx except cricothyroid | 4th arch: CN X (superior laryngeal branch) simply swallow  
6th arch: CN X (recurrent/ inferior laryngeal branch) speak | Arches 3 and 4 form posterior ⅔ of tongue; arch 5 makes no major developmental contributions |

*These are the only CNs with both motor and sensory components (except V₂, which is sensory only).

When at the restaurant of the golden arches, children tend to first chew (1), then smile (2), then swallow stylishly (3) or simply swallow (4), and then speak (6).
Branchial pouch derivatives

<table>
<thead>
<tr>
<th>POUCH</th>
<th>DERIVATIVES</th>
<th>NOTES</th>
<th>MNEMONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st branchial pouch</td>
<td>Middle ear cavity, eustachian tube, mastoid air cells.</td>
<td>1st pouch contributes to endoderm-lined structures of ear.</td>
<td>Ear, tonsils, bottom-to-top: 1 (ear), 2 (tonsils), 3 dorsal (bottom for inferior parathyroids), 4 ventral (to = thymus)</td>
</tr>
<tr>
<td>2nd branchial pouch</td>
<td>Epithelial lining of palatine tonsil.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd branchial pouch</td>
<td>Dorsal wings ( \rightarrow ) inferior parathyroids. Ventral wings ( \rightarrow ) thymus.</td>
<td>3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids). 3rd-pouch structures end up below 4th-pouch structures.</td>
<td></td>
</tr>
<tr>
<td>4th branchial pouch</td>
<td>Dorsal wings ( \rightarrow ) superior parathyroids. Ventr al wings ( \rightarrow ) ultimobranchial body ( \rightarrow ) parafollicular (C) cells of thyroid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DiGeorge syndrome

Chromosome 22q11 deletion. Aberrant development of 3rd and 4th pouches \( \rightarrow \) T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development). Associated with cardiac defects (conotruncal anomalies).

Cleft lip and cleft palate

Cleft lip—failure of fusion of the maxillary and merged medial nasal processes (formation of 1° palate).

Cleft palate—failure of fusion of the two lateral palatine shelves or failure of fusion of lateral palatine shelves with the nasal septum and/or median palatine shelf (formation of 2° palate).

Cleft lip and cleft palate have distinct, multifactorial etiologies, but often occur together.
Genital embryology

Female
Default development. Mesonephric duct degenerates and paramesonephric duct develops.

Male
SRY gene on Y chromosome—produces testis-determining factor \( \rightarrow \) testes development. Sertoli cells secrete Müllerian inhibitory factor (MIF) that suppresses development of paramesonephric ducts. Leydig cells secrete androgens that stimulate development of mesonephric ducts.

Paramesonephric (Müllerian) duct
Develops into female internal structures—fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). Male remnant is appendix testis. Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)—may present as 1° amenorrhea (due to a lack of uterine development) in females with fully developed 2° sexual characteristics (functional ovaries).

Mesonephric (Wolffian) duct
Develops into male internal structures (except prostate)—Seminal vesicles, Epididymis, Ejaculatory duct, Ductus deferens (SEED). Female remnant is Gartner duct.

Sexual differentiation

1. No Sertoli cells or lack of Müllerian inhibitory factor \( \rightarrow \) develop both male and female internal genitalia and male external genitalia
2. 5α-reductase deficiency—inability to convert testosterone into DHT \( \rightarrow \) male internal genitalia, ambiguous external genitalia until puberty (when \( \uparrow \) testosterone levels cause masculinization)
In the testes:
Leydig cells lead to male (internal and external) sexual differentiation.
Sertoli cells shut down female (internal) sexual differentiation.
Uterine (Müllerian duct) anomalies

**Septate uterus**  

**Bicornuate uterus**  
Incomplete fusion of Müllerian ducts. ↑ risk of complicated pregnancy, early pregnancy loss, malpresentation, prematurity.

**Uterus didelphys**  
Complete failure of fusion → double uterus, cervix, vagina. Pregnancy possible.

---

Male/female genital homologs

---

**Dihydrotestosterone**

- Glans penis
- Corpus cavernosum
- and spongiosum
- Bulbourethral glands
- (of Cowper)
- Prostate gland
- Ventral shaft of penis
- (penile urethra)
- Scrotum

**Estrogen**

- Glans clitoris
- Vestibular bulbs
- Greater vestibular glands
- (of Bartholin)
- Urethral and pararethral
  glands (of Skene)
- Labia minora
- Labia majora
Congenital penile abnormalities

**Hypospadias**
Abnormal opening of penile urethra on ventral surface of penis due to failure of urethral folds to fuse. Hypospadias is more common than epispadias. Associated with inguinal hernia and cryptorchidism. **Hypo** is below.

**Epispadias**
Abnormal opening of penile urethra on dorsal surface of penis due to faulty positioning of genital tubercle. **Exstrophy** of the bladder is associated with Epispadias. When you have Epispadias, you hit your Eye when you pEE.

Descent of testes and ovaries

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>MALE REMNANT</th>
<th>FEMALE REMNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gubernaculum</strong></td>
<td>Anchors testes within scrotum.</td>
<td>Ovarian ligament + round ligament of uterus.</td>
</tr>
<tr>
<td><strong>Processus vaginalis</strong></td>
<td>Forms tunica vaginalis.</td>
<td>Obliterated.</td>
</tr>
</tbody>
</table>

Gonadal drainage

**Venous drainage**
- Left ovary/testis → left gonadal vein → left renal vein → IVC.
- Right ovary/testis → right gonadal vein → IVC.

**Lymphatic drainage**
- Ovaries/testes → para-aortic lymph nodes.
- Body of uterus/superior bladder → external iliac nodes.
- Prostate/cervix/corpus cavernosum/proximal vagina → internal iliac nodes.
- Distal vagina/vulva/scrotum/distal anus → superficial inguinal nodes.
- Glans penis → deep inguinal nodes.

“Left gonadal vein takes the Longest way.” Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right → left venous pressure > right venous pressure → varicocele more common on the left.
### Female reproductive anatomy

<table>
<thead>
<tr>
<th>LIGAMENT</th>
<th>CONNECTS</th>
<th>STRUCTURES CONTAINED</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infundibulopelvic ligament</td>
<td>Ovaries to lateral pelvic wall</td>
<td>Ovarian vessels</td>
<td>Also called suspensory ligament of the ovary. Ligate vessels during oophorectomy to avoid bleeding. Ureter courses retroperitoneally, close to gonadal vessels at risk of injury during ligation of ovarian vessels.</td>
</tr>
<tr>
<td>Cardinal ligament</td>
<td>Cervix to side wall of pelvis</td>
<td>Uterine vessels</td>
<td>Ureter at risk of injury during ligation of uterine vessels in hysterectomy. Not shown in diagram.</td>
</tr>
<tr>
<td>Round ligament of the uterus</td>
<td>Uterine horn to labia majora</td>
<td></td>
<td>Derivative of gubernaculum. Travels through round inguinal canal; above the artery of Sampson.</td>
</tr>
<tr>
<td>Broad ligament</td>
<td>Uterus, fallopian tubes, and ovaries to pelvic side wall</td>
<td>Ovaries, fallopian tubes, round ligaments of uterus</td>
<td>Fold of peritoneum that comprises the mesosalpinx, mesometrium, and mesovarium.</td>
</tr>
<tr>
<td>Ovarian ligament</td>
<td>Medial pole of ovary to uterine horn</td>
<td></td>
<td>Derivative of gubernaculum. Ovarian Ligament Latches to Lateral uterus.</td>
</tr>
</tbody>
</table>
### Female reproductive epithelial histology

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Histology/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td>Stratified squamous epithelium, nonkeratinized</td>
</tr>
<tr>
<td>Ectocervix</td>
<td>Stratified squamous epithelium, nonkeratinized</td>
</tr>
<tr>
<td>Transformation zone</td>
<td>Squamocolumnar junction (most common area for cervical cancer)</td>
</tr>
<tr>
<td>Endocervix</td>
<td>Simple columnar epithelium</td>
</tr>
<tr>
<td>Uterus</td>
<td>Simple columnar epithelium with long tubular glands in proliferative phase; coiled glands in secretory phase</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Simple columnar epithelium, ciliated</td>
</tr>
<tr>
<td>Ovary, outer surface</td>
<td>Simple cuboidal epithelium (germinal epithelium covering surface of ovary)</td>
</tr>
</tbody>
</table>

### Male reproductive anatomy

Pathway of sperm during ejaculation—**SEVEN UP:**
- Seminiferous tubules
- Epididymis
- Vas deferens
- Ejaculatory ducts
- (Nothing)
- Urethra
- Penis

![Male reproductive anatomy](image-url)
**Urethral injury**

Occurs almost exclusively in men. Suspect if blood seen at urethral meatus. Urethral catheterization is relatively contraindicated.

<table>
<thead>
<tr>
<th>PART OF URETHRA</th>
<th>POSTERIOR URETHRAL INJURY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior urethral injury</td>
<td>Posterior urethral injury</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Membranous urethra</td>
</tr>
<tr>
<td>Location of urine leak/blood accumulation</td>
<td>Pelvic fracture</td>
</tr>
<tr>
<td>Blood accumulates in scrotum</td>
<td>Urine leaks into retropubic space</td>
</tr>
<tr>
<td>If Buck fascia is torn, urine escapes into perineal space</td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td>Blood at urethral meatus and high-riding prostate</td>
</tr>
<tr>
<td>Blood at urethral meatus and scrotal hematoma</td>
<td></td>
</tr>
</tbody>
</table>

**Autonomic innervation of male sexual response**

Erection—Parasympathetic nervous system (pelvic splanchnic nerves, S2-S4):
- NO → cGMP → smooth muscle relaxation → vasodilation → proerectile.
- Norepinephrine → ↑ [Ca^{2+}]_{in} → smooth muscle contraction → vasoconstriction → antierectile.

Emission—Sympathetic nervous system (hypogastric nerve, T11-L2).

Ejaculation—visceral and Somatic nerves (pudendal nerve).

Point, Squeeze, and Shoot.

PDE-5 inhibitors (eg, sildenafil) ↓ cGMP breakdown.
### Seminiferous tubules

<table>
<thead>
<tr>
<th>Cell</th>
<th>Function</th>
<th>Location/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spermatogonia</td>
<td>Maintain germ cell pool and produce 1(^{\circ}) spermatocytes.</td>
<td>Line seminiferous tubules [A]                                                               Germ cells</td>
</tr>
<tr>
<td>Sertoli cells</td>
<td>Secrete inhibin B (\rightarrow) inhibit FSH.</td>
<td>Line seminiferous tubules [A]</td>
</tr>
<tr>
<td></td>
<td>Secrete androgen-binding protein (\rightarrow) maintain local levels of testosterone.</td>
<td>Non-germ cells</td>
</tr>
<tr>
<td></td>
<td>Produce MIF.</td>
<td>Convert testosterone and androstenedione to estrogens via aromatase</td>
</tr>
<tr>
<td></td>
<td>Tight junctions between adjacent Sertoli cells (\rightarrow) isolate gametes from autoimmune attack.</td>
<td>Sertoli cells [^{\text{Support Sperm Synthesis and inhibit FSH}}]</td>
</tr>
<tr>
<td></td>
<td>Support and nourish developing spermatozoa.</td>
<td>Homolog of female granulosa cells</td>
</tr>
<tr>
<td></td>
<td>Regulate spermatogenesis.</td>
<td>[^{\text{temperature seen in varicocele, cryptorchidism}}]</td>
</tr>
<tr>
<td></td>
<td>Temperature sensitive; (\downarrow) sperm production and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(\downarrow) inhibin B with (\uparrow) temperature.</td>
<td></td>
</tr>
<tr>
<td>Leydig cells</td>
<td>Secrete testosterone in the presence of LH;</td>
<td>Interstitium</td>
</tr>
<tr>
<td></td>
<td>testosterone production unaffected by temperature.</td>
<td>Endocrine cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homolog of female theca interna cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LH stimulates Leydig cells</td>
</tr>
</tbody>
</table>

---

**Diagram:**

- **HYPOTHALAMUS**
- **Anterior pituitary**
- **LH**
- **FSH**
- **Inhibin B**
- **Spermatogonium**
- **Spermatid**
- **Spermatozoon**
- **Capillary**
- **Lumen of seminiferous tubule**
- **Sertoli cell nucleus**
- **Sertoli cell cytoplasm**
- **Testosterone**
- **Leydig cell**
- **GnRH**

**Spermatogenesis**
**Estrogen**

**SOURCE**
- Ovary (17β-estradiol), placenta (estriol), adipose tissue (estrone via aromatization).

**FUNCTION**
- Development of genitalia and breast, female fat distribution.
- Growth of follicle, endometrial proliferation, ↑ myometrial excitability.
- Upregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion.
- ↑ transport proteins, SHBG; ↑ HDL; ↓ LDL.

**Potency:** estradiol > estrone > estriol

**Pregnancy:**
- 50-fold ↑ in estradiol and estrone
- 1000-fold ↑ in estriol (indicator of fetal well-being)

Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen.

**Progesterone**

**SOURCE**
- Corpus luteum, placenta, adrenal cortex, testes.

**FUNCTION**
- Stimulation of endometrial glandular secretions and spiral artery development.
- Maintenance of pregnancy.
- ↓ myometrial excitability.
- Production of thick cervical mucus, which inhibits sperm entry into uterus.
- ↑ body temperature.
- Inhibition of gonadotropins (LH, FSH).
- Uterine smooth muscle relaxation (preventing contractions).
- ↓ estrogen receptor expression.
- Prevents endometrial hyperplasia.

Fall in progesterone after delivery disinhibits prolactin → lactation. ↑ progesterone is indicative of ovulation.

**Progesterone is pro-gestation.**

**Prolactin is pro-lactation.**
**Oogenesis**

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation. Meiosis I is arrested in prophase I for years until ovulation (1° oocytes). Meiosis II is arrested in metaphase II until fertilization (2° oocytes). “An egg meets a sperm.” If fertilization does not occur within 1 day, the 2° oocyte degenerates.

![Diagram of Oogenesis](image)

**Ovulation**

† estrogen, † GnRH receptors on anterior pituitary. Estrogen surge then stimulates LH release → ovulation (rupture of follicle).

† temperature (progesterone induced).

**Mittelschmerz**—transient mid-cycle ovulatory pain (“Middle hurts”); classically associated with peritoneal irritation (eg, follicular swelling/rupture, fallopian tube contraction). Can mimic appendicitis.
Menstrual cycle

Follicular phase can vary in length. Luteal phase is 14 days. Ovulation day + 14 days = menstruation.
Follicular growth is fastest during 2nd week of the follicular phase.
Estrogen stimulates endometrial proliferation.
Progesterone maintains endometrium to support implantation.
↓ progesterone → ↓ fertility.

### PHASES OF OVARIAN CYCLE:

<table>
<thead>
<tr>
<th>PHASES OF OVARIAN CYCLE:</th>
<th>FOLLICULAR PHASE</th>
<th>LUTEAL PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>Stimulates</td>
<td>Corpus luteum Produces</td>
</tr>
<tr>
<td>Anterior pituitary</td>
<td>FSH</td>
<td>LH</td>
</tr>
<tr>
<td>FSH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>Primordial follicles</td>
<td>Developing follicle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Produces Estrogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Progesterone</td>
</tr>
<tr>
<td>Follicular phase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PHASES OF UTERINE CYCLE:

<table>
<thead>
<tr>
<th>PHASES OF UTERINE CYCLE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Menses</th>
<th>Proliferative</th>
<th>Ovulation</th>
<th>Secretory</th>
<th>Menses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Abnormal uterine bleeding

Characterized as either heavy menstrual bleeding (AUB/HMB) or intermenstrual bleeding (AUB/IMB).
These are further subcategorized by PALM-COEIN:
- Structural causes (PALM): Polyp, Adenomyosis, Leiomyoma, or Malignancy/hyperplasia
- Non-structural causes (COEIN): Coagulopathy, Ovulatory, Endometrial, Latrogenic, Not yet classified

Terms such as dysfunctional uterine bleeding, menorrhagia, oligomenorrhea are no longer recommended.

Pregnancy

Fertilization most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation.
Implantation within the wall of the uterus occurs 6 days after fertilization.
Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after conception and on home test in urine 2 weeks after conception.
Gestational age—calculated from date of last menstrual period.
Embryonic age—calculated from date of conception (gestational age minus 2 weeks).
Physiologic adaptations in pregnancy:
- ↑ cardiac output (↓ preload, ↓ afterload, ↑ HR → ↑ placental and uterus perfusion)
- Anemia (↑ plasma, ↑ RBCs)
- Hypercoagulability (to ↓ blood loss at delivery)
- Hyperventilation (eliminate fetal CO₂)

Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks.

Human chorionic gonadotropin

SOURCE Syncytiotrophoblast of placenta.

FUNCTION Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of pregnancy by acting like LH (otherwise no luteal cell stimulation → abortion). After 8–10 weeks, placenta synthesizes its own estril and progesterone and corpus luteum degenerates.
Used to detect pregnancy because it appears early in urine (see above).
Has identical α subunit as LH, FSH, TSH (states of ↑ hCG can cause hyperthyroidism). β subunit is unique (pregnancy tests detect β subunit). hCG is ↑ in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is ↓ in ectopic/failing pregnancy, Edwards syndrome, and Patau syndrome.
**Human placental lactogen**

Also known as chorionic somatomammotropin.

**SOURCE**
Syncytiotrophoblast of placenta.

**FUNCTION**
Stimulates insulin production; overall ↑ insulin resistance. Maternal hypoglycemia from insulin resistance leads to lipolysis, which preserves available glucose and amino acids for the fetus. Gestational diabetes can occur if maternal pancreatic function cannot overcome the insulin resistance.

**Apgar score**

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Score 2</th>
<th>Score 1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pink</td>
<td>Extremities blue</td>
<td>Pale or blue</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulse</th>
<th>Score 2</th>
<th>Score 1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100 bpm</td>
<td>&lt; 100 bpm</td>
<td>No pulse</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grimace</th>
<th>Score 2</th>
<th>Score 1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cries and pulls away</td>
<td>Grimaces or weak cry</td>
<td>No response to stimulation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score 2</th>
<th>Score 1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active movement</td>
<td>Arms, legs flexed</td>
<td>No movement</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiration</th>
<th>Score 2</th>
<th>Score 1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong cry</td>
<td>Slow, irregular</td>
<td>No breathing</td>
<td></td>
</tr>
</tbody>
</table>

Assessment of newborn vital signs following delivery via a 10-point scale evaluated at 1 minute and 5 minutes. Apgar score is based on Appearance, Pulse, Grimace, Activity, and Respiration. Apgar scores < 7 require further evaluation. If Apgar score remains low at later time points, there is ↑ risk the child will develop long-term neurologic damage.
### Infant/child development

Milestone dates are ranges that have been approximated and vary by source. Children not meeting milestones may need assessment for potential developmental delay.

<table>
<thead>
<tr>
<th>Age</th>
<th>Motor</th>
<th>Social</th>
<th>Verbal/Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 mo</td>
<td>Primitive reflexes disappear—Moro (by 3 mo), rooting (by 4 mo), palmar (by 6 mo), Babinski (by 12 mo)</td>
<td>Social smile (by 2 mo)</td>
<td>Orient—first to voice (by 4 mo), then to name and gestures (by 9 mo)</td>
</tr>
<tr>
<td></td>
<td>Posture—lifts head up prone (by 1 mo), rolls and sits (by 6 mo), crawls (by 8 mo), stands (by 10 mo), walks (by 12–18 mo)</td>
<td>Stranger anxiety (by 6 mo)</td>
<td>Object permanence (by 9 mo)</td>
</tr>
<tr>
<td></td>
<td>Picks—passes toys hand to hand (by 6 mo), Pincer grasp (by 10 mo)</td>
<td>Separation anxiety (by 9 mo)</td>
<td>Oratory—says “mama” and “dada” (by 10 mo)</td>
</tr>
<tr>
<td></td>
<td>Points to objects (by 12 mo)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Toddler

<table>
<thead>
<tr>
<th>Child</th>
<th>Rearing</th>
<th>Working</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–36 mo</td>
<td>Cruises, takes first steps (by 12 mo)</td>
<td>Recreation—parallel play (by 24–36 mo)</td>
</tr>
<tr>
<td></td>
<td>Climbs stairs (by 18 mo)</td>
<td>Rapprochement—moves away from and returns to mother (by 24 mo)</td>
</tr>
<tr>
<td></td>
<td>Cubes stacked—number = age (yr) × 3</td>
<td>Realization—core gender identity formed (by 36 mo)</td>
</tr>
<tr>
<td></td>
<td>Cutlery—feeds self with fork and spoon (by 20 mo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kicks ball (by 24 mo)</td>
<td>Words—200 words by age 2 (2 zeros), 2-word sentences</td>
</tr>
</tbody>
</table>

### Preschool

<table>
<thead>
<tr>
<th>Don’t</th>
<th>Forget, they’re still</th>
<th>Learning!</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–5 yr</td>
<td>Drive—tricycle (3 wheels at 3 yr)</td>
<td>Freedom—comfortably spends part of day away from mother (by 3 yr)</td>
</tr>
<tr>
<td></td>
<td>Drawings—copies line or circle, stick figure (by 4 yr)</td>
<td>Friends—cooperative play, has imaginary friends (by 4 yr)</td>
</tr>
<tr>
<td></td>
<td>Dexterity—hops on one foot (by 4 yr), uses buttons or zippers, grooms self (by 5 yr)</td>
<td>Language—1000 words by age 3 (3 zeros), uses complete sentences and prepositions (by 4 yr)</td>
</tr>
</tbody>
</table>

### Low birth weight

Defined as < 2500 g. Caused by prematurity or intrauterine growth restriction (IUGR). Associated with ↑ risk of sudden infant death syndrome (SIDS) and with ↑ overall mortality. Other problems include impaired thermoregulation and immune function, hypoglycemia, polycythemia, and impaired neurocognitive/emotional development. Complications include infections, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and persistent fetal circulation.
**Lactation**

After parturition and delivery of placenta, rapid ↓ in progesterone disinhibits and initiates lactation. Suckling is required to maintain milk production and ejection, since ↑ nerve stimulation → ↑ oxytocin and prolactin.

Prolactin—induces and maintains lactation and ↓ reproductive function. Oxytocin—assists in milk letdown; also promotes uterine contractions. Breast milk is the ideal nutrition for infants < 6 months old. Contains maternal immunoglobulins (conferring passive immunity; mostly IgA), macrophages, lymphocytes. Breast milk reduces infant infections and is associated with ↓ risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Guidelines recommend exclusively breastfed infants get vitamin D and possibly iron supplementation.

Breastfeeding ↓ maternal risk of breast and ovarian cancer and facilitates mother-child bonding.

---

**Menopause**

Diagnosed by amenorrhea for 12 months. ↓ estrogen production due to age-linked decline in number of ovarian follicles. Average age at onset is 51 years (earlier in smokers). Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, ↑ androgens → hirsutism. ↑↑ FSH is specific for menopause (loss of negative feedback on FSH due to ↓ estrogen).

Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH. Causes HAVOCS: Hot flashes, Atrophy of the Vagina, Osteoporosis, Coronary artery disease, Sleep disturbances.

Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure).

---

**Androgens**

Testosterone, dihydrotestosterone (DHT), androstenedione.

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>TESTOSTERONE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHT and testosterone (testis), AnDrostenedione (ADrenal)</td>
<td>TESTOSTERONE:</td>
</tr>
<tr>
<td>POTENCY: DHT &gt; testosterone &gt; androstenedione.</td>
<td></td>
</tr>
</tbody>
</table>

**FUNCTION**

Testosterone:
- Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate).
- Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs.
- Deepening of voice.
- Closing of epiphyseal plates (via estrogen converted from testosterone).
- Libido.

DHT:
- Early—differentiation of penis, scrotum, prostate.
- Late—prostate growth, balding, sebaceous gland activity.

Testosterone is converted to DHT by 5α-reductase, which is inhibited by finasteride.

In the male, androgens are converted to estrogen by cytochrome P-450 aromatase (primarily in adipose tissue and testis).

Aromatase is the key enzyme in conversion of androgens to estrogen.

Exogenous testosterone → inhibition of hypothalamic–pituitary–gonadal axis → ↓ intratesticular testosterone → ↓ testicular size → azoospernia.
Spermatogenesis

Spermatogenesis begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermiogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoon.

“Gonium” is going to be a sperm; “Zoon” is “Zooming” to egg.

---

**Spermatogonium**
- Diploid (2N, 2C)

**1° spermatocyte**
- Diploid (2N, 4C)

**2° spermatocyte**
- Haploid (1N, 2C)

**Spermatid**
- Haploid (1N, 1C)

**Mature spermatozoon**
- Haploid (1N, 1C)

**Blood-testis barrier**

**Meiosis I**
- 46 single chromosomes (sex= X-Y)
- Replication (interphase)
- 46 sister chromatids (sex= X-X)
- 23 sister chromatids (sex= Y-Y)
- Meiosis I

**Meiosis II**

**Sperm**
- 23 single (sex= X)
- 23 single (sex= X)
- 23 single (sex= Y)
- 23 single (sex= Y)

**Acrosome**

**Head**

**Nucleus**

**Neck**

**Middle piece**

**Tail**

---

Note: Impaired tail mobility can lead to infertility (seen in ciliary dyskinesia/Kartagener syndrome).
Tanner stages of sexual development

Tanner stage is assigned independently to genitalia, pubic hair, and breast (e.g., a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair).

Stage I: No sexual hair.
- Flat-appearing chest with raised nipple.
- Pre-pubertal.
- Usually > 15 years.

Stage II: Pubic hair appears.
- Pubarche.
- Testicular enlargement.
- Breast bud forms.
- Thelarche.
- ~8–11.5 years.

Stage III: Coarsening of pubic hair.
- Breast enlarges, mound forms.
- ~11.5–13 years.

Stage IV: Coarse hair across pubis, sparing thigh.
- Breast enlarges, raised areola.
- Mound on mound.
- ~13–15 years.

Stage V: Coarse hair across pubis and medial thigh.
- Penis and testes enlarge to adult size.
- Adult breast contour, areola flattens.
- Usually > 15 years.
## REPRODUCTIVE—PATHOLOGY

**Sex chromosome disorders**

- **Klinefelter syndrome**
  - Male, 47,XXY.
  - Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution. May present with developmental delay. Presence of inactivated X chromosome (Barr body). Common cause of hypogonadism seen in infertility work-up.
  - Dysgenesis of seminiferous tubules → ↓ inhibin B → ↑ FSH.
  - Abnormal Leydig cell function → ↓ testosterone → ↑ LH → ↑ estrogen.

- **Turner syndrome**
  - Female, 45,XO.
  - Short stature (if untreated; preventable with growth hormone therapy), ovarian dysgenesis (streak ovary), shield chest, bicuspid aortic valve, coarctation (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney.
  - Most common cause of 1° amenorrhea. No Barr body.
  - Menopause before menarche.
  - ↓ estrogen leads to ↑ LH, FSH.
  - Sometimes due to mitotic error → mosaicism (eg, 45,XO/46,XX).
  - Pregnancy is possible in some cases (IVF, exogenous estradiol-17β and progesterone).

- **Double Y males**
  - 47, XYY.
  - Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.

- **Ovotesticular disorder of sex development**
  - 46,XX > 46,XY.
  - Both ovarian and testicular tissue present (ovotestis); ambiguous genitalia. Previously called true hermaphroditism.
### Diagnosing disorders of sex hormones

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>LH</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>Defective androgen receptor</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>Testosterone-secreting tumor, exogenous steroids</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>Hypergonadotropic hypogonadism (1°)</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>Hypogonadotropic hypogonadism (2°)</td>
</tr>
</tbody>
</table>

### Other disorders of sex development

Disagreement between the phenotypic sex (external genitalia, influenced by hormonal levels) and the gonadal sex (testes vs ovaries, corresponds with Y chromosome). Includes the terms pseudohermaphrodite, hermaphrodite, and intersex.

- **46,XX DSD**
  - Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (eg, congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).

- **46,XY DSD**
  - Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).

### Disorders by physical characteristics

<table>
<thead>
<tr>
<th>Uterus</th>
<th>Breasts</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>⊕</td>
<td>⊝</td>
<td>Hypergonadotropic hypogonadism (eg, Turner syndrome, genetic mosaicism, pure gonadal dysgenesis) Hypogonadotropic hypogonadism (eg, CNS lesions, Kallmann syndrome)</td>
</tr>
<tr>
<td>⊝</td>
<td>⊕</td>
<td>Uterovaginal agenesis in genotypic female or androgen insensitivity in genotypic male</td>
</tr>
<tr>
<td>⊝</td>
<td>⊝</td>
<td>Male genotype with insufficient production of testosterone</td>
</tr>
</tbody>
</table>

### Placental aromatase deficiency

Inability to synthesize estrogens from androgens. Masculinization of female (46,XX DSD) infants (ambiguous genitalia), ↑ serum testosterone and androstenedione. Can present with maternal virilization during pregnancy (fetal androgens cross the placenta).

### Androgen insensitivity syndrome

Defect in androgen receptor resulting in normal-appearing female (46,XY DSD); female external genitalia with scant axillary and pubic hair, rudimentary vagina; uterus and fallopian tubes absent. Patients develop normal functioning testes (often found in labia majora; surgically removed to prevent malignancy). ↑ testosterone, estrogen, LH (vs sex chromosome disorders).

### 5α-reductase deficiency

Autosomal recessive; sex limited to genetic males (46,XY DSD). Inability to convert testosterone to DHT. Ambiguous genitalia until puberty, when ↑ testosterone causes masculinization/↑ growth of external genitalia. Testosterone/estrogen levels are normal; LH is normal or ↑. Internal genitalia are normal.

### Kallmann syndrome

Hydatidiform mole

Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast). Presents with vaginal bleeding, uterine enlargement more than expected, pelvic pressure/pain. Associated with hCG-mediated sequelae: early preeclampsia (before 20 weeks), theca-lutein cysts, hyperemesis gravidarum, hyperthyroidism. Treatment: dilation and curettage and methotrexate. Monitor β-hCG.

<table>
<thead>
<tr>
<th></th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td>46,XX; 46,XY</td>
<td>69,XXX; 69,XXY; 69,XY Y</td>
</tr>
<tr>
<td>Components</td>
<td>Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA)</td>
<td>2 sperm + 1 egg</td>
</tr>
<tr>
<td>Fetal parts</td>
<td>No</td>
<td>Yes (partial = fetal parts)</td>
</tr>
<tr>
<td>Uterine size</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>hCG</td>
<td>↑↑↑↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Imaging</td>
<td>“Honeycombed” uterus or “clusters of grapes” A, “snowstorm” on ultrasound B</td>
<td>Fetal parts</td>
</tr>
<tr>
<td>Risk of Malignancy (gestational trophoblastic neoplasia)</td>
<td>15–20%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Risk of Choriocarcinoma</td>
<td>2%</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Choriocarcinoma

Rare; can develop during or after pregnancy in mother or baby. Malignancy of trophoblastic tissue A (cytotrophoblasts, syncytiotrophoblasts); no chorionic villi present. ↑ frequency of bilateral/multiple theca-lutein cysts. Presents with abnormal ↑ β-hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs → “cannonball” metastases B.
Pregnancy complications

**Abruptio placentae**
Premature separation (partial or complete) of placenta from uterine wall before delivery of infant. Risk factors: trauma (e.g., motor vehicle accident), smoking, hypertension, preeclampsia, cocaine abuse.
Presentation: **abrupt**, painful bleeding (concealed or apparent) in third trimester; possible DIC, maternal shock, fetal distress. Life threatening for mother and fetus.

**Morbidly adherent placenta**
Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section or uterine surgery involving myometrium, inflammation, placenta previa, advanced maternal age, multiparity. Three types distinguishable by the depth of penetration:
- **Placenta accreta**—placenta attaches to myometrium without penetrating it; most common type.
- **Placenta increta**—placenta penetrates into myometrium.
- **Placenta percreta**—placenta penetrates (“perforates”) through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder (can result in hematuria).

Presentation: often detected on ultrasound prior to delivery. No separation of placenta after delivery → postpartum bleeding (can cause Sheehan syndrome).

**Placenta previa**
Attachment of placenta to lower uterine segment over (or < 2 cm from) internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding. A “previ”ew of the placenta is visible through cervix.
Pregnancy complications (continued)

**Vasa previa**
Fetal vessels run over, or in close proximity to, cervical os. May result in vessel rupture, exsanguination, fetal death. Presents with triad of membrane rupture, painless vaginal bleeding, fetal bradycardia (< 110 beats/min). Emergency C-section usually indicated. Frequently associated with velamentous umbilical cord insertion (cord inserts in chorioamniotic membrane rather than placenta → fetal vessels travel to placenta unprotected by Wharton jelly).

**Postpartum hemorrhage**
Due to 4 T’s: Tone (uterine atony; most common), Trauma (lacerations, incisions, uterine rupture), Thrombin (coagulopathy), Tissue (retained products of conception).

**Ectopic pregnancy**
Implantation of fertilized ovum in a site other than the uterus, most often in ampulla of fallopian tube. Suspect with history of amenorrhea, lower-than-expected rise in hCG based on dates, and sudden lower abdominal pain; confirm with ultrasound. Often clinically mistaken for appendicitis. Pain +/- bleeding.

Risk factors:
- Prior ectopic pregnancy
- History of infertility
- Salpingitis (PID)
- Ruptured appendix
- Prior tubal surgery
- Smoking
- Advanced maternal age

**Amniotic fluid abnormalities**

**Polyhydramnios**
Too much amniotic fluid. Often idiopathic, but associated with fetal malformations (eg, esophageal/duodenal atresia, anencephaly; both result in inability to swallow amniotic fluid), maternal diabetes, fetal anemia, multiple gestations.

**Oligohydramnios**
Too little amniotic fluid. Associated with placental insufficiency, bilateral renal agenesis, posterior urethral valves (in males) and resultant inability to excrete urine. Any profound oligohydramnios can cause Potter sequence.
### Hypertension in pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational hypertension</strong></td>
<td>BP &gt; 140/90 mm Hg after 20th week of gestation. No pre-existing hypertension. No proteinuria or end-organ damage.</td>
<td>Treatment: antihypertensives (Hydralazine, α-Methyldopa, Labetalol, Nifedipine), deliver at 37–39 weeks. <strong>Hypertensive Moms Love Nifedipine.</strong></td>
</tr>
<tr>
<td><strong>Preeclampsia</strong></td>
<td>New-onset hypertension with either proteinuria or end-organ dysfunction after 20th week of gestation (&lt; 20 weeks suggests molar pregnancy). Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. Incidence in patients with pre-existing hypertension, diabetes, chronic renal disease, autoimmune disorders (eg, antiphospholipid antibody syndrome). Complications: placental abruption, coagulopathy, renal failure, pulmonary edema, uteroplacental insufficiency; may lead to eclampsia (+ seizures) and/or HELLP syndrome.</td>
<td>Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery of fetus.</td>
</tr>
<tr>
<td><strong>Eclampsia</strong></td>
<td>Preeclampsia + maternal seizures. Maternal death due to stroke, intracranial hemorrhage, or ARDS.</td>
<td>Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.</td>
</tr>
</tbody>
</table>

### Gynecologic tumor epidemiology

Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination. Prognosis: **Cervical** (best prognosis, diagnosed < 45 years old) > **Endometrial** (middle-aged, about 55 years old) > **Ovarian** (worst prognosis, > 65 years). CEOs often go from **best** to **worst** as they get older.
# Vulvar pathology

<table>
<thead>
<tr>
<th>Non-neoplastic</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bartholin cyst and abscess</strong></td>
<td>Due to blockage of Bartholin gland duct causing accumulation of gland fluid. May lead to abscess 2° to obstruction and inflammation. Usually in reproductive-age females. Associated with <em>Neisseria gonorrhoeae</em> infections.</td>
<td></td>
</tr>
<tr>
<td><strong>Lichen sclerosus</strong></td>
<td>Thinning of epidermis with fibrosis/sclerosis of dermis. Presents with porcelain-white plaques with a red or violet border. Skin fragility with erosions can be observed. Most common in postmenopausal women. Benign, but slightly increased risk for SCC.</td>
<td></td>
</tr>
<tr>
<td><strong>Lichen simplex chronicus</strong></td>
<td>Hyperplasia of vulvar squamous epithelium. Presents with leathery, thick vulvar skin with enhanced skin markings due to chronic rubbing or scratching. Benign, no risk of SCC.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neoplastic</th>
<th></th>
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<tbody>
<tr>
<td><strong>Vulvar carcinoma</strong></td>
<td>Carcinoma from squamous epithelial lining of vulva. Rare. Presents with leukoplakia, biopsy often required to distinguish carcinoma from other causes. HPV-related vulvar carcinoma—associated with high-risk HPV types 16, 18. Risk factors: multiple partners, early coitarche. Usually in reproductive-age females. Non-HPV vulvar carcinoma—usually from long-standing lichen sclerosus. Females &gt; 70 years old.</td>
<td></td>
</tr>
<tr>
<td><strong>Extramammary Paget disease</strong></td>
<td>Intraepithelial adenocarcinoma. Carcinoma in situ, low risk of underlying carcinoma. Presents with pruritus, erythema, crusting, ulcers.</td>
<td></td>
</tr>
</tbody>
</table>

![Images of vulvar pathology](image1.png)

### Vaginal tumors

<p>| | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Vaginal squamous cell carcinoma</strong></td>
<td>Usually 2° to cervical SCC; 1° vaginal carcinoma rare.</td>
<td></td>
</tr>
<tr>
<td><strong>Clear cell adenocarcinoma</strong></td>
<td>Affects women who had exposure to DES in utero.</td>
<td></td>
</tr>
<tr>
<td><strong>Sarcoma botryoides</strong></td>
<td>Embryonal rhabdomyosarcoma variant. Affects girls &lt; 4 years old; spindle-shaped cells; desmin. Presents with clear, grape-like, polypoid mass emerging from vagina.</td>
<td></td>
</tr>
</tbody>
</table>
Cervical pathology

**Dysplasia and carcinoma in situ**

Disordered epithelial growth; begins at basal layer of squamocolumnar junction (transformation zone) and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (severe, irreversible dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV-16 and HPV-18, which produce both the E6 gene product (inhibits p53) and E7 gene product (inhibits pRb); koilocytes are pathognomonic of HPV infection. May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital).

Risk factors: multiple sexual partners (#1), smoking, early coitarche, DES exposure, immunocompromise (eg, HIV, transplant).

**Invasive carcinoma**

Often squamous cell carcinoma. Pap smear can detect cervical dysplasia before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → renal failure.

---

**Primary ovarian insufficiency**

Also known as premature ovarian failure. Premature atresia of ovarian follicles in women of reproductive age. Most often idiopathic; associated with chromosomal abnormalities (especially in females <30 years). Need karyotype screening. Patients present with signs of menopause after puberty but before age 40. ↓ estrogen, ↓ LH, ↑ FSH.

---

**Most common causes of anovulation**

Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency, chromosomal abnormalities (eg, Turner syndrome).

---

**Polycystic ovarian syndrome**

Also known as Stein-Leventhal syndrome. Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH, ↓ androgens (eg, testosterone) from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of ↓ fertility in women.

Enlarged, bilateral cystic ovaries presents with amenorrhea/oligomenorrhea, hirsutism, acne, ↓ fertility. Associated with obesity. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.

Treatment: cycle regulation via weight reduction (↓ peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene, metformin to induce ovulation; spironolactone, ketoconazole (antiandrogens) to treat hirsutism.
### Ovarian cysts

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular cyst</td>
<td>Distention of unruptured graafian follicle. May be associated with hyperestrogenism, endometrial hyperplasia. Most common ovarian mass in young women.</td>
</tr>
<tr>
<td>Theca-lutein cyst</td>
<td>Often bilateral/multiple. Due to gonadotropin stimulation. Associated with choriocarcinoma and hydatidiform moles.</td>
</tr>
</tbody>
</table>

### Ovarian neoplasms

Most common adnexal mass in women > 55 years old. Can be benign or malignant. Arise from surface epithelium, germ cells, or sex cord stromal tissue. Majority of malignant tumors are epithelial (serous cystadenocarcinoma most common). Risk ↑ with advanced age, infertility, endometriosis, PCOS, genetic predisposition BRCA1 or BRCA2 mutation, Lynch syndrome, strong family history. Risk ↑ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation. Presents with adnexal mass, abdominal distension, bowel obstruction, pleural effusion. Monitor response to therapy/relapse by measuring CA 125 levels (not good for screening).

#### Surface epithelium tumors (benign)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous cystadenoma</td>
<td>Multiloculated, large. Lined by mucus-secreting epithelium.</td>
</tr>
<tr>
<td>Endometrioma</td>
<td>Endometriosis within ovary with cyst formation. Presents with pelvic pain, dysmenorrhea, dyspareunia; symptoms may vary with menstrual cycle. “Chocolate cyst”—endometrioma filled with dark, reddish-brown blood. Complex mass on ultrasound.</td>
</tr>
</tbody>
</table>

#### Germ cell tumors (benign)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature cystic teratoma</td>
<td>Germ cell tumor, most common ovarian tumor in females 10–30 years old. Cystic mass containing elements from all 3 germ layers (eg, teeth, hair, sebum). Can present with pain due to ovarian enlargement or torsion. A monodermal form with thyroid tissue (struma ovarii) uncommonly presents with hyperthyroidism.</td>
</tr>
</tbody>
</table>

#### Sex cord stromal tumor (benign)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thecoma</td>
<td>Like granulosa cell tumors, may produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal woman.</td>
</tr>
</tbody>
</table>

#### Other (benign)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</table>
**Ovarian neoplasms (continued)**

<table>
<thead>
<tr>
<th>Surface epithelium tumors (malignant)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serous cystadenocarcinoma</strong></td>
<td>Most common malignant ovarian neoplasm, frequently bilateral. Psammoma bodies.</td>
</tr>
<tr>
<td><strong>Mucinous cystadenocarcinoma</strong></td>
<td>Rare malignant mucinous ovarian epithelial tumor. May be metastatic from appendiceal or other GI tumors. Can result in pseudomyxoma peritonei—intraperitoneal accumulation of mucinous material.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Germ cell tumors (malignant)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysgerminoma</strong></td>
<td>Most common in adolescents. Equivalent to male seminoma but rarer. 1% of all ovarian tumors; 30% of germ cell tumors. Sheets of uniform “fried egg” cells. hCG, LDH = tumor markers.</td>
</tr>
<tr>
<td><strong>Immature teratoma</strong></td>
<td>Aggressive, contains fetal tissue, neuroectoderm. Commonly diagnosed before age 20. Typically represented by immature/embryonic-like neural tissue.</td>
</tr>
<tr>
<td><strong>Yolk sac tumor</strong></td>
<td>Also known as ovarian endodermal sinus tumor. Aggressive, in ovaries or testes and sacrococcygeal area in young children. Most common tumor in male infants. Yellow, friable (hemorrhagic), solid mass. 50% have Schiller-Duval bodies (resemble glomeruli). AFP = tumor marker.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex cord stromal tumors (malignant)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Granulosa cell tumor</strong></td>
<td>Most common malignant stromal tumor. Predominantly women in their 50s. Often produces estrogen and/or progesterone and presents with postmenopausal bleeding, sexual precocity (in pre-adolescents), breast tenderness. Histology shows Call-Exner bodies (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles). “Give Granny a Call!”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other (malignant)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Krukenberg tumor</strong></td>
<td>GI malignancy that metastasizes to ovaries → mucin-secreting signet cell adenocarcinoma. Commonly presents as bilateral ovarian masses.</td>
</tr>
</tbody>
</table>
### Endometrial conditions

**Polyp**
Well-circumscribed collection of endometrial tissue within uterine wall. May contain smooth muscle cells. Can extend into endometrial cavity in the form of a polyp. May be asymptomatic or present with painless abnormal uterine bleeding.

**Adenomyosis**
Extension of endometrial tissue (glandular) into uterine myometrium. Caused by hyperplasia of basal layer of endometrium. Presents with dysmenorrhea, menorrhagia, uniformly enlarged, soft, globular uterus.
Treatment: GnRH agonists, hysterectomy or excision of an organized adenomyoma.

**Asherman syndrome**
Adhesions and/or fibrosis of the endometrium. Presents with infertility, recurrent pregnancy loss, abnormal uterine bleeding, pelvic pain. Often associated with dilation and curettage of intrauterine cavity.

**Leiomyoma (fibroid)**
Most common tumor in females. Often presents with multiple discrete tumors. Incidence in African Americans. Benign smooth muscle tumor; malignant transformation to leiomyosarcoma is rare. Estrogen sensitive—tumor size with pregnancy and with menopause. Peak occurrence at 20–40 years old. May be asymptomatic, cause abnormal uterine bleeding, or result in miscarriage. Severe bleeding may lead to iron deficiency anemia. Whorled pattern of smooth muscle bundles with well-demarcated borders.

**Endometrial hyperplasia**
Abnormal endometrial gland proliferation usually caused by excess estrogen stimulation. Risk for endometrial carcinoma; nuclear atypia is greater risk factor than complex (vs simple) architecture. Presents as postmenopausal vaginal bleeding. Risk factors include anovulatory cycles, hormone replacement therapy, polycystic ovarian syndrome, granulosa cell tumor.

**Endometrial carcinoma**

**Endometritis**
Inflammation of endometrium associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (eg, IUD). Retained material in uterus promotes infection by bacterial flora from vagina or intestinal tract. Chronic endometritis characterized by presence of plasma cells on histology. Treatment: gentamicin + clindamycin +/- ampicillin.

**Endometriosis**
Non-neoplastic endometrium-like glands/stroma outside endometrial cavity. Can be found anywhere; most common sites are ovary (frequently bilateral), pelvis, peritoneum. In ovary, appears as endometrioma (blood-filled “chocolate cysts” oval structures above and below asterisks in E)). May be due to retrograde flow, metaplastic transformation of multipotent cells, transportation of endometrial tissue via lymphatic system. Characterized by cyclic pelvic pain, bleeding, dysmenorrhea, dyspareunia, dyschezia (pain with defecation), infertility; normal-sized uterus. Treatment: NSAIDs, continuous OCPs, progestins, GnRH agonists, danazol, laparoscopic removal.
Breast pathology

Benign breast disease

**Fibrocystic changes**
Most common in premenopausal women < 35 years old. Present with premenstrual breast pain or lumps; often bilateral and multifocal. Nonproliferative lesions include simple cysts (fluid-filled duct dilation, blue dome), papillary apocrine change/metaplasia, stromal fibrosis. Risk of cancer is usually not increased. Subtypes include:

- **Sclerosing adenosis**—acini and stromal fibrosis, associated with calcifications. Slight (1.5–2 ×) ↑ risk for cancer.
- **Epithelial hyperplasia**—cells in terminal ductal or lobular epithelium. ↑ risk of carcinoma with atypical cells.

**Inflammatory processes**
Fat necrosis—benign, usually painless, lump due to injury to breast tissue. Calcified oil cyst on mammography; necrotic fat and giant cells on biopsy. Up to 50% of patients may not report trauma. **Lactational mastitis**—occurs during breastfeeding, ↑ risk of bacterial infection through cracks in nipple. *S. aureus* is most common pathogen. Treat with antibiotics and continue breastfeeding.

**Benign tumors**
Fibroadenoma—most common in women < 35 years old. Small, well-defined, mobile mass. ↑ size and tenderness with ↑ estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased.

*Intraductal papilloma*—small fibroepithelial tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight (1.5–2 ×) ↑ risk for cancer.

**Phyllodes tumor**—large mass of connective tissue and cysts with “leaf-like” lobulations. Most common in 5th decade. Some may become malignant.

**Gynecomastia**
Breast enlargement in males due to ↑ estrogen compared with androgen activity. Physiologic in newborn, pubertal, and elderly males, but may persist after puberty. Other causes include cirrhosis, hypogonadism (eg, Klinefelter syndrome), testicular tumors, and drugs (Spironolactone, **Hormones**, Cimetidine, Finasteride, Ketoconazole: “Some Hormones Create Funny Knockers”).
Malignant breast tumors

Commonly postmenopausal. Usually arise from terminal duct lobular unit. Amplification/overexpression of estrogen/progesterone receptors or c-erbB2 (HER-2, an EGF receptor) is common; triple negative (ER $\odot$, PR $\odot$, and Her2/Neu $\odot$) more aggressive; type affects therapy and prognosis. Axillary lymph node involvement indicating metastasis is the most important prognostic factor in early-stage disease. Most often located in upper-outer quadrant of breast.

Risk factors: ↑ estrogen exposure, ↑ total number of menstrual cycles, older age at 1st live birth, obesity (↑ estrogen exposure as adipose tissue converts androstenedione to estrone), BRCA1 or BRCA2 gene mutations, African American ethnicity (↑ risk for triple $\ominus$ breast cancer).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CHARACTERISTICS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>Fills ductal lumen (black arrow in A indicates neoplastic cells in duct; blue arrow shows engorged blood vessel). Arises from ductal atypia. Often seen early as microcalcifications on mammography.</td>
<td>Early malignancy without basement membrane penetration.</td>
</tr>
<tr>
<td>Comedocarcinoma</td>
<td>Ductal, central necrosis (arrow in B). Subtype of DCIS.</td>
<td></td>
</tr>
<tr>
<td>Paget disease</td>
<td>Results from underlying DCIS or invasive breast cancer. Eczematous patches on nipple C. Paget cells = intraepithelial adenocarcinoma cells.</td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>Firm, fibrous, “rock-hard” mass with sharp margins and small, glandular, duct-like cells. Tumor can deform suspensory ligaments → dimpling of skin. Classic morphology: “stellate” infiltration.</td>
<td>Most common (~ 75% of all breast cancers).</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>Orderly row of cells (“single file” D), due to ↓ E-cadherin expression.</td>
<td>Often bilateral with multiple lesions in the same location.</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Fleshy, cellular, lymphocytic infiltrate.</td>
<td>Good prognosis.</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>Dermal lymphatic invasion by breast carcinoma. Peau d’orange (skin texture resembles orange peel E due to edema leading to tightening of Cooper’s suspensory ligament); neoplastic cells block lymphatic drainage.</td>
<td>Poor prognosis (50% survival at 5 years). Often mistaken for mastitis or Paget disease.</td>
</tr>
</tbody>
</table>
### Penile pathology

#### Peyronie disease

#### Ischemic priapism
Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs block venous drainage of corpus cavernosum vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

#### Squamous cell carcinoma
More common in Asia, Africa, South America. Precursor in situ lesions: Bowen disease (in penile shaft, presents as leukoplakia), erythroplasia of Queyrat (carcinoma in situ of the glans, presents as erythroplakia), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with uncircumcised males and HPV.

### Cryptorchidism
Undescended testis (one or both); impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are mostly unaffected by temperature); associated with ↑ risk of germ cell tumors. Prematurity ↑ risk of cryptorchidism. ↓ inhibin B, ↑ FSH, ↑ LH; testosterone ↓ in bilateral cryptorchidism, normal in unilateral.

### Testicular torsion
Rotation of testicle around spermatic cord and vascular pedicle. Commonly presents in males 12–18 years old. Characterized by acute, severe pain, high-riding testis, and absent cremasteric reflex.
Treatment: surgical correction (orchiopexy) within 6 hours, manual detorsion if surgical option unavailable in timeframe. If testis is not viable, orchiectomy. Orchiopexy, when performed, should be bilateral because the contralateral testis is at risk for subsequent torsion.

### Varicocele
Dilated veins in pampiniform plexus due to ↑ venous pressure; most common cause of scrotal enlargement in adult males; most often on left side because of ↑ resistance to flow from left gonadal vein drainage into left renal vein; can cause infertility because of ↑ temperature; diagnosed by standing clinical exam/Valsalva maneuver (distension on inspection and “bag of worms” on palpation; augmented by Valsalva) or ultrasound with Doppler; does not transilluminate.
Treatment: consider surgical ligation or embolization if associated with pain or infertility.

### Extragonadal germ cell tumors
Arise in midline locations. In adults, most commonly in retroperitoneum, mediastinum, pineal, and suprasellar regions. In infants and young children, sacrococcygeal teratomas are most common.
### Scrotal masses
Benign scrotal lesions present as testicular masses that can be transilluminated (vs solid testicular tumors).

### Congenital hydrocele
Common cause of scrotal swelling due to incomplete obliteration of processus vaginalis. Most spontaneously resolve by 1 year old. Transilluminating swelling.

### Acquired hydrocele
Scrotal fluid collection usually due to infection, trauma, tumor. If bloody → hematocele.

### Spermatocele
Cyst due to dilated epididymal duct or rete testis. Paratesticular fluctuant nodule.

### Testicular germ cell tumors
~95% of all testicular tumors. Most often occur in young men. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Do not transilluminate. Usually not biopsied (risk of seeding scrotum), removed via radical orchiectomy.

#### Seminoma
Malignant; painless, homogenous testicular enlargement; most common testicular tumor. Does not occur in infancy. Large cells in lobules with watery cytoplasm and “fried egg” appearance. ↑ placental ALP. Highly radiosensitive. Late metastasis, excellent prognosis. Similar to dysgerminoma in females.

#### Yolk sac tumor
Also known as testicular endodermal sinus tumor. Yellow, mucinous. Aggressive malignancy of testes, analogous to ovarian yolk sac tumor. Schiller-Duval bodies resemble primitive glomeruli. ↑ AFP is highly characteristic. Most common testicular tumor in boys < 3 years old.

#### Choriocarcinoma
Malignant, ↑ hCG. Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain. May produce gynecomastia, symptoms of hyperthyroidism (β-subunit of hCG is structurally similar to LH, FSH, TSH).

#### Teratoma
Unlike in females, mature teratoma in adult males may be malignant. Benign in children.

#### Embryonal carcinoma
Malignant, hemorrhagic mass with necrosis; painful; worse prognosis than seminoma. Often glandular/papillary morphology. “Pure” embryonal carcinoma is rare; most commonly mixed with other tumor types. May be associated with ↑ hCG and normal AFP levels when pure (↑ AFP when mixed).

### Testicular non–germ cell tumors
5% of all testicular tumors. Mostly benign.

#### Leydig cell tumor
Golden brown color; contains Reinke crystals (eosinophilic cytoplasmic inclusions). Produces androgens or estrogens → gynecomastia in men, precocious puberty in boys.

#### Sertoli cell tumor
Androblastoma from sex cord stroma.

#### Testicular lymphoma
Most common testicular cancer in older men. Not a 1° cancer; arises from metastatic lymphoma to testes. Aggressive.
Benign prostatic hyperplasia

Common in men > 50 years old. Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of periurethral (lateral and middle) lobes, which compress the urethra into a vertical slit. Not premalignant. Often presents with ↑ frequency of urination, nocturia, difficulty starting and stopping urine stream, dysuria. May lead to distention and hypertrophy of bladder, hydronephrosis, UTIs. ↑ free prostate-specific antigen (PSA).

Treatment: $\alpha_1$-antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; 5α-reductase inhibitors (eg, finasteride); PDE-5 inhibitors (eg, tadalafil); surgical resection (eg, TURP, ablation).

Prostatitis

Characterized by dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate. Acute bacterial prostatitis—in older men most common bacterium is $E$ coli; in young males consider $C$ trachomatis, $N$ gonorrhoeae.

Chronic prostatitis—either bacterial or nonbacterial (eg, 2° to previous infection, nerve problems, chemical irritation).

Prostatic adenocarcinoma

Common in men > 50 years old. Arises most often from posterior lobe (peripheral zone) of prostate gland and is most frequently diagnosed by ↑ PSA and subsequent needle core biopsies. Prostatic acid phosphatase (PAP) and PSA are useful tumor markers (↑ total PSA, with ↓ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by lower back pain and ↓ serum ALP and PSA.
Control of reproductive hormones

Hypothalamus

via blocking negative feedback

GnRH antagonists

GnRH agonists

Anterior pituitary

LH FSH

Ovary Testis

FSH LH

Testosterone

5α-reductase

Dihydrotestosterone

Androgen-receptor complex

Gene expression in androgen-responsive cells

Androstenedione

P-450c17

Aromatase

Estradiol

Estrone

Estriol

Anastrozole

Selective estrogen-receptor modulators

Gene expression in estrogen-responsive cells

Oral contraceptives Danazol

Ketoconazole Danazol

Anastrozole

Selective estrogen-receptor modulators

Gene expression in estrogen-responsive cells

Ketoconazole

Danazol

Oral contraceptives Danazol

Anastrozole

Selective estrogen-receptor modulators

Gene expression in estrogen-responsive cells

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Selective estrogen-receptor modulators

Gene expression in estrogen-responsive cells

Ketoconazole

Danazol
**Leuprolide**

**MECHANISM**
GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion (downregulates GnRH receptor in pituitary → ↓ FSH and ↓ LH).

**CLINICAL USE**
Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility.

**ADVERSE EFFECTS**
Hypogonadism, ↓ libido, erectile dysfunction, nausea, vomiting.

Leuprolide can be used in lieu of GnRH.

---

**Estrogens**

Ethinyl estradiol, DES, mestranol.

**MECHANISM**
Bind estrogen receptors.

**CLINICAL USE**
Hypogonadism or ovarian failure, menstrual abnormalities (combined OCPs), hormone replacement therapy in postmenopausal women.

**ADVERSE EFFECTS**
↑ risk of endometrial cancer (when given without progesterone), bleeding in postmenopausal women, clear cell adenocarcinoma of vagina in females exposed to DES in utero, ↑ risk of thrombi. Contraindications—ER ⊕ breast cancer, history of DVTs, tobacco use in women > 35 years old.

---

**Selective estrogen receptor modulators**

**Clomiphene**
Antagonist at estrogen receptors in hypothalamus. Prevents normal feedback inhibition and ↑ release of LH and FSH from pituitary, which stimulates ovulation. Used to treat infertility due to anovulation (eg, PCOS). SERMs may cause hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances.

**Tamoxifen**
Antagonist at breast; agonist at bone, uterus; ↑ risk of thromboembolic events and endometrial cancer. Used to treat and prevent recurrence of ER/PR ⊕ breast cancer.

**Raloxifene**
Antagonist at breast, uterus; agonist at bone; ↑ risk of thromboembolic events but no increased risk of endometrial cancer (vs tamoxifen); used primarily to treat osteoporosis.

---

**Aromatase inhibitors**

Anastrozole, letrozole, exemestane.

**MECHANISM**
Inhibit peripheral conversion of androgens to estrogen.

**CLINICAL USE**
ER ⊕ breast cancer in postmenopausal women.

---

**Hormone replacement therapy**

Used for relief or prevention of menopausal symptoms (eg, hot flashes, vaginal atrophy), osteoporosis (↑ estrogen, ↓ osteoclast activity).

Unopposed estrogen replacement therapy; ↑ risk of endometrial cancer, progesterone/progestin is added. Possible increased cardiovascular risk.
### Progestins
Levonorgestrel, medroxyprogesterone, etonogestrel, norethindrone, megestrol, and many others when combined with estrogen.

**MECHANISM**
Bind progesterone receptors, ↑ growth and ↑ vascularization of endometrium, thicken cervical mucus.

**CLINICAL USE**
Contraception (forms include pill, intrauterine device, implant, depot injection), endometrial cancer, abnormal uterine bleeding. Progestin challenge: presence of withdrawal bleeding excludes anatomic defects (eg, Asherman syndrome) and chronic anovulation without estrogen.

### Antiprogestins
Mifepristone, ulipristal.

**MECHANISM**
Competitive inhibitors of progestins at progesterone receptors.

**CLINICAL USE**
Termination of pregnancy (mifepristone with misoprostol); emergency contraception (ulipristal).

### Combined contraception
Progestins and ethinyl estradiol; forms include pill, patch, vaginal ring. Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge → no LH surge → no ovulation. Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus. Progestins also inhibit endometrial proliferation → endometrium is less suitable to the implantation of an embryo. Contraindications: smokers > 35 years old (↑ risk of cardiovascular events), patients with ↑ risk of cardiovascular disease (including history of venous thromboembolism, coronary artery disease, stroke), migraine (especially with aura), breast cancer, liver disease.

### Copper intrauterine device
Produces local inflammatory reaction toxic to sperm and ova, preventing fertilization and implantation; hormone free.

**CLINICAL USE**
Long-acting reversible contraception. Most effective emergency contraception.

**ADVERSE EFFECTS**
Heavier or longer menses, dysmenorrhea. Risk of PID with insertion (contraindicated in active pelvic infection).

### Tocolytics
Medications that relax the uterus; include terbutaline (β₂-agonist action), nifedipine (Ca²⁺ channel blocker), indomethacin (NSAID). Used to ↓ contraction frequency in preterm labor and allow time for administration of steroids (to promote fetal lung maturity) or transfer to appropriate medical center with obstetrical care.

### Danazol
Synthetic androgen that acts as partial agonist at androgen receptors.

**CLINICAL USE**
Endometriosis, hereditary angioedema.

**ADVERSE EFFECTS**
Weight gain, edema, acne, hirsutism, masculinization, ↓ HDL levels, hepatotoxicity, pseudotumor cerebri.
### Testosterone, methyltestosterone

**MECHANISM**
Agonists at androgen receptors.

**CLINICAL USE**
Treat hypogonadism and promote development of 2° sex characteristics; stimulate anabolism to promote recovery after burn or injury.

**ADVERSE EFFECTS**
Masculinization in females; ↑ intratesticular testosterone in males by inhibiting release of LH (via negative feedback) → gonadal atrophy. Premature closure of epiphyseal plates. ↑ LDL, ↓ HDL.

### Antiandrogens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finasteride</strong></td>
<td>5α-reductase inhibitor (↑ conversion of testosterone to DHT). Used for BPH and male-pattern baldness. Adverse effects: gynecomastia and sexual dysfunction.</td>
<td>Testosterone 5α-reductase DHT (more potent).</td>
</tr>
<tr>
<td><strong>Flutamide</strong></td>
<td>Nonsteroidal competitive inhibitor at androgen receptors. Used for prostate carcinoma.</td>
<td></td>
</tr>
<tr>
<td><strong>Ketoconazole</strong></td>
<td>Inhibits steroid synthesis (inhibits 17,20 desmolase/17α-hydroxylase).</td>
<td>Used in PCOS to reduce androgenic symptoms. Both can cause gynecomastia and amenorrhea.</td>
</tr>
<tr>
<td><strong>Spironolactone</strong></td>
<td>Inhibits steroid binding, 17,20 desmolase/17α-hydroxylase.</td>
<td></td>
</tr>
</tbody>
</table>

### Tamsulosin

α1-antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for α1A/D receptors (found on prostate) vs vascular α1B receptors.

### Phosphodiesterase type 5 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sildenafil, vardenafil, tadalafil</strong></td>
<td>Inhibit PDE-5 → ↑ cGMP → prolonged smooth muscle relaxation in response to NO → ↑ blood flow in corpus cavernosum of penis, ↓ pulmonary vascular resistance.</td>
<td>Sildenafil, vardenafil, and tadalafil fill the penis.</td>
</tr>
<tr>
<td><strong>Tamsulosin</strong></td>
<td>α1-antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for α1A/D receptors (found on prostate) vs vascular α1B receptors.</td>
<td>Erectile dysfunction, pulmonary hypertension, BPH (tadalafil only).</td>
</tr>
<tr>
<td><strong>Minoxidil</strong></td>
<td>Direct arteriolar vasodilator.</td>
<td>Androgenetic alopecia (pattern baldness), severe refractory hypertension.</td>
</tr>
</tbody>
</table>

**ADVERSE EFFECTS**
“There’s so much pollution in the air now that if it weren’t for our lungs, there’d be no place to put it all.”

—Robert Orben

“Freedom is the oxygen of the soul.”

—Moshe Dayan

“Whenever I feel blue, I start breathing again.”

—L. Frank Baum

“Life is not the amount of breaths you take; it’s the moments that take your breath away.”

—Will Smith, Hitch

Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Know obstructive vs restrictive lung disorders, V/Q mismatch, lung volumes, mechanics of respiration, and hemoglobin physiology. Lung cancers and other causes of lung masses are high yield. Be comfortable reading basic chest X-rays, CT scans, and PFTs.
Lung development

Occurs in five stages. Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4. Every Pulmonologist Can See Alveoli.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>STRUCTURAL DEVELOPMENT</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic (weeks 4–7)</td>
<td>Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.</td>
<td>Errors at this stage can lead to tracheoesophageal fistula.</td>
</tr>
<tr>
<td>Canalicular (weeks 16–25)</td>
<td>Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.</td>
<td>Airways increase in diameter. Respiration capable at 25 weeks. Pneumocytes develop starting at 20 weeks.</td>
</tr>
<tr>
<td>Saccular (week 26–birth)</td>
<td>Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae.</td>
<td></td>
</tr>
<tr>
<td>Alveolar (week 36–8 years)</td>
<td>Terminal sacs → adult alveoli (due to 2° septation). In utero, “breathing” occurs via aspiration and expulsion of amniotic fluid → ↑ vascular resistance through gestation. At birth, fluid gets replaced with air → ↓ in pulmonary vascular resistance.</td>
<td>At birth: 20–70 million alveoli. By 8 years: 300–400 million alveoli.</td>
</tr>
</tbody>
</table>

Congenital lung malformations

**Pulmonary hypoplasia**
Poorly developed bronchial tree with abnormal histology. Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis (Potter sequence).

**Bronchogenic cysts**
Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined, fluid-filled densities on CXR (air-filled if infected). Generally asymptomatic but can drain poorly, causing airway compression and/or recurrent respiratory infections.
**Club cells**  
Nonciliated; low columnar/cuboidal with secretory granules. Located in bronchioles. Degrade toxins; secrete component of surfactant; act as reserve cells.

**Alveolar cell types**

<table>
<thead>
<tr>
<th>Type I pneumocytes</th>
<th>97% of alveolar surfaces. Line the alveoli. Squamous; thin for optimal gas diffusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II pneumocytes</td>
<td>Secrete surfactant from lamellar bodies (arrow in A) → ↓ alveolar surface tension, prevents alveolar collapse, ↓ lung recoil, and ↓ compliance. Cuboidal and clustered B. Also serve as precursors to type I cells and other type II cells. Proliferate during lung damage. Collapsing pressure ( (P) = \frac{2}{r} \text{(surface tension)} ) radius. Alveoli have ↓ tendency to collapse on expiration as radius ↓ (law of Laplace). Pulmonary surfactant is a complex mix of lecithins, the most important of which is dipalmitoylphosphatidylcholine (DPPC). Surfactant synthesis begins around week 20 of gestation, but mature levels are not achieved until around week 35. Corticosteroids important for fetus surfactant production and lung development.</td>
</tr>
</tbody>
</table>

**Alveolar macrophages**  
Phagocytose foreign materials; release cytokines and alveolar proteases. Hemosiderin-laden macrophages may be seen in pulmonary hemorrhage.

**Neonatal respiratory distress syndrome**

Surfactant deficiency → ↑ surface tension → alveolar collapse (“ground-glass” appearance of lung fields) A.  
Risk factors: prematurity, maternal diabetes (due to ↑ fetal insulin), C-section delivery (↑ release of fetal glucocorticoids; less stressful than vaginal delivery).  
Complications: PDA, necrotizing enterocolitis. Treatment: maternal steroids before birth; exogenous surfactant for infant. Therapeutic supplemental O₂ can result in Retinopathy of prematurity, Intraventricular hemorrhage, Bronchopulmonary dysplasia (RIB).  
Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid (≥ 2 is healthy; < 1.5 predictive of NRDS), foam stability index, surfactant-albumin ratio. Persistently low O₂ tension ↑ risk of PDA.

<table>
<thead>
<tr>
<th>Gestational age (wk)</th>
<th>Concentration (mg %)</th>
<th>L/S ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2</td>
<td>Immature</td>
</tr>
<tr>
<td>26</td>
<td>5</td>
<td>Transitional</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>Mature</td>
</tr>
<tr>
<td>35</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid (≥ 2 is healthy; < 1.5 predictive of NRDS), foam stability index, surfactant-albumin ratio. Persistently low O₂ tension ↑ risk of PDA.
Respiratory tree

Conducting zone

Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance).

Warms, humidifies, and filters air but does not participate in gas exchange → “anatomic dead space.”

Cartilage and goblet cells extend to the end of bronchi.

Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator).

Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point).

Respiratory zone

Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange.

Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli. Cilia terminate in respiratory bronchioles. Alveolar macrophages clear debris and participate in immune response.
Right lung has 3 lobes; **Left has Less Lobes** (2) and Lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart **A**.

Relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS—** Right Anterior, **L**eft Superior. Carina is posterior to ascending aorta and anteromedial to descending aorta **B**.

Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

- **While supine**—usually enters right lower lobe.
- **While lying on right side**—usually enters right upper lobe.
- **While upright**—usually enters right lower lobe.

**Diaphragm structures**

- Structures perforating diaphragm:
  - At T8: IVC, right phrenic nerve
  - At T10: esophagus, vagus (CN 10; 2 trunks)
  - At T12: aorta (red), thoracic duct (white), azygos vein (blue) (“At T1-2 it’s the red, white, and blue”)

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

- Number of letters = T level:
  - T8: vena cava
  - T10: “oesophagus”
  - T12: aortic hiatus

I (IVC) ate (8) **ten (10) eggs** (esophagus) at (aorta) **twelve (12)**.

C3, 4, 5 keeps the diaphragm **alive**.

Other bifurcations:
- The common carotid bifurcates at C4.
- The trachea bifurcates at T4.
- The abdominal aorta bifurcates at L4.
Lung volumes

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory reserve volume</td>
<td>Air that can still be breathed in after normal inspiration</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>Air that moves into lung with each quiet inspiration, typically 500 mL</td>
</tr>
<tr>
<td>Expiratory reserve volume</td>
<td>Air that can still be breathed out after normal expiration</td>
</tr>
<tr>
<td>Residual volume</td>
<td>Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry</td>
</tr>
<tr>
<td>Inspiratory capacity</td>
<td>IRV + TV, air that can be breathed in after normal exhalation</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>RV + ERV, volume of gas in lungs after normal expiration</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>TV + IRV + ERV, maximum volume of gas that can be expired after a maximal inspiration</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>IRV + TV + ERV + RV, volume of gas present in lungs after a maximal inspiration</td>
</tr>
</tbody>
</table>

Determination of physiologic dead space

\[ V_D = \frac{V_T \times (P_aCO_2 - P_eCO_2)}{P_aCO_2} \]

\( V_D \) = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. Volume of inspired air that does not take part in gas exchange.

\( V_T \) = tidal volume.
\( P_aCO_2 \) = arterial \( P_aCO_2 \).
\( P_eCO_2 \) = expired air \( P_eCO_2 \).

Ventilation

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Normal values:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation</td>
<td>Total volume of gas entering lungs per minute ( V_E = V_T \times RR )</td>
<td>Respiratory rate (RR) = 12–20 breaths/min ( V_T = 500 \text{ mL/breath} )</td>
</tr>
<tr>
<td>Alveolar ventilation</td>
<td>Volume of gas that reaches alveoli each minute ( V_A = (V_T - V_D) \times RR )</td>
<td>( V_D = 150 \text{ mL/breath} )</td>
</tr>
</tbody>
</table>
Lung and chest wall

Elastic recoil—tendency for lungs to collapse inward and chest wall to spring outward. At FRC, inward pull of lung is balanced by outward pull of chest wall, and system pressure is atmospheric.

At FRC, airway and alveolar pressures equal atmospheric pressure (called zero), and intrapleural pressure is negative (prevents atelectasis). The inward pull of the lung is balanced by the outward pull of the chest wall. System pressure is atmospheric. PVR is at a minimum.

Compliance—change in lung volume for a change in pressure; expressed as ΔV/ΔP and is inversely proportional to wall stiffness. High compliance = lung easier to fill (emphysema, normal aging), lower compliance = lung harder to fill (pulmonary fibrosis, pneumonia, NRDS, pulmonary edema). Surfactant increases compliance.

Hysteresis—lung inflation curve follows a different curve than the lung deflation curve due to need to overcome surface tension forces in inflation.

Respiratory system changes in the elderly

† lung compliance (loss of elastic recoil)
↓ chest wall compliance (↑ chest wall stiffness)
↑ RV
↓ FVC and FEV₁
Normal TLC
† ventilation/perfusion mismatch
↑ A-a gradient
↓ respiratory muscle strength

Hemoglobin

Hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:
- Deoxygenated form has low affinity for O₂, thus promoting release/unloading of O₂.
- Oxygenated form has high affinity for O₂ (300×). Hb exhibits positive cooperativity and negative allostery.

† Ca²⁺, H⁺, CO₂, 2,3-BPG, and temperature favor deoxygenated form over oxygenated form (shifts dissociation curve right → ↓ O₂ unloading).

Fetal Hb (2α and 2γ subunits) has a higher affinity for O₂ than adult Hb, driving diffusion of oxygen across the placenta from mother to fetus. ↑ O₂ affinity results from ↓ affinity of HbF for 2,3-BPG.

Hemoglobin acts as buffer for H⁺ ions.

Myoglobin is composed of a single polypeptide chain associated with one heme moiety. Higher affinity for oxygen than Hb.
Hemoglobin modifications

**Methemoglobin**

Oxidized form of Hb (ferrie, Fe³⁺), does not bind O₂ as readily as Fe²⁺, but has ↑ affinity for cyanide. Fe²⁺ binds O₂.

Iron in Hb is normally in a reduced state (ferrous, Fe²⁺; “just the 2 of us”).

Methemoglobinemia may present with cyanosis and chocolate-colored blood.

*Methemoglobinemia* can be treated with methylene blue and vitamin C.

**Carboxyhemoglobin**

Form of Hb bound to CO in place of O₂.

Causes ↓ oxygen-binding capacity with left shift in oxygen-hemoglobin dissociation curve. ↓ O₂ unloading in tissues.

CO binds competitively to Hb and with 200× greater affinity than O₂.

CO poisoning can present with headaches, dizziness, and cherry red skin. May be caused by fires, car exhaust, or gas heaters. Treat with 100% O₂ and hyperbaric O₂.

Cyanide poisoning

Usually due to inhalation injury (eg, fires). Inhibits aerobic metabolism via complex IV inhibition → hypoxia unresponsive to supplemental O₂ and ↑ anaerobic metabolism. Findings: almond breath odor, pink skin, cyanosis. Rapidly fatal if untreated. Treat with induced methemoglobinemia: first give nitrites (oxidize hemoglobin to methemoglobin, which can trap cyanide as cyanmethemoglobin), then thiosulfates (convert cyanide to thiocyanate, which is renally excreted).
**Oxygen-hemoglobin dissociation curve**

Sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can bind 4 O₂ molecules and has higher affinity for each subsequent O₂ molecule bound). Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

Shifting the curve to the right → ↑ Hb affinity for O₂ (facilitates unloading of O₂ to tissue) → ↑ P₅₀ (higher P₀₂ required to maintain 50% saturation).

Shifting the curve to the left → ↓ O₂ unloading → renal hypoxia → ↑ EPO synthesis → compensatory erythrocytosis.

Fetal Hb has higher affinity for O₂ than adult Hb (due to low affinity for 2,3-BPG), so its dissociation curve is shifted left.

### Oxygen content of blood

O₂ content = (1.34 × Hb × Sa₀₂) + (0.003 × Pao₂)

Hb = hemoglobin level

Sa₀₂ = arterial O₂ saturation

Pao₂ = partial pressure of O₂ in arterial blood

Normally 1 g Hb can bind 1.34 mL O₂; normal Hb amount in blood is 15 g/dL.

O₂ binding capacity ≈ 20.1 mL O₂/dL of blood.

With ↓ Hb there is ↓ O₂ content of arterial blood, but no change in O₂ saturation and Pao₂.

O₂ delivery to tissues = cardiac output × O₂ content of blood.

<table>
<thead>
<tr>
<th></th>
<th>Hb CONCENTRATION</th>
<th>% O₂ SAT OF Hb</th>
<th>DISSOLVED O₂ (Pao₂)</th>
<th>TOTAL O₂ CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO poisoning</td>
<td>Normal</td>
<td>↓ (CO competes with O₂)</td>
<td>Normal</td>
<td>↓</td>
</tr>
<tr>
<td>Anemia</td>
<td>↓</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
<td>↑</td>
</tr>
</tbody>
</table>
**Pulmonary circulation**

Normally a low-resistance, high-compliance system. \( P_{O_2} \) and \( P_{CO_2} \) exert opposite effects on pulmonary and systemic circulation. A ↓ in \( P_{O_2} \) causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—\( O_2 \) (normal health), \( CO_2 \), \( N_2O \). Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.

Diffusion limited—\( O_2 \) (emphysema, fibrosis, exercise), \( CO \). Gas does not equilibrate by the time blood reaches the end of the capillary.

A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure.

Diffusion: \[ V_{\text{gas}} = A \times D_k \times \frac{P_1 - P_2}{T} \]

\( A \) = area, \( T \) = alveolar wall thickness, \( D_k \) = diffusion coefficient of gas, \( P_1 - P_2 \) = difference in partial pressures.
- ↑ in emphysema.
- ↑ in pulmonary fibrosis.

\( D_{L,CO} \) is the extent to which \( CO_2 \), a surrogate for \( O_2 \), passes from air sacs of lungs into blood.

---

**Pulmonary vascular resistance**

\[ P_{\text{V}} = \frac{P_{pulm \text{ artery}} - P_{L \text{ atrium}}}{\text{cardiac output}} \]

Remember: \( \Delta P = Q \times R \), so \( R = \Delta P / Q \)

\[ R = \frac{8\eta l}{\pi r^4} \]

---

**Alveolar gas equation**

\[ P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} \]

\[ \approx 150 \text{ mm Hg} - \frac{P_{A_{CO_2}}}{0.8} \]

\( ^{a} \)At sea level breathing room air

\( P_{O_2} \) = alveolar \( P_{O_2} \) (mm Hg)

\( P_{I_{O_2}} = P_{O_2} \) in inspired air (mm Hg)

\( P_{A_{CO_2}} = \) arterial \( P_{CO_2} \) (mm Hg)

\( R \) = respiratory quotient = \( CO_2 \) produced/\( O_2 \) consumed

\( \Delta A\text{-a gradient} = P_{A_{O_2}} - P_{A_{CO_2}} \). Normal range = 10–15 mm Hg

↑ A-a gradient may occur in hypoxemia; causes may include shunting, \( V/Q \) mismatch, fibrosis (impairs diffusion)
### Oxygen deprivation

<table>
<thead>
<tr>
<th>Hypoxia (↓ O₂ delivery to tissue)</th>
<th>Hypoxemia (↓ PaO₂)</th>
<th>Ischemia (loss of blood flow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ cardiac output</td>
<td>Normal A-a gradient</td>
<td>Impeded arterial flow</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>High altitude</td>
<td>↓ venous drainage</td>
</tr>
<tr>
<td>Anemia</td>
<td>Hypoventilation (eg, opioid use)</td>
<td></td>
</tr>
<tr>
<td>CO poisoning</td>
<td>↑ A-a gradient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V/Q mismatch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffusion limitation (eg, fibrosis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right-to-left shunt</td>
<td></td>
</tr>
</tbody>
</table>

#### Ventilation/perfusion mismatch

Ideally, ventilation is matched to perfusion (ie, V/Q = 1) for adequate gas exchange.

**Lung zones:**
- V/Q at apex of lung = 3 (wasted ventilation)
- V/Q at base of lung = 0.6 (wasted perfusion)

Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung. With exercise (↑ cardiac output), there is vasodilation of apical capillaries → V/Q ratio approaches 1.

Certain organisms that thrive in high O₂ (eg, TB) flourish in the apex. 

V/Q = 0 = “airway” obstruction (shunt). In shunt, 100% O₂ does not improve PaO₂ (eg, foreign body aspiration).

V/Q = ∞ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O₂ improves PaO₂ (eg, pulmonary embolus).
Carbon dioxide transport

CO₂ is transported from tissues to lungs in 3 forms:
1. HCO₃⁻ (70%).
2. Carbaminohemoglobin or HbCO₂ (21–25%). CO₂ bound to Hb at N-terminus of globin (not heme). CO₂ favors deoxygenated form (O₂ unloaded).
3. Dissolved CO₂ (5–9%).

In lungs, oxygenation of Hb promotes dissociation of H⁺ from Hb. This shifts equilibrium toward CO₂ formation; therefore, CO₂ is released from RBCs (Haldane effect). In peripheral tissue, ↑ H⁺ from tissue metabolism shifts curve to right, unloading O₂ (Bohr effect). Majority of blood CO₂ is carried as HCO₃⁻ in the plasma.

Response to high altitude
↓ atmospheric oxygen (PO₂) → ↓ Pao₂ → ↑ ventilation → ↓ PaCO₂ → respiratory alkalosis → altitude sickness.
Chronic ↑ in ventilation.
↑ erythropoietin → ↑ Hct and Hb (due to chronic hypoxia).
↑ 2,3-BPG (binds to Hb causing left shift so that Hb releases more O₂).
Cellular changes (↑ mitochondria).
↑ renal excretion of HCO₃⁻ to compensate for respiratory alkalosis (can augment with acetazolamide).
Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

Response to exercise
↑ CO₂ production.
↑ O₂ consumption.
↑ ventilation rate to meet O₂ demand.
V/Q ratio from apex to base becomes more uniform.
↑ pulmonary blood flow due to ↑ cardiac output.
↓ pH during strenuous exercise (2° to lactic acidosis).
No change in Pao₂ and Paco₂, but ↑ in venous CO₂ content and ↓ in venous O₂ content.
Rhinosinusitis

Obstruction of sinus drainage into nasal cavity → inflammation and pain over affected area. Typically affects maxillary sinuses, which drain against gravity due to ostia located superomedially (red arrow points to fluid-filled right maxillary sinus in A).

Most common acute cause is viral URI; may lead to superimposed bacterial infection, most commonly S pneumoniae, H influenzae, M catarrhalis. Infections in sphenoid or ethmoid sinuses may extend to cavernous sinus and cause complications (eg, cavernous sinus syndrome).

Epistaxis

Nose bleed. Most commonly occurs in anterior segment of nostril (Kiesselbach plexus). Life-threatening hemorrhages occur in posterior segment (sphenopalatine artery, a branch of maxillary artery). Common causes include foreign body, trauma, allergic rhinitis, and nasal angiofibromas (common in adolescent males).

Kiesselbach drives his Lexus with his LEGS: superior Labial artery, anterior and posterior Ethmoidal arteries, Greater palatine artery, Sphenopalatine artery.

Head and neck cancer

Mostly squamous cell carcinoma. Risk factors include tobacco, alcohol, HPV-16 (oropharyngeal), EBV (nasopharyngeal). Field cancerization: carcinogen damages wide mucosal area → multiple tumors that develop independently after exposure.

Deep venous thrombosis

Blood clot within a deep vein → swelling, redness, warmth, pain. Predisposed by Virchow triad (SHE):

* Stasis (eg, post-op, long drive/flight)
* Hypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden; oral contraceptive use)
* Endothelial damage (exposed collagen triggers clotting cascade)

D-dimer lab test used clinically to rule out DVT (high sensitivity, low specificity).

Most pulmonary emboli arise from proximal deep veins of lower extremity. Use unfractionated heparin or low-molecular-weight heparins (eg, enoxaparin) for prophylaxis and acute management. Use oral anticoagulants (eg, warfarin, rivaroxaban) for treatment (long-term prevention). Imaging test of choice is compression ultrasound with Doppler.
**Pulmonary emboli**

V/Q mismatch, hypoxemia, respiratory alkalosis. Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia. Large emboli or saddle embolus may cause sudden death due to electromechanical dissociation.

Lines of Zahn are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi.

Types: Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor.

Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash.

Air emboli—nitrogen bubbles precipitate in ascending divers (caisson disease/decompression sickness); treat with hyperbaric O₂; or, can be iatrogenic 2° to invasive procedures (eg, central line placement).

Amniotic fluid emboli—can lead to DIC, especially postpartum.

CT pulmonary angiography is imaging test of choice for PE (look for filling defects). May have SIQ3T3 abnormality on ECG.

An embolus moves like a **FAT BAT**.
Flow-volume loops

<table>
<thead>
<tr>
<th>FLOW-VOLUME PARAMETER</th>
<th>Obstructive lung disease</th>
<th>Restrictive lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>FRC</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>TLC</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>FVC</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>FEV₁ decreased more than FVC</td>
<td>Normal or ↑ FEV₁ decreased proportionately to FVC</td>
</tr>
</tbody>
</table>

Flow (L/sec) | Expiration | Inspiration |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>8</td>
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<td>6</td>
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<td>0</td>
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Volume (L) | TLC | VC |
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<tbody>
<tr>
<td>8</td>
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<td>2</td>
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<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>
Obstructive lung diseases

Obstruction of air flow → air trapping in lungs. Airways close prematurely at high lung volumes → ↑ FRC, ↑ RV, ↑ TLC. PFTs: ↓ FEV₁, ↓ FVC → ↓ FEV₁/FVC ratio (hallmark), V̇Q mismatch. Chronic, hypoxic pulmonary vasoconstriction can lead to cor pulmonale. Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis and emphysema. “Frickin’ RV needs some increased TLC, but it’s hard with COPD!”

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PRESENTATION</th>
<th>PATHOLOGY</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis (“blue bloater”)</td>
<td>Findings: wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, CO₂ retention, 2° polycythemia.</td>
<td>Hypertrophy and hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) &gt; 50%. D_{LCO} usually normal.</td>
<td>Diagnostic criteria: productive cough for &gt; 3 months in a year for &gt; 2 consecutive years.</td>
</tr>
<tr>
<td>Asthma</td>
<td>Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/expiratory ratio, pulsus paradoxus, mucus plugging ▲. Triggers: viral URIs, allergens, stress. Diagnosis supported by spirometry and methacholine challenge.</td>
<td>Hyperresponsive bronchi → reversible bronchoconstriction. Smooth muscle hypertrophy and hyperplasia, Gurschmann spirals ▲ (shed epithelium forms whorled mucus plugs), and Charcot-Leyden crystals ▲ (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). D_{LCO} normal or ↑.</td>
<td>Type I hypersensitivity reaction. Aspirin-induced asthma is a combination of COX inhibition (leukotriene overproduction → airway constriction), chronic sinusitis with nasal polyps, and asthma symptoms.</td>
</tr>
</tbody>
</table>
## Obstructive lung diseases (continued)

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PRESENTATION</th>
<th>PATHOLOGY</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>Findings: purulent sputum, recurrent infections, hemoptysis, digital clubbing.</td>
<td>Chronic necrotizing infection of bronchi or obstruction → permanently dilated airways.</td>
<td>Associated with bronchial obstruction, poor ciliary motility (eg, smoking, Kartagener syndrome), cystic fibrosis, allergic bronchopulmonary aspergillosis.</td>
</tr>
</tbody>
</table>

### Restrictive lung diseases

Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs: ↑ FEV₁/FVC ratio. Patient presents with short, shallow breaths.

**Types:**
- Poor breathing mechanics (extrapulmonary, peripheral hypoventilation, normal A-a gradient):
  - Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome
  - Poor structural apparatus—scoliosis, morbid obesity
- Interstitial lung diseases (pulmonary ↓ diffusing capacity, ↑ A-a gradient):
  - Pneumoconioses (eg, coal workers’ pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca²⁺
  - Idiopathic pulmonary fibrosis (repeated cycles of lung injury and wound healing with ↑ collagen deposition, “honeycomb” lung appearance and digital clubbing)
  - Goodpasture syndrome
  - Granulomatosis with polyangiitis (Wegener)
  - Pulmonary Langerhans cell histiocytosis (cosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate)

**Hypersensitivity pneumonitis**—mixed type III/IV hypersensitivity reaction to environmental antigen. Causes dyspnea, cough, chest tightness, headache. Often seen in farmers and those exposed to birds. Reversible in early stages if stimulus is avoided.
Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas, elevated serum ACE levels, and elevated CD4+/CD8+ ratio in bronchoalveolar lavage fluid. More common in African-American females. Often asymptomatic except for enlarged lymph nodes. Findings on CXR of bilateral adenopathy and coarse reticular opacities. CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy.

Associated with Bell palsy, Uveitis, Granulomas (epithelioid, containing microscopic Schaumann and asteroid bodies), Lupus pernio (skin lesions on face resembling lupus), Interstitial fibrosis (restrictive lung disease), Erythema nodosum, Rheumatoid arthritis-like arthropathy, hypercalcemia (due to 1α-hydroxylase–mediated vitamin D activation in macrophages). A facial droop is UGLIER.

Treatment: steroids (if symptomatic).

Inhalation injury and sequelae

Complication of smoke inhalation from fires or other noxious substances. Caused by heat, particulates (< 1 µm diameter), or irritants (eg, NH₃) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2nd to burns, CO inhalation, cyanide poisoning, or arsenic poisoning. Singed nasal hairs common on exam.

Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A, 18 hours after inhalation injury; B, resolution at 11 days after injury).
### Pneumoconioses

**Asbestos** is from the **roof** (was common in insulation), but affects the **base** (lower lobes). **Silica and coal** are from the **base** (earth), but affect the **roof** (upper lobes).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asbestosis</strong></td>
<td>Associated with shipbuilding, roofing, plumbing. “Ivory white,” calcified,</td>
<td>Affects lower lobes. Asbestos (ferruginous) bodies are golden-brown</td>
</tr>
<tr>
<td></td>
<td>supradiaphragmatic A and pleural B plaques are pathognomonic of asbestosis.</td>
<td>fusiform rods resembling dumbbells C, found in alveolar sputum sample,</td>
</tr>
<tr>
<td></td>
<td>Risk of bronchogenic carcinoma &gt; risk of mesothelioma.</td>
<td>visualized using Prussian blue stain, often obtained by bronchoalveolar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lavage.</td>
</tr>
<tr>
<td><strong>Berylliosis</strong></td>
<td>Associated with exposure to beryllium in aerospace and manufacturing industries.</td>
<td>Affects upper lobes.</td>
</tr>
<tr>
<td></td>
<td>Granulomatous (noncaseating) D on histology and therefore occasionally responsive to steroids.</td>
<td></td>
</tr>
<tr>
<td><strong>Coal workers’ pneumoconiosis</strong></td>
<td>Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis. Also known as black lung disease.</td>
<td>Affects upper lobes. Small, rounded nodular opacities seen on imaging.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Anthracosis</strong>—asymptomatic condition found in many urban dwellers exposed to sooty air.</td>
</tr>
<tr>
<td><strong>Silicosis</strong></td>
<td>Associated with sandblasting, foundries, mines. Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB.</td>
<td>Affects upper lobes. “Eggshell” calcification of hilar lymph nodes on CXR. The silly egg sandwich I found is mine!</td>
</tr>
</tbody>
</table>

---

A

B

C

D
Mesothelioma

Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening.

Psammoma bodies seen on histology. Calretinin $\oplus$ in almost all mesotheliomas, $\ominus$ in most carcinomas. Smoking not a risk factor.

Acute respiratory distress syndrome

PATHOPHYSIOLOGY

Alveolar insult $\rightarrow$ release of pro-inflammatory cytokines $\rightarrow$ neutrophil recruitment, activation, and release of toxic mediators (e.g., reactive oxygen species, proteases, etc) $\rightarrow$ capillary endothelial damage and vessel permeability $\rightarrow$ leakage of protein-rich fluid into alveoli $\rightarrow$ formation of intra-alveolar hyaline membranes (arrows in A) and noncardiogenic pulmonary edema (normal PCWP).

Loss of surfactant also contributes to alveolar collapse.

CAUSES

Sepsis (most common), aspiration, pneumonia, trauma, pancreatitis.

DIAGNOSIS

Diagnosis of exclusion with the following criteria (ARDS):

- Abnormal chest X-ray (bilateral lung opacities)
- Respiratory failure within 1 week of alveolar insult
- Decreased $\text{PaO}_2/\text{FiO}_2$ (ratio $< 300$, hypoxemia due to increased intrapulmonary shunting and diffusion abnormalities)
- Symptoms of respiratory failure are not due to HF/fluid overload

CONSEQUENCES

Impaired gas exchange

- Lung compliance
- Pulmonary hypertension

MANAGEMENT

Treat the underlying cause

Mechanical ventilation: ↓ tidal volumes, ↑ PEEP
### Sleep apnea
Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Diagnosis confirmed by sleep study. Normal Pao₂ during the day. Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death.

Hypoxia → ↑ EPO release → ↑ erythropoiesis.

### Obstructive sleep apnea

### Central sleep apnea
Impaired respiratory effort due to CNS injury/toxicity, HF, opioids. May be associated with Cheyne-Stokes respirations (oscillations between apnea and hyperpnea). Treat with positive airway pressure.

### Obesity hypoventilation syndrome
Obesity (BMI ≥ 30 kg/m²) → hypoventilation → ↑ PaCO₂ during waking hours (retention); ↓ Pao₂ and ↑ PacO₂ during sleep. Also known as Pickwickian syndrome.

### Pulmonary hypertension
Normal mean pulmonary artery pressure = 10–14 mm Hg; pulmonary hypertension ≥ 25 mm Hg at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. Course: severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.

#### Etiologies

| Pulmonary arterial hypertension | Often idiopathic. Heritable PAH can be due to an inactivating mutation in BMPR2 gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Pulmonary vasculature endothelial dysfunction results in ↑ vasoconstrictors (eg, endothelin) and ↓ vasodilators (eg, NO and prostacyclins). Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis. |
| Left heart disease | Causes include systolic/diastolic dysfunction and valvular disease. |
| Lung diseases or hypoxia | Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxic vasoconstriction (eg, obstructive sleep apnea, living in high altitude). |
| Chronic thromboembolic | Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed. |
| Multifactorial | Causes include hematologic, systemic, and metabolic disorders, along with compression of the pulmonary vasculature by a tumor. |
## Lung—physical findings

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Breath Sounds</th>
<th>Percussion</th>
<th>Fremitus</th>
<th>Tracheal Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>↓</td>
<td>Dull</td>
<td>↓</td>
<td>None if small away from side of lesion if large</td>
</tr>
<tr>
<td>Atelectasis (bronchial obstruction)</td>
<td>↓</td>
<td>Dull</td>
<td>↓</td>
<td>Toward side of lesion</td>
</tr>
<tr>
<td>Simple pneumothorax</td>
<td>↓</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>None</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>↓</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>Away from side of lesion</td>
</tr>
<tr>
<td>Consolidation (lobar pneumonia, pulmonary edema)</td>
<td></td>
<td>Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Pleural effusions
Excess accumulation of fluid between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid.

- **Transudate**
  - ↑ protein content. Due to ↑ hydrostatic pressure (e.g., HF) or ↓ oncotic pressure (e.g., nephrotic syndrome, cirrhosis).
- **Exudate**
  - ↑ protein content, cloudy. Due to malignancy, pneumonia, collagen vascular disease, trauma (occurs in states of ↑ vascular permeability). Must be drained due to risk of infection.
- **Lymphatic**
  - Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; ↑ triglycerides.
<table>
<thead>
<tr>
<th>Pneumothorax</th>
<th>Accumulation of air in pleural space. Dyspnea, uneven chest expansion. Chest pain, tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary spontaneous pneumothorax</td>
<td>Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males and smokers.</td>
</tr>
<tr>
<td>Secondary spontaneous pneumothorax</td>
<td>Due to diseased lung (eg, bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.</td>
</tr>
<tr>
<td>Traumatic pneumothorax</td>
<td>Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>Can be from any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung. Needs immediate needle decompression and chest tube placement. May lead to ↑ intrathoracic pressure → ↓ venous return → ↓ cardiac function.</td>
</tr>
</tbody>
</table>
Pneumonia

<table>
<thead>
<tr>
<th>TYPE</th>
<th>TYPICAL ORGANISMS</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar pneumonia</td>
<td><em>S. pneumoniae</em> most frequently, also <em>Legionella, Klebsiella</em></td>
<td>Intra-alveolar exudate → consolidation (\text{A}), may involve entire lobe (\text{B}) or the whole lung.</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td><em>S. pneumoniae, S. aureus, H. influenzae, Klebsiella</em></td>
<td>Acute inflammatory infiltrates (\text{C}) from bronchioles into adjacent alveoli; patchy distribution involving (\geq 1 \text{ lobe}) (\text{D}).</td>
</tr>
<tr>
<td>Interstitial (atypical)</td>
<td><em>Mycoplasma, Chlamydia pneumoniae, Chlamydia psittaci, Legionella, viruses</em></td>
<td>Diffuse patchy inflammation localized to interstitial areas at alveolar walls; diffuse distribution involving (\geq 1 \text{ lobe}) (\text{E}). Generally follows a more indolent course (“walking” pneumonia).</td>
</tr>
<tr>
<td>Cryptogenic organizing</td>
<td>Etiology unknown. Secondary organizing pneumonia caused by chronic inflammatory</td>
<td>Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.</td>
</tr>
<tr>
<td>pneumonia</td>
<td>diseases (eg, rheumatoid arthritis) or medication side effects (eg, amiodarone).</td>
<td></td>
</tr>
</tbody>
</table>

Natural history of lobar pneumonia

<table>
<thead>
<tr>
<th>DAYS</th>
<th>FINDINGS</th>
<th>Congestion</th>
<th>Red hepatization</th>
<th>Gray hepatization</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td></td>
<td>Red-purple, partial consolidation of parenchyma</td>
<td>3–4</td>
<td>Red-brown, consolidated Exudate with fibrin, bacteria, RBCs, and WBCs</td>
<td>Uniformly gray Exudate full of WBCs, lysed RBCs, and fibrin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exudate with mostly bacteria</td>
<td>5–7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Lung cancer**

Leading cause of cancer death. Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic “coin” lesion on CXR or noncalcified nodule on CT. Sites of metastases from lung cancer: adrenals, brain, bone (pathologic fracture), liver (jaundice, hepatomegaly). In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

**SPHERE of complications:**
- Superior vena cava/thoracic outlet syndromes
- Pancoast tumor
- Horner syndrome
- Endocrine (paraneoplastic)
- Recurrent laryngeal nerve compression (hoarseness)
- Effusions (pleural or pericardial)

Risk factors include smoking, secondhand smoke, radon, asbestos, family history.

Squamous and Small cell carcinomas are Central (central) and often caused by Smoking.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>LOCATION</th>
<th>CHARACTERISTICS</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell</td>
<td>Central</td>
<td>Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), SIADH, or Antibodies against presynaptic Ca&lt;sup&gt;2+&lt;/sup&gt; channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encéphalitides, subacute cerebellar degeneration). Amplification of myc oncogenes common. Managed with chemotherapy +/- radiation.</td>
<td>Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells. Chromogranin A⁺, neuron-specific enolase +, synaptophysin +.</td>
</tr>
<tr>
<td>Non–small cell</td>
<td>Adenocarcinoma</td>
<td>Peripheral</td>
<td>Most common 1° lung cancer. More common in women than men, most likely to arise in nonsmokers. Activating mutations include KRAS, EGFR, and ALK. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis. Bronchial carcinoid and bronchioalveolar cell carcinoma have lesser association with smoking.</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>Central</td>
<td>Hilar mass arising from bronchus; Cavitation; Cigarettes; hyperCalcemia (produces PTHrP).</td>
</tr>
<tr>
<td></td>
<td>Large cell carcinoma</td>
<td>Peripheral</td>
<td>Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically. Strong association with smoking.</td>
</tr>
<tr>
<td></td>
<td>Bronchial carcinoid tumor</td>
<td>Central or peripheral</td>
<td>Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).</td>
</tr>
</tbody>
</table>
Lung abscess

Localized collection of pus within parenchyma. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcoholics, epileptics]) or bronchial obstruction (eg, cancer).

Treatment: antibiotics.

Air-fluid levels often seen on CXR. Fluid levels common in cavities; presence suggests cavitation. Due to anaerobes (eg, Bacteroides, Fusobacterium, Peptostreptococcus) or S aureus.

Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient’s position during aspiration.

Pancoast tumor

Also known as superior sulcus tumor. Carcinoma that occurs in the apex of lung may cause Pancoast syndrome by invading cervical sympathetic chain.

Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve → hoarseness
- Stellate ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Brachiocephalic vein → brachiocephalic syndrome (unilateral symptoms)
- Brachial plexus → sensorimotor deficits

Superior vena cava syndrome

An obstruction of the SVC that impairs blood drainage from the head (“facial plethora”; note blanching after fingertip pressure in A), neck (jugular venous distention), and upper extremities (edema). Commonly caused by malignancy (eg, mediastinal mass, Pancoast tumor) and thrombosis from indwelling catheters. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, ↑ risk of aneurysm/rupture of intracranial arteries.
### RESPIRATORY—PHARMACOLOGY

#### Histamine-1 blockers
Reversible inhibitors of \( H_1 \) histamine receptors.

**First generation**
- Diphenhydramine,
dimenhydrinate,
chlorpheniramine.

**CLINICAL USE**
- Allergy, motion sickness, sleep aid.

**ADVERSE EFFECTS**
- Sedation, antimuscarinic, anti-\( \alpha \)-adrenergic.

**Second generation**
- Loratadine,
fexofenadine,
desloratadine,
cetirizine.

**CLINICAL USE**
- Allergy.

**ADVERSE EFFECTS**
- Far less sedating than 1st generation because of
\( \downarrow \) entry into CNS.

#### Guaifenesin
Expectorant—thins respiratory secretions; does not suppress cough reflex.

#### N-acetylcysteine
Mucolytic—liquifies mucus in chronic bronchopulmonary diseases (eg, COPD, CF) by disrupting disulfide bonds. Also used as an antidote for acetaminophen overdose.

#### Dextromethorphan
Antitussive (agonizes NMDA glutamate receptors). Synthetic codeine analog. Has mild opioid effect when used in excess. Naloxone can be given for overdose. Mild abuse potential. May cause serotonin syndrome if combined with other serotonergic agents.

#### Pseudoephedrine, phenylephrine
- \( \alpha \)-adrenergic agonists, used as nasal decongestants.

**CLINICAL USE**
- Reduce hyperemia, edema, nasal congestion; open obstructed eustachian tubes.

**ADVERSE EFFECTS**
- Hypertension. Rebound congestion if used more than 4–6 days. Can also cause CNS stimulation/anxiety (pseudoephedrine).

#### Pulmonary hypertension drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endothelin receptor</strong></td>
<td>Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance.</td>
<td>Hepatotoxic (monitor LFTs). Example: bosentan.</td>
</tr>
<tr>
<td><strong>antagonists</strong></td>
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<td><strong>PDE-5 inhibitors</strong></td>
<td>Inhibits PDE-5 → ↑ cGMP → prolonged vasodilatory effect of NO.</td>
<td>Also used to treat erectile dysfunction. Contraindicated when taking nitroglycerin or other nitrates. Example: sildenafil.</td>
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<td><strong>Prostacyclin analogs</strong></td>
<td>PGI(_2) (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.</td>
<td>Side effects: flushing, jaw pain. Examples: epoprostenol, iloprost.</td>
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**Asthma drugs**

Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.

**β₂-agonists**


*Salbutamol, formoterol*—long-acting agents for prophylaxis. Adverse effects are tremor and arrhythmia.

**Inhaled corticosteroids**

*Fluticasone, budesonide*—inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, the transcription factor that induces production of TNF-α and other inflammatory agents. 1st-line therapy for chronic asthma. Use a spacer or rinse mouth after use to prevent oral thrush.

**Muscarinic antagonists**

*Tiotropium, ipratropium*—competitively block muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.

**Antileukotrienes**

*Montelukast, zafirlukast*—block leukotriene receptors (CysLT1). Especially good for aspirin-induced and exercise-induced asthma.


**Anti-IgE monoclonal therapy**

*Omalizumab*—binds mostly unbound serum IgE and blocks binding to FcεRI. Used in allergic asthma with high IgE levels resistant to inhaled steroids and long-acting β₂-agonists.

**Methylxanthines**

*Theophylline*—likely causes bronchodilation by inhibiting phosphodiesterase → ↑ cAMP levels due to ↓ cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine.

**Mast cell stabilizers**

*Cromolyn, nedocromil*—prevent release of inflammatory mediators from mast cells. Used for prevention of bronchospasm, not for acute bronchodilation.

**Methacholine**

Nonselective muscarinic receptor (M₃) agonist. Used in bronchial challenge test to help diagnose asthma.
“Study without thought is vain: thought without study is dangerous.”  
—Confucius

“It is better, of course, to know useless things than to know nothing.”  
—Lucius Annaeus Seneca

“For every complex problem there is an answer that is clear, simple, and wrong.”  
—H. L. Mencken

The following tables represent a collection of high-yield associations of diseases with their clinical findings, treatments, and pathophysiology. They can be quickly reviewed in the days before the exam.
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<td>Hyporeflexia, hypotonia, atrophy, fasciculations</td>
<td>LMN damage</td>
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<td>Unilateral facial drooping involving forehead</td>
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<td>Episodic vertigo, tinnitus, hearing loss</td>
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<td>Ptosis, miosis, anhidrosis</td>
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<td>Conjugate horizontal gaze palsy, horizontal diplopia</td>
<td>Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral)</td>
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<td>Polyuria, renal tubular acidosis type II, growth failure, electrolyte imbalances, hypophosphatemic rickets</td>
<td>Fanconi syndrome (multiple combined dysfunction of the proximal convoluted tubule)</td>
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<td>Bluish line on gingiva</td>
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<td>Periorbital and/or peripheral edema, proteinuria (&gt; 3.5g/day), hypoalbuminemia, hypercholesterolemia</td>
<td>Nephrotic syndrome</td>
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<td>Hereditary nephritis, sensorineural hearing loss, cataracts</td>
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<td>Streak ovaries, congenital heart disease, horseshoe kidney, cystic hygroma at birth, short stature, webbed neck, lymphedema</td>
<td>Turner syndrome (45,XO)</td>
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<td>Fibrous plaques in soft tissue of penis with abnormal curvature</td>
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### Clinical Presentation

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<td>Pink complexion, dyspnea, hyperventilation</td>
<td>Emphysema (&quot;pink puffer,&quot; centriacinar [smoking] or panacinar [α1-antitrypsin deficiency])</td>
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<td>Bilateral hilar adenopathy, uveitis</td>
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### Classic Labs/Findings

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<td>middle or lower lung lobes (can calcify)</td>
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<td>Sheets of medium-sized lymphoid cells with scattered pale, tingible body–laden macrophages (“starry sky” histology)</td>
<td>Burkitt lymphoma ([t(8:14] c-my activation, associated with EBV; “starry sky” made up of malignant cells)</td>
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<td>Multiple myeloma</td>
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**LAB/DIAGNOSTIC/FOUNDING** | **DIAGNOSIS/DISEASE** | **PAGE**
---|---|---
Monoclonal antibody spike | Multiple myeloma (usually IgG or IgA)  
Monoclonal gammopathy of undetermined significance (MGUS consequence of aging)  
Waldenström (M protein = IgM) macroglobulinemia  
Primary amyloidosis | 419
Stacks of RBCs | Rouleaux formation (high ESR, multiple myeloma) | 419
Azurophilic peroxidase + granular inclusions in granulocytes and myeloblasts | Auer rods (AML, especially the promyelocytic [M3] type) | 420
WBCs that look “smudged” | CLL (almost always B cell) | 420
“Tennis racket”-shaped cytoplasmic organelles (EM) in Langerhans cells | Birbeck granules (Langerhans cell histiocytosis) | 422
“Brown” tumor of bone | Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color) | 451
Raised periosteum (creating a “Codman triangle”) | Aggressive bone lesion (eg, osteosarcoma, Ewing sarcoma, osteomyelitis) | 452
“Soap bubble” in femur or tibia on x-ray | Giant cell tumor of bone (generally benign) | 452
“Onion skin” periosteal reaction | Ewing sarcoma (malignant small blue cell tumor) | 453
Anti-IgG antibodies | Rheumatoid arthritis (systemic inflammation, joint pannus, boutonniere and swan neck deformities) | 454
Rhomboid crystals, ⊕ birefringent | Pseudogout (calcium pyrophosphate dihydrate crystals) | 455
Needle-shaped, ⊥ birefringent crystals | Gout (monosodium urate crystals) | 455
↑ uric acid levels | Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics | 455
“Bamboo spine” on x-ray | Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27) | 457
Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA) | SLE (type III hypersensitivity) | 458
Anti-topoisomerase antibodies | Diffuse systemic scleroderma | 460
Keratin pearls on a skin biopsy | Squamous cell carcinoma | 469
Antihistone antibodies | Drug-induced SLE (eg, hydralazine, isoniazid, phenytoin, procainamide) | 472
Bloody or yellow tap on lumbar puncture | Subarachnoid hemorrhage | 497
Yellowish CSF | Xanthochromia (eg, due to subarachnoid hemorrhage) | 497
Eosinophilic cytoplasmic inclusion in neuron | Lewy body (Parkinson disease and Lewy body dementia) | 504
Extracellular amyloid deposition in gray matter of brain | Senile plaques (Alzheimer disease) | 504
Depigmentation of neurons in substantia nigra | Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia) | 504
Protein aggregates in neurons from hyperphosphorylation of tau protein | Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease) | 504
Silver-staining spherical aggregation of tau proteins in neurons | Pick bodies (Pick disease: progressive dementia, changes in personality) | 504
Pseudopalisading tumor cells on brain biopsy | Glioblastoma multiforme | 510
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<td>Homer-Wright rosettes (neuroblastoma, medulloblastoma)</td>
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<td>Nodular hyaline deposits in glomeruli</td>
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<td>Anti–glomerular basement membrane antibodies</td>
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<td>Cellular crescents in Bowman capsule</td>
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<td>“Wire loop” glomerular capillary appearance on light microscopy</td>
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<td>Linear appearance of IgG deposition on glomerular and alveolar basement membranes</td>
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<td>“Lumpy bumpy” appearance of glomeruli on immunofluorescence</td>
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<td>Renal epithelial casts in urine</td>
<td>Intrinsic renal failure (eg, ischemia or toxic injury)</td>
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<td>Choriocarcinoma, hydatidiform mole (occurs with and without embryo, and multiple pregnancy)</td>
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<td>Thrombi made of white/red layers</td>
<td>Lines of Zahn (arterial thrombus, layers of platelets/RBCs)</td>
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### Lab/Diagnostic/Finding

| Hexagonal, double-pointed, needle-like crystals in bronchial secretions | Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules) | 656 |
| Desquamated epithelium casts in sputum | Curschmann spirals (bronchial asthma; can result in whorled mucous plugs) | 656 |
| “Honeycomb lung” on x-ray or CT | Interstitial pulmonary fibrosis | 657 |
| Colonies of mucoid *Pseudomonas* in lungs | Cystic fibrosis (autosomal recessive mutation in CFTR gene → fat-soluble vitamin deficiency and mucous plugs) | 657 |
| Iron-containing nodules in alveolar septum | Ferruginous bodies (asbestosis: ↑ chance of lung cancer) | 659 |
| Bronchogenic apical lung tumor on imaging | Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome) | 666 |

### Classic/Relevant Treatments

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<td><em>Clostridium tetani</em></td>
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<td><em>Streptococcus pyogenes</em></td>
<td>Penicillin prophylaxis</td>
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<td><em>Streptococcus pneumoniae</em></td>
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<td><em>Streptococcus bovis</em></td>
<td>Penicillin prophylaxis; evaluation for colon cancer if linked to endocarditis</td>
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<td>Vancomycin, aminopenicillins/cephalosporins</td>
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<td>Amoxicillin ± clavulanate (mucosal infections), ceftriaxone (meningitis), rifampin (prophylaxis)</td>
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<td><em>Cryptococcus neoformans</em></td>
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<td>Influenza</td>
<td>Oseltamivir, zanamivir</td>
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<td>CMV</td>
<td>Ganciclovir, foscarnet, cidofovir</td>
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<td>Neisseria gonorrhoeae</td>
<td>Ceftriaxone (add doxycycline to cover likely concurrent <em>C. trachomatis</em>)</td>
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<tr>
<td>Clostridium difficile</td>
<td>Oral metronidazole; if refractory, oral vancomycin</td>
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<td>Mycobacterium tuberculosis</td>
<td>RIPE (rifampin, isoniazid, pyrazinamide, ethambutol)</td>
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<td>Chronic hepatitis B or C</td>
<td>IFN-α (HBV and HCV); ribavirin, simeprevir, sofosbuvir (HCV)</td>
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<td>Patent ductus arteriosus</td>
<td>Close with indomethacin; keep open with PGE analogs</td>
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<td>Arrhythmia in damaged cardiac tissue</td>
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<td>Prolactinoma</td>
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<td>Diabetes insipidus</td>
<td>Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic)</td>
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<td>Fluid restriction, IV hypertonic saline, conivaptan/tolvaptan, demeclocycline</td>
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<td>Diabetes mellitus type 1</td>
<td>Dietary intervention (low carbohydrate) + insulin replacement</td>
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<td>Diabetes mellitus type 2</td>
<td>Dietary intervention, oral hypoglycemics, and insulin (if refractory)</td>
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<td>Diabetic ketoacidosis</td>
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<td>Carcinoid syndrome</td>
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<td>HER2/neu + breast cancer</td>
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<td>Osteoporosis</td>
<td>Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)</td>
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<td>Osteomalacia/rickets</td>
<td>Vitamin D supplementation</td>
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<td>Migraine</td>
<td>Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis (eg, propranolol, topiramate, CCBs, amitriptyline)</td>
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<td>Trigeminal neuralgia (tic douloureux)</td>
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<td>Multiple sclerosis</td>
<td>Disease-modifying therapies (eg, β-interferon, natalizumab); for acute flares, use IV steroids</td>
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<td>Tabes dorsalis (3° syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spinocerebellar tracts affected)</td>
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<td>Schizophrenia (positive symptoms)</td>
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### Key Associations

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<tr>
<td>S4 heart sound</td>
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<td>TB (developing world); idiopathic, viral illness (developed world)</td>
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<td>Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia)</td>
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<td>Temporal arteritis</td>
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<td>Recurrent inflammation/thrombosis of small/medium vessels in extremities</td>
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<td>• Calcium = radiopaque</td>
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<td>• Struvite (ammonium) = radiopaque (formed by urease + organisms such as <em>Klebsiella</em>, <em>Proteus</em> species, and <em>S saprophyticus</em>)</td>
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<tr>
<td></td>
<td>• Uric acid = radiolucent</td>
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<td>• Cystine = faintly radiopaque</td>
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<td>Hypercoagulability, endothelial damage, blood stasis</td>
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</tbody>
</table>
DISEASE/FINDING | MOST COMMON/IMPORTANT ASSOCIATIONS | PAGE
--- | --- | ---
Pulmonary hypertension | Idiopathic, heritable, left heart disease (eg, HF), lung disease (eg, COPD), hypoxic vasoconstriction (eg, OSA), thromboembolic (eg, PE) | 661
SIADH | Small cell carcinoma of the lung | 665

### EQUATION REVIEW

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SECTION IV

Top-Rated Review Resources

“Some books are to be tasted, others to be swallowed, and some few to be chewed and digested.”
—Sir Francis Bacon

“How to Use the Database”
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“How to Use the Question Banks”
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“How to Use the Question Books”
692

“How to Use the Web and Mobile Apps”
692

“How to Use the Comprehensive”
693

“How to Use the Anatomy, Embryology, and Neuroscience”
693

“How to Use the Behavioral Science”
694

“How to Use the Biochemistry”
694

“How to Use the Cell Biology and Histology”
694

“How to Use the Microbiology and Immunology”
695

“How to Use the Pathology”
695

“How to Use the Pharmacology”
696

“How to Use the Physiology”
696

“Always read something that will make you look good if you die in the middle of it.”
—P.J. O’Rourke

“So many books, so little time.”
—Frank Zappa

“If one cannot enjoy reading a book over and over again, there is no use in reading it at all.”
—Oscar Wilde
HOW TO USE THE DATABASE

This section is a database of top-rated basic science review books, sample examination books, software, websites, and apps that have been marketed to medical students studying for the USMLE Step 1. For each recommended resource, we list (where applicable) the Title, the First Author (or editor), the Current Publisher, the Copyright Year, the Number of Pages, the Approximate List Price, the Format of the resource, and the Number of Test Questions. Finally, each recommended resource receives a Rating. Within each section, resources are arranged first by Rating and then alphabetically by the first author within each Rating group.

For a complete list of resources, including summaries that describe their overall style and utility, go to www.firstaidteam.com/bonus.

A letter rating scale with six different grades reflects the detailed student evaluations for Rated Resources. Each rated resource receives a rating as follows:

- **A+** Excellent for boards review.
- **A** Very good for boards review; choose among the group.
- **A−**
- **B+** Good, but use only after exhausting better resources.
- **B**
- **B−** Fair, but there are many better resources in the discipline; or low-yield subject material.

The Rating is meant to reflect the overall usefulness of the resource in helping medical students prepare for the USMLE Step 1. This is based on a number of factors, including:
- The cost
- The readability of the text or usability of the app
- The appropriateness and accuracy of the material
- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the illustrations (eg, graphs, diagrams, photographs)
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline
- The importance of the discipline for the USMLE Step 1

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1. Many books with lower ratings are well written and informative but are not ideal for boards
preparation. We have not listed or commented on general textbooks available in the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publishers’ prices change frequently.
- Bookstores often charge an additional markup.
- New editions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. (See p. xvi, How to Contribute.) In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books or suggestions for alternate modes of study that may be useful in preparing for the examination, such as flash cards, computer software, commercial review courses, apps, and websites.

Disclaimer/Conflict of Interest Statement

No material in this book, including the ratings, reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at www.firstaidteam.com. Please note that USMLE-Rx and the entire First Aid for the USMLE series are publications by the senior authors of this book; the following ratings are based solely on recommendations from the student authors of this book as well as data from the student survey and feedback forms.
## Top-Rated Review Resources

### Question Banks

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<tbody>
<tr>
<td>A+</td>
<td>UWorld Qbank</td>
<td>UWorld <a href="http://www.uworld.com">www.uworld.com</a></td>
<td>Test/2400 q</td>
<td>$169–$599</td>
</tr>
<tr>
<td>A</td>
<td>NBME Practice Exams</td>
<td>National Board of Medical Examiners</td>
<td>Test/200 q</td>
<td>$60</td>
</tr>
<tr>
<td>A+</td>
<td>USMLE-Rx Qmax</td>
<td>USMLE-Rx <a href="http://www.usmle-rx.com">www.usmle-rx.com</a></td>
<td>Test/2300 q</td>
<td>$99–$299</td>
</tr>
<tr>
<td>B+</td>
<td>Kaplan Qbank</td>
<td>Kaplan <a href="http://www.kaptest.com">www.kaptest.com</a></td>
<td>Test/2200 q</td>
<td>$99–$299</td>
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</table>

### Question Books

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<tr>
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<th>Author/Publisher</th>
<th>Type/Quantity</th>
<th>Price</th>
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<tr>
<td>B+</td>
<td>First Aid Q&amp;A for the USMLE Step 1</td>
<td>Le McGraw-Hill, 2012, 784 pages</td>
<td>Test/1000 q</td>
<td>$46.00</td>
</tr>
<tr>
<td>B</td>
<td>Kaplan USMLE Step 1 Qbook</td>
<td>Kaplan, 2015, 456 pages</td>
<td>Test/850 q</td>
<td>$49.99</td>
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</table>

### Web and Mobile Apps

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<th>Type/Quantity</th>
<th>Price</th>
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<tr>
<td>A</td>
<td>SketchyMedical</td>
<td><a href="http://www.SketchyMedical.com">www.SketchyMedical.com</a></td>
<td>Review</td>
<td>$169–$249</td>
</tr>
<tr>
<td>A*</td>
<td>Boards and Beyond</td>
<td><a href="https://www.boardsbeyond.com">https://www.boardsbeyond.com</a></td>
<td>Review</td>
<td>$89–$149</td>
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<tr>
<td>A*</td>
<td>Cram Fighter</td>
<td><a href="http://www.cramfighter.com">www.cramfighter.com</a></td>
<td>Study plan</td>
<td>$29–$99</td>
</tr>
<tr>
<td>A*</td>
<td>First Aid Step 1 Express</td>
<td><a href="http://www.usmle-rx.com">www.usmle-rx.com</a></td>
<td>Review/Test</td>
<td>$99–$299</td>
</tr>
<tr>
<td>A*</td>
<td>First Aid Step 1 Flash Facts</td>
<td><a href="https://www.usmle-rx.com">https://www.usmle-rx.com</a></td>
<td>Flash cards</td>
<td>$49–$149</td>
</tr>
<tr>
<td>A*</td>
<td>WebPath: The Internet Pathology Laboratory</td>
<td><a href="http://library.med.utah.edu/WebPath/webpath.html">http://library.med.utah.edu/WebPath/webpath.html</a></td>
<td>Review/Test</td>
<td>Free</td>
</tr>
<tr>
<td>B+</td>
<td>Dr. Najeeb Lectures</td>
<td><a href="http://www.drnajeeblectures.com">www.drnajeeblectures.com</a></td>
<td>Review</td>
<td>$49–$199</td>
</tr>
<tr>
<td>B+</td>
<td>Firecracker</td>
<td>Firecracker Inc. <a href="http://www.firecracker.me">www.firecracker.me</a></td>
<td>Review/Test</td>
<td>$100–$400</td>
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<tr>
<td>B+</td>
<td>Medical School Pathology</td>
<td><a href="http://www.medicalschoolpathology.com">www.medicalschoolpathology.com</a></td>
<td>Review</td>
<td>Free</td>
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<tr>
<td>B+</td>
<td>Osmosis</td>
<td><a href="http://www.osmosis.org">www.osmosis.org</a></td>
<td>Test</td>
<td>$31–$599</td>
</tr>
<tr>
<td>B+</td>
<td>The Whole Brain Atlas</td>
<td>Johnson <a href="http://www.med.harvard.edu/aanlib/">www.med.harvard.edu/aanlib/</a></td>
<td>Review</td>
<td>Free</td>
</tr>
<tr>
<td>B+</td>
<td>USMLE Step 1 Mastery</td>
<td>usmle.usmlemastery.com</td>
<td>Test/1400 q</td>
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## Top-Rated Review Resources

### Comprehensive

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<td>First Aid for the Basic Sciences: General Principles</td>
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<td>O'Connell/Elsevier, 2013, 680 pages</td>
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### Anatomy, Embryology, and Neuroscience

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## Cell Biology and Histology

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## Abbreviations and Symbols

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<td>deep venous thrombosis</td>
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<td>5-hydroxyindoleacetic acid</td>
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<tr>
<td>HIE</td>
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<tr>
<td>His</td>
<td>histidine</td>
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<tr>
<td>HIT</td>
<td>heparin-induced thrombocytopenia</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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*Image abbreviation only
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>IO</td>
<td>inferior oblique [muscle]</td>
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<tr>
<td>IOP</td>
<td>intraocular pressure</td>
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<tr>
<td>IP$_3$</td>
<td>inositol triphosphate</td>
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<tr>
<td>IPV</td>
<td>inactivated polio vaccine</td>
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<tr>
<td>IR</td>
<td>current × resistance [Ohm’s law], inferior rectus [muscle]</td>
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<tr>
<td>IRV</td>
<td>inspiratory reserve volume</td>
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<tr>
<td>ITP</td>
<td>idiopathic thrombocytopenic purpura</td>
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<td>IUD</td>
<td>intratracheal device</td>
</tr>
<tr>
<td>IUCR</td>
<td>intratracheal growth restriction</td>
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<td>IV</td>
<td>intravenous</td>
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<td>IVC</td>
<td>inferior vena cava</td>
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<td>IVDU</td>
<td>intravenous drug use</td>
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<tr>
<td>IVIG</td>
<td>intravenous immunoglobulin</td>
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<td>JAK/STAT'</td>
<td>Janus kinase/signal transducer and activator of transcription [pathway]</td>
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<td>juxtaglomerular apparatus</td>
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<td>JVD</td>
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<tr>
<td>JVP</td>
<td>jugular venous pulse</td>
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<td>K+</td>
<td>potassium ion</td>
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<td>elimination constant</td>
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<td>Michaelis-Menten constant</td>
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<td>potassium hydroxide</td>
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<td>L</td>
<td>left, liver</td>
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<td>LA</td>
<td>left atrial, left atrium</td>
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<td>LAD</td>
<td>left anterior descending coronary artery</td>
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<td>LAF</td>
<td>left anterior fascicle</td>
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<td>leukocyte alkaline phosphatase</td>
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<td>Lat cond*</td>
<td>lateral condyle</td>
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<td>Lb*</td>
<td>lamellar body</td>
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<td>left coronary artery</td>
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<td>lecithin-cholesterol acyltransferase</td>
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<td>LCC*</td>
<td>left common carotid artery</td>
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<td>LCFA</td>
<td>long-chain fatty acid</td>
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<td>LCL</td>
<td>lateral collateral ligament</td>
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<td>LCME</td>
<td>Liaison Committee on Medical Education</td>
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<td>LC MV*</td>
<td>lymphocytic choriomeningitis virus</td>
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<td>LCX</td>
<td>left circumflex coronary artery</td>
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<td>LD$_{50}$</td>
<td>median lethal dose</td>
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<td>lactate dehydrogenase</td>
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<td>low-density lipoprotein</td>
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<td>LGN</td>
<td>lateral geniculate nucleus</td>
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<td>LGV</td>
<td>left gastric vein</td>
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<td>LH</td>
<td>lutetizing hormone</td>
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<td>LLL*</td>
<td>left lower lobe (of lung)</td>
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<td>LLQ</td>
<td>left lower quadrant</td>
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<tr>
<td>LM</td>
<td>light microscopy, left main coronary artery</td>
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<td>L MN</td>
<td>lower motor neuron</td>
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*Image abbreviation only
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<td>mitral stenosis, multiple sclerosis</td>
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<td>MSH</td>
<td>melanocyte-stimulating hormone</td>
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<td>MSM</td>
<td>men who have sex with men</td>
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<td>mtDNA</td>
<td>mitochondrial DNA</td>
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<tr>
<td>mtRNA</td>
<td>mitochondrial RNA</td>
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<td>mTOR</td>
<td>mammalian target of rapamycin</td>
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<td>metatarsophalangeal [joint]</td>
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<td>MTX</td>
<td>methotrexate</td>
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<td>MUAP</td>
<td>Medically Underserved Area and Population</td>
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<td>MVO₂</td>
<td>myocardial oxygen consumption</td>
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<td>MVP</td>
<td>mitral valve prolapse</td>
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<td>N⁺</td>
<td>nucleus</td>
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<td>Na⁺</td>
<td>sodium ion</td>
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<td>nuclear factor of activated T-cell</td>
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<td>N-methyl-d-aspartate</td>
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<td>neuroleptic malignant syndrome</td>
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<td>nitrous oxide</td>
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<td>NPH</td>
<td>neutral protamine Hagedorn, normal pressure hydrocephalus</td>
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<td>NRI</td>
<td>norepinephrine receptor inhibitor</td>
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<td>NRITI</td>
<td>non-nucleotide reverse transcriptase inhibitor</td>
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<td>Nu⁺</td>
<td>nucleolus</td>
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<td>oxaloacetic acid</td>
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<tr>
<td>OH₂</td>
<td>dihydroxy</td>
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<td>3⁰ OH</td>
<td>hydroxy</td>
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<td>polycystic kidney disease</td>
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<td>PKR</td>
<td>interferon-γ-induced protein kinase</td>
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<td>PKU</td>
<td>phenylketonuria</td>
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<td>PLP</td>
<td>pyridoxal phosphate</td>
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<td>PLS</td>
<td>Personalized Learning System</td>
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<td>PMN</td>
<td>polymorphonuclear leukocyte</td>
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<td>Pn</td>
<td>net filtration pressure</td>
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<tr>
<td>PNET</td>
<td>primitive neuroectodermal tumor</td>
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<td>PNS</td>
<td>peripheral nervous system</td>
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<tr>
<td>P02</td>
<td>partial pressure of oxygen</td>
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<td>PO4</td>
<td>salt of phosphoric acid</td>
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<td>phosphate</td>
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<td>Pop a</td>
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<td>Post</td>
<td>posterior</td>
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<td>peroxisome proliferator-activated receptor</td>
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<td>purified protein derivative</td>
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<td>proton pump inhibitor</td>
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<td>prostate-specific antigen</td>
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<td>PSS</td>
<td>progressive systemic sclerosis</td>
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<td>PT</td>
<td>prothrombin time</td>
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<td>PTH</td>
<td>parathyroid hormone</td>
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<td>PTHrP</td>
<td>parathyroid hormone-related protein</td>
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<td>PTSD</td>
<td>post-traumatic stress disorder</td>
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<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
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<tr>
<td>PV</td>
<td>plasma volume, venous pressure</td>
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<td>Pv</td>
<td>pulmonary vein</td>
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<td>PVC</td>
<td>polyvinyl chloride</td>
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<td>PVR</td>
<td>pulmonary vascular resistance</td>
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<td>correlation coefficient, right, R variable [group]</td>
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<td>Registration, Ranking, &amp; Results [system]</td>
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<td>right atrium</td>
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<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
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<td>RANKL</td>
<td>receptor activator of nuclear factor-κB ligand</td>
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<td>Ras</td>
<td>reticular activator</td>
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<td>RBF</td>
<td>renal blood flow</td>
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<tr>
<td>RCA</td>
<td>right coronary artery</td>
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<tr>
<td>REM</td>
<td>rapid eye movement</td>
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<td>RER</td>
<td>rough endoplasmic reticulum</td>
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<tr>
<td>Rh</td>
<td>rhesus antigen</td>
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<tr>
<td>RLL</td>
<td>right lower lobe (of lung)</td>
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<tr>
<td>RLQ</td>
<td>right lower quadrant</td>
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<td>RML</td>
<td>right middle lobe (of lung)</td>
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<td>ribonucleic acid</td>
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<td>RNP</td>
<td>ribonucleoprotein</td>
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<td>ROS</td>
<td>reactive oxygen species</td>
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<td>RPF</td>
<td>renal plasma flow</td>
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*Image abbreviation only*
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<td>single-stranded ribonucleic acid</td>
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<td>stomach</td>
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<td>St*</td>
<td>Shiga toxin</td>
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<td>STAR</td>
<td>Steroidogenic acute regulatory protein</td>
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<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
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<td>STI</td>
<td>sexually transmitted infection</td>
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<tr>
<td>STN</td>
<td>subthalamic nucleus</td>
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<td>SV</td>
<td>splenic vein, stroke volume</td>
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<td>superior vena cava</td>
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<td>SVT</td>
<td>supratentorial tachycardia</td>
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<td>trachea</td>
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<td>t1/2</td>
<td>half-life</td>
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<td>triiodothyronine</td>
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<td>thyroxine</td>
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<td>TAPVR</td>
<td>total anomalous pulmonary venous return</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<td>TBG</td>
<td>thyroxine-binding globulin</td>
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<td>TCA</td>
<td>tricarboxylic acid [cycle], tricyclic antidepressant</td>
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<td>cytotoxic T cell</td>
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<td>T-cell receptor</td>
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<td>triglyceride</td>
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<td>trans-Golgi apparatus</td>
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<td>trans-Golgi network</td>
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<td>Th cell</td>
<td>helper T cell</td>
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<td>tetrahydrofolic acid</td>
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<td>transient ischemic attack</td>
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<td>thymus</td>
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<td>TIBC</td>
<td>total iron-binding capacity</td>
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<td>TIPS</td>
<td>transjugular intrahepatic portosystemic shunt</td>
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<td>TLC</td>
<td>total lung capacity</td>
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<td>Tm</td>
<td>maximum rate of transport</td>
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<td>TMP</td>
<td>trimethoprim</td>
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<td>TN</td>
<td>true negative</td>
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<td>TNF</td>
<td>tumor necrosis factor</td>
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<td>tumor, node, metastases [staging]</td>
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<td>ToRChES</td>
<td>Toxoplasma gondii, rubella, CMV, HIV, HSV-2, syphilis</td>
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<td>true positive</td>
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<td>tPA</td>
<td>tissue plasminogen activator</td>
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<td>TPO</td>
<td>thyroid peroxidase, thrombopoietin</td>
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<td>TPP</td>
<td>thiamine pyrophosphate</td>
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<tr>
<td>TPR</td>
<td>total peripheral resistance</td>
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<tr>
<td>TR</td>
<td>tricuspid regurgitation</td>
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<td>TRAP</td>
<td>tartrate-resistant acid phosphatase</td>
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<td>thyrotropin-releasing hormone</td>
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<td>tRNA</td>
<td>transfer ribonucleic acid</td>
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<td>TSH</td>
<td>thyroid-stimulating hormone</td>
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<td>TSI</td>
<td>triple sugar iron</td>
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<td>toxic shock syndrome</td>
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<td>TSST</td>
<td>toxic shock syndrome toxin</td>
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<td>thrombotic thrombocytopenic purpura</td>
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<td>transthyretin</td>
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<td>uridine triphosphate</td>
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<td>ultraviolet</td>
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<td>vital capacity</td>
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<td>volume of distribution</td>
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<td>VD</td>
<td>physiologic dead space</td>
</tr>
<tr>
<td>V(D)J</td>
<td>heavy-chain hypervariable region [antibody]</td>
</tr>
<tr>
<td>VDRL</td>
<td>Venereal Disease Research Laboratory</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>Vh</td>
<td>variable region, heavy chain [antibody]</td>
</tr>
<tr>
<td>VHL</td>
<td>von Hippel-Lindau [disease]</td>
</tr>
<tr>
<td>VIP</td>
<td>vasoactive intestinal peptide</td>
</tr>
<tr>
<td>VIPoma</td>
<td>vasoactive intestinal polypeptide-secreting tumor</td>
</tr>
<tr>
<td>Vl</td>
<td>light-chain hypervariable region [antibody]</td>
</tr>
<tr>
<td>VL</td>
<td>ventral lateral [nucleus], variable region, light chain [antibody]</td>
</tr>
<tr>
<td>VLDL</td>
<td>very low density lipoprotein</td>
</tr>
<tr>
<td>VMA</td>
<td>vanillylmandelic acid</td>
</tr>
<tr>
<td>VMAT</td>
<td>vesicular monoamine transporter</td>
</tr>
<tr>
<td>Vmax</td>
<td>maximum velocity</td>
</tr>
<tr>
<td>VPL</td>
<td>ventral posterior nucleus, lateral</td>
</tr>
<tr>
<td>VPM</td>
<td>ventral posterior nucleus, medial</td>
</tr>
<tr>
<td>VPN</td>
<td>vancomycin, polymyxin, mexitelin [media]</td>
</tr>
<tr>
<td>VQ</td>
<td>ventilation/perfusion [ratio]</td>
</tr>
<tr>
<td>VRE</td>
<td>vancomycin-resistant enterococci</td>
</tr>
<tr>
<td>VSD</td>
<td>ventricular septal defect</td>
</tr>
<tr>
<td>Vt</td>
<td>tidal volume</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>VZV</td>
<td>varicella-zoster virus</td>
</tr>
<tr>
<td>VMAT</td>
<td>vesicular monoamine transporter</td>
</tr>
<tr>
<td>XR</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>X:XY</td>
<td>normal complement of sex chromosomes for female/male</td>
</tr>
<tr>
<td>ZDV</td>
<td>zidovudine [formerly AZT]</td>
</tr>
</tbody>
</table>

*Image abbreviation only
SECTION IV

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Biochemistry


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70 Vitamin D. X-ray of lower extremity in child with rickets. This image is a derivative work, adapted from the following source, available under. Courtesy of Dr. Michael L. Richardson. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under.

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85 Cystinuria. Hexagonal stones in urine. This image is a derivative work, adapted from the following source, available under. Courtesy of Cayla Devine.

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Immunology

98 Spleen. Red and white pulp. This image is a derivative work, adapted from the following source, available under Heinrichs S, Conover LF, Bueso-Ramos CE, et al. MYB2 is a sub-haplosufficient tumor suppressor gene in myeloid malignancy. eLife. 2013;2:e00825. DOI: 10.7554/eLife.00825. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.


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Microbiology


126 Stains: Image B. Trepheryma whipplei on periodic acid-Schiff stain. This image is a derivative work, adapted from the following source, available under. Courtesy of Dr. Ed Uthman.


126 **Stains:** Image E. *Coccioides immittis* on silver stain. Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

128 **Encapsulated bacteria.** Capsular swelling of *Streptococcus pneumoniae* using the Neufeld-Quellung test. Courtesy of the US Department of Health and Human Services.

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136 **Streptococcus pneumoniae.** Courtesy of the US Department of Health and Human Services and Dr. Mike Miller.

136 **Streptococcus pyogenes (group A streptococci).** Gram stain. This image is a derivative work, adapted from the following source, available under https://doi.org/10.1186/gb-2008-9-7-r114. Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under https://creativecommons.org/licenses/by/3.0/.

137 **Bacillus anthracis.** Ulcer with black eschar. Courtesy of the US Department of Health and Human Services and James H. Steele.


138 **Clostridia (with exotoxins): Image B.** Pseudomembranous enterocolitis on colonoscopy. This image is a derivative work, adapted from the following source, available under https://doi.org/10.1186/gb-2008-9-7-r114. Courtesy of Klinikum Dritter Orden für die Überlassung des Bildes zur Veröffentlichung. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under https://creativecommons.org/licenses/by/3.0/.

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140 **Mycobacteria.** Acid-fast stain. Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

140 **Tuberculosis.** Langhans giant cell in caseating granuloma. Courtesy of J. Hayman.

141 **Leprosy (Hansen disease): Image A.** “Glove and stocking” distribution. This image is a derivative work, adapted from the following source, available under https://doi.org/10.1186/gb-2008-9-7-r114. Courtesy of Bruno Jehle.

142 **Neisseria: Image A.** Intracellular *N gonorrhoeae*. Courtesy of the US Department of Health and Human Services and Dr. Mike Miller.

142 **Haemophilus influenzae: Image A.** Epiglottitis. This image is a derivative work, adapted from the following source, available under https://doi.org/10.1186/gb-2008-9-7-r114. Courtesy of Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.


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145 **Klebsiella.** Courtesy of the US Department of Health and Human Services.


146 Helicobacter pylori. Courtesy of the US Department of Health and Human Services, Dr. Patricia Fields, and Dr. Collette Fitzgerald.


147 Syphilis: Image A. Painless chancre in 1° syphilis. Courtesy of the US Department of Health and Human Services and James Guthany.


148 Gardnerella vaginalis. Courtesy of the US Department of Health and Human Services and Dr. Leanor McClenan.

149 Blastomyces dermatitidis. Courtesy of the US Department of Health and Human Services and Dr. D.T. McLennan.


150 Mycoplasma pneumoniae. This image is a derivative work, adapted from the following source, available under . Rotten S, Kosower ND, Komspan JD. Contamination of tissue cultures by Mycoplasma. In: Ceccherini-Nelli L, ed: Biomedical tissue culture. 2016. DOI: 10.5772/51518.


150 Cutaneous mycoses: Image G. Tinea versicolor. This image is a derivative work, adapted from the following source, available under . Courty of Sarah (Rosenau) Kof. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .

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150 Opportunistic fungal infections: Image B. Germ tubes of Candida albicans. This image is a derivative work, adapted from the following source, available under . Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .


150 Opportunistic fungal infections: Image G. Cryptococcus neoformans on India ink stain. Courtesy of the US Department of Health and Human Services and Dr. Leanor Haley.


156 Protozoa—CNS infections: Image B. Toxoplasma gondii tachyzoite. Courtesy of the US Department of Health and Human Services and Dr. L.L. Moore, Jr.


158 Protozoa—others: Image A. Trypanosoma cruzi. Courtesy of the US Department of Health and Human Services and Dr. Mae Melvin.

158 Protozoa—others: Image B. Leishmania donovani. Courtesy of the US Department of Health and Human Services and Dr. Francis W. Chandler. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.


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165 Herpesviruses: Image B. Herpes labialis. Courtesy of the US Department of Health and Human Services and Dr. Herrmann.


165 Herpesviruses: Image G. Atypical lymphocytes in Epstein-Barr virus infection. This image is a derivative work, adapted from the following source, available under https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609005/PDF/mednet_01859.pdf. Courtesy of Dr. Ed Uhlman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.


166 HSV identification. Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609005/PDF/mednet_01859.pdf. Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609005/PDF/mednet_01859.pdf. Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609005/PDF/mednet_01859.pdf.

168 Rotavirus. Courtesy of the US Department of Health and Human Services and Erskine Palmer.


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182 ToRCHeS infections: Image B. Periventricular calcifications in congenital cytomegalovirus infection. This image is a derivative work, adapted from the following source, available under https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609005/PDF/mednet_01859.pdf. Bonthius D, Perlman S. Congenital viral infections of the brain: lessons learned from lymphocytic choriomeningitis virus in the neonatal rat. PLoS Pathog. 2007;3:e149. DOI: 10.1371/journal.ppat.0030149. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

183 Red rashes of childhood: Image C. Child with scarlet fever. This image is a derivative work, adapted from the following source, available under https://www.badobadop.co.uk. Red man syndrome. This image is a derivative work, adapted from the following source, available under https://www.badobadop.co.uk. Red rashes of childhood: Image D. Chicken pox. Courtesy of the US Department of Health and Human Services.

184 Sexually transmitted infections. Donorania. Courtesy of the US Department of Health and Human Services and Dr. Pinozzi.

185 Pelvic inflammatory disease: Image A. Purulent cervical discharge. This image is a derivative work, adapted from the following source, available under https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609005/PDF/mednet_01859.pdf. Courtesy of SOS-AIDS Amsterdam. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3609005/PDF/mednet_01859.pdf.


Pathology

209 Necrosis: Image A. Coagulative necrosis. Courtesy of the US Department of Health and Human Services and Dr. Steven Rosenberg.


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212 Acute inflammation. Courtesy of Dr. Douglas Mata.


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224 Psammoma bodies. Courtesy of the US Department of Health and Human Services and the Armed Forces Institute of Pathology.

226 Common metastases: Image A. Brain metastases from breast cancer. This image is a derivative work, adapted from the following source, available under Creative Commons Attribution License. Courtesy of Jmarchn. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under Creative Commons Attribution License.


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Cardiovascular

Congenital heart diseases: Image A. Tetralogy of Fallot. This image is a derivative work, adapted from the following source, available under [access]. Rashid AKM: Heart diseases in Down syndrome. In: Dey S, ed: Down syndrome. DOI: 10.5772/46009. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.


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Bacterial endocarditis: Image B. Courtesy of Dr. Nicholas Malone.


Bacterial endocarditis: Image D. Janeway lesions on sole. This image is a derivative work, adapted from the following source, available under [access]. Courtesy of DeNanneke.

Rheumatic fever. Aochoff body and Autschakow cells. This image is a derivative work, adapted from the following source, available under [access]. Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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309 **Vasculitides: Image A.** Temporal arteritis histology. This image is a derivative work, adapted from the following source, available under [credit]. Courtesy of Marvin. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [credit].

309 **Vasculitides: Image B.** Angiogram in patient with Takayasu arteritis. [Credit] Courtesy of the US Department of Health and Human Services and Justin Ly.

309 **Vasculitides: Image C.** Microaneurysms in polyarteritis nodosa. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

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Renal

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Reproductive

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