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.
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### SECTION III  
**HIGH-YIELD ORGAN SYSTEMS**  

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Preface

With the 26th 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:

- 50+ entirely new facts, including a new section on quality improvement principles and safety science.
- Hundreds of major fact updates culled from more than 100,000 comments and suggestions.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of more than 30 student authors who excelled on their Step 1 examinations and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- Updated with more than 250 new or revised full-color photos to help visualize various disorders, descriptive findings, and basic science concepts. Labeled and captioned photographs have been optimized to aid retention by engaging visual memory in a manner complementary to mnemonics.
- Updated with dozens of new and revised diagrams. We continue to expand our collaboration with USMLE-Rx (MedIQ Learning, LLC) to develop and enhance illustrations with improved information design to help students integrate pathophysiology, therapeutics, and diseases into memorable frameworks for annotation and personalization.
- Thicker, embossed cover and heavy-duty binding for increased durability and longevity.
- A revised exam preparation guide with updated data from the NBME and NRMP. The guide also features new high-yield techniques for efficient and effective test preparation. The updated supplemental guide for IMGs, osteopathic and podiatry students, and students with a disability can be found at our blog, www.firstaidteam.com.
- An updated summary guide to student-recommended USMLE Step 1 review resources, including mobile apps for iOS and Android. The full resource guide with detailed descriptions can be found at our blog, www.firstaidteam.com.
- Real-time Step 1 updates and corrections can also be found exclusively on our blog.

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*.


For help on the First Aid Team blog, thanks to Mark Ard (Editor), Edison Cano, Tim Durso, Luke Murray, Ryan Nguyen, and Joe Savarese. For support and encouragement throughout the process, we are grateful to Thao Pham and Jonathan Kirsch, Esq. Thanks to Louise Petersen for organizing and supporting the project. Thanks to our publisher, McGraw-Hill, for the valuable assistance of its staff, including Midge Haramis and Jeffrey Herzich. For enthusiasm, support, and commitment for this ongoing and ever-challenging project, thanks to our editor, Catherine Johnson.

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 collaborative editing platform, which allows us to efficiently manage thousands of contributions. Thanks to Dr. Richard Usatine for his outstanding dermatologic and clinical 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. We especially thank Dr. Kristine Krafts for many insightful text and image contributions throughout the extensive revision.

For exceptional editorial support, enormous thanks to our tireless senior editor, Emma D. Underdown, and her team of editors, Christine Diedrich, Allison Battista, Linda Davoli, Janene Matragrano, Isabel Nogueira, Rebecca Stigall, and Hannah Warnshuis. Many thanks to Tara Price for page design and all-around InDesign expertise. Special thanks to Jan Bednarczuk for a greatly improved index. We are also grateful to our medical illustrators, Hans Neuhart and Diana Kryski, for their creative work on the new and updated illustrations. In particular, we thank Diana and Dr. Krafts for optimizing all of our photographs. 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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Athens, Ohio           | Patrick Sylvester
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.

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.

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.

Contributions submitted by May 15, 2016, receive priority consideration for the 2017 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 2016, 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.
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.

LET FIRST AID BE YOUR GUIDE: 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, green for UWorld Step 1 Qbank, blue for USMLE-Rx Step 1 Qmax).
- 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, such as course syllabi.

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>Blood, Plasma, Serum</th>
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<th>SI Reference Intervals</th>
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</thead>
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<tr>
<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>
<td></td>
<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>&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</td>
<td>136–145 mEq/L.</td>
<td>136–145 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95–105 mEq/L.</td>
<td>95–105 mmol/L</td>
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<tr>
<td>*Potassium</td>
<td>3.5–5.0 mEq/L.</td>
<td>3.5–5.0 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22–28 mEq/L.</td>
<td>22–28 mmol/L</td>
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<tr>
<td>Magnesium</td>
<td>1.5 mEq/L.</td>
<td>0.75–1.0 mmol/L</td>
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<td>Gases, arterial blood (room air)</td>
<td></td>
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<tr>
<td>$P_O_2$</td>
<td>75–105 mm Hg</td>
<td>10.0–14.0 kPa</td>
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<tr>
<td>$P_CO_2$</td>
<td>33–44 mm Hg</td>
<td>4.4–5.9 kPa</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Proteins, serum</td>
<td></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>
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<thead>
<tr>
<th>Cerebrospinal Fluid Reference Range SI Reference Intervals</th>
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<tr>
<td>Glucose 40–70 mg/dL 2.2–3.9 mmol/L</td>
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**Hematologic**

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

**Leukocyte count and differential**

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

**Sweat**

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

**Urine**

| 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 (e.g., 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 (e.g., 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 (e.g., 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. You are allowed to review notes/study material during breaks on exam day.

## After the Exam
- Celebrate, regardless.
- Send feedback to us on our website at [www.firstaidteam.com](http://www.firstaidteam.com).
"A mind of moderate capacity which closely pursues one study must infallibly arrive at great proficiency in that study."
—Mary Shelley, Frankenstein

"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
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 more resources than you can ever use
- 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.

The test at a glance:
- 8-hour exam
- Total of 308 multiple choice items
- 7 test blocks (60 min/block)
- 44 test items per block
- 45 minutes of break time, plus another 15 if you skip the tutorial

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:

**DISCIPLINE**
Behavioral Sciences  
Biochemistry  
Genetics  
Gross Anatomy & Embryology  
Histology & Cell Biology  
Microbiology & Immunology  
Nutrition  
Pathology  
Pharmacology  
Physiology

**ORGAN SYSTEM**
Behavioral Health & Nervous Systems/Special Senses  
Biostatistics & Epidemiology/Population Health  
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

In 2015, a new, detailed, 31-page content outline was released. However, it is too early to say how useful the information will be in determining high-yield topics.

**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 44 questions each for a total of 308 questions, 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—unless the questions are part of a sequential item test set (see p. 4).

**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 132 practice questions 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.

The typical question screen in the CBT consists of a question followed by a number of choices on which an examinee can click, together with several navigational buttons on the top of the screen. 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 USMLE also has a sequential item test format. These questions are grouped together in the list of questions on the left side of the screen and must be completed in order. After an examinee answers the first question, he or she will be given the option to proceed to the next item but will be warned that the answer to the first question will be locked. After proceeding, examinees will not be able to change the answer selected for that question.
The question stem and the answer chosen will be available to the examinee as he or she answers the next question(s) in the sequence.

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. Finally, 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. Being familiar with these features can save time and may help you better 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 (150 questions) available on the USMLE website, www.usmle.org, are used at these sessions. No new items will be presented. The session is divided into a short tutorial and three 1-hour blocks of 44 test items each at a cost of $75, if your testing region is in the United States or Canada. 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 2015 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 voice-mail 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 (e.g., 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. 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:

- 15 minutes  Tutorial (skip if familiar with test format and features)
- 7 hours  Seven 60-minute question blocks
- 45 minutes  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 78 seconds).

The computer will 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.

Forty-five minutes is the minimum break time for the day, 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 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?**

One-best-answer multiple choice items (either singly or as part of a sequential
item set) are the only question type on the exam. 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.

Be careful to watch the clock on your break time.

Nearly three fourths of Step 1 questions begin
with a description of a patient.
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 308 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.

The NBME provides a three-digit test score based on the total number of items answered correctly on the examination (see Figure 1). 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. The most recent mean score was 230 with a standard deviation of 20.

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.

The mean Step 1 score for US medical students continues to rise, from 200 in 1991 to 230 in 2015.
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.

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.

Practice questions may be easier than the actual exam.

| TABLE 1. Passing Rates for the 2013–2014 USMLE Step 1.2 |
|---------------------------------|---|---|---|---|
|                                | 2013 | % Passing | 2014 | % Passing |
| Allopathic 1st takers          | 19,108 | 97% | 19,582 | 96% |
| Repeaters                      | 915 | 72% | 812 | 68% |
| Allopathic total               | 20,023 | 95% | 20,394 | 95% |
| Osteopathic 1st takers         | 2,680 | 94% | 2,810 | 93% |
| Repeaters                      | 46 | 74% | 36 | 69% |
| Osteopathic total              | 2,726 | 94% | 2,846 | 93% |
| Total US/Canadian              | 22,749 | 95% | 23,240 | 95% |
| IMG 1st takers                 | 14,649 | 79% | 15,149 | 78% |
| Repeaters                      | 3,772 | 44% | 2,889 | 38% |
| IMG total                      | 18,421 | 72% | 18,038 | 72% |
| Total Step 1 examinees         | 41,170 | 85% | 41,278 | 85% |
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.

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. Please note that the CBSSAs do not list the correct answers to the questions at the end of the session. However, forms can be purchased with an extended feedback option; these tests show you which questions you answered incorrectly, but do not show you the correct answer or explain why your choice was wrong. Feedback from the self-assessment takes the form of a performance profile and nothing more. The NBME charges $50 for assessments without feedback and $60 for assessments with expanded feedback. The fees are payable by credit card or money order. For more information regarding the CBSE and the CBSSA, visit the NBME’s website at www.nbme.org.

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

### 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>
</tr>
<tr>
<td>88</td>
<td>245</td>
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<tr>
<td>86</td>
<td>240</td>
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<td>84</td>
<td>235</td>
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<td>78</td>
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<td>74</td>
<td>210</td>
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<tr>
<td>72</td>
<td>205</td>
</tr>
<tr>
<td>70</td>
<td>200</td>
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<td>68</td>
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<td>48</td>
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<td>46</td>
<td>140</td>
</tr>
<tr>
<td>≤ 44</td>
<td>≤ 135</td>
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</tbody>
</table>
TABLE 3. CBSSA to USMLE Score Prediction.

<table>
<thead>
<tr>
<th>CBSSA Score</th>
<th>Approximate USMLE Step 1 Score</th>
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<tbody>
<tr>
<td>150</td>
<td>153</td>
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<tr>
<td>200</td>
<td>164</td>
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<td>250</td>
<td>175</td>
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<tr>
<td>750</td>
<td>281</td>
</tr>
<tr>
<td>800</td>
<td>292</td>
</tr>
</tbody>
</table>

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.

Certain highly competitive residency programs, such as those in plastic surgery and orthopedic surgery, have acknowledged their use of Step 1 scores in the selection process. In such residency programs, greater emphasis may be placed on attaining a high score, so students who seek to enter these programs may wish to consider aiming for a very high score on the Step 1 exam (see Figure 2). 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.

FIGURE 2. Median USMLE Step 1 Score by Specialty for Matched US Seniors.²

²Vertical lines show interquartile range.
Step 1. Below are three study methods to use during the preclinical years and their effectiveness for Step 1 preparation. 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.

**Highlight, Read, and Reread**

The most passive of the three methods, this generally consists of sitting through lectures and highlighting relevant material (sometimes in an assortment of colors). Notes are jotted in the margins, but the general bulk of information is in the same order presented by the various lecturers. Students then go home and reread the notes, focusing on the highlights. It is difficult to test integration of concepts. These notes (usually in the thousands of pages) are almost useless for Step 1 preparation.

**Flash cards**

There is no shortage of flash card applications, from make-your-own cards to purchasable premade decks. Self-made flash cards, if done correctly, offer the ability to objectively test necessary facts. Written in an open-ended format and coupled with spaced repetition, they train both recognition and recall. Apps exist for various smartphones and tablets, so the flash cards are always accessible. However, the ease of quickly creating digital cards and sharing 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 many for Step 1 preparation. Unless you have specified high-yield cards (and checked the content with high-yield resources), stick to premade cards by reputable sources that curate the vast amount of knowledge for you.

**Tables and Summaries**

This is the most active (and time intensive) form of learning. It consists of integrating the pertinent information from paragraphs on each subject into tables that cut across topics within the same category. The key is to synthesize the sequentially presented material. Sensitive and specific findings should be highlighted. While many review sources offer this material in various styles and formats, your own class notes may in fact be concise enough to use as an adjunct for Step 1 preparation, and they have the added benefit of being organized to your liking.
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 3). 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.3

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.

FIGURE 3. Typical Timeline for the USMLE Step 1.
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 school work 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 150 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 46 questions 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. xvii, How to Contribute). Sharing your experience will benefit fellow medical students and IMGs.
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.

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 (e.g., drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent across 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 308 questions. Note that each one-hour block contains 44 questions. This works out to about 82 seconds per question. If you find yourself spending too much time on a question, mark the question, make an educated guess, and move on. If time permits, come back to the question later. 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. 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.
IF YOU FAILED

Even if you came out of the exam room feeling that you failed, seeing that failing grade can be traumatic, and it is natural to feel upset. Different people react in different ways: For some it is a stimulus to buckle down and study harder; for others it may “take the wind out of their sails” for a few days; and it may even lead to a reassessment of individual goals and abilities. In some instances, however, failure may trigger weeks or months of sadness, feelings of hopelessness, social withdrawal, and inability to concentrate—in other words, true clinical depression. If you think you are depressed, please seek help.

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


Please visit www.usmle-rx.com/bonus/ to view this section.

- First Aid for the International Medical Graduate  2
- First Aid for the Osteopathic Medical Student  12
- First Aid for the Podiatric Medical Student  17
- First Aid for the Student with a Disability  19
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 2016 edition of First Aid for the USMLE Step 1 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 behavioral science, biochemistry, microbiology, immunology, basic pathology, and basic pharmacology. 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.
”It is a mathematical fact that fifty percent of all doctors graduate in the bottom half of their class.”
—Author Unknown

”It’s psychosomatic. You need a lobotomy. I’ll get a saw.”
—Calvin, “Calvin & Hobbes”

”There are two kinds of statistics: the kind you look up and the kind you make up.”
—Rex Stout

”On a long enough time line, the survival rate for everyone drops to zero.”
—Chuck Palahniuk

A heterogeneous mix of epidemiology, biostatistics, ethics, psychology, public health, and more falls under the heading of behavioral science. The exam has recently added an emphasis on patient safety and quality improvement topics. Many medical students do not diligently study this discipline because the material is felt to be easy or a matter of common sense. In our opinion, this is a missed opportunity.

Behavioral science questions may seem less concrete than questions from other disciplines, as they require an awareness of the psychosocial aspects of medicine. For example, if a patient does or says something, what should you do or say in response? These so-called quote questions now constitute much of the behavioral science section. Medical ethics and medical law are also appearing with increasing frequency. In addition, the key aspects of the doctor-patient relationship (eg, communication skills, open-ended questions, facilitation, silence) are high yield, as are biostatistics and epidemiology, which are the foundations of evidence-based medicine. Make sure you can apply biostatistical concepts such as sensitivity, specificity, and predictive values in a problem-solving format.
### Observational studies

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>DESIGN</th>
<th>MEASURES/EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional study</td>
<td>Collects data from a group of people to assess frequency of disease (and related risk factors) at a particular point in time. Asks, “What is happening?”</td>
<td>Disease prevalence. Can show risk factor association with disease, but does not establish causality.</td>
</tr>
<tr>
<td>Case-control study</td>
<td>Compares a group of people with disease to a group without disease. Looks for prior exposure or risk factor. Asks, “What happened?”</td>
<td>Odds ratio (OR). “Patients with COPD had higher odds of a history of smoking than those without COPD.”</td>
</tr>
<tr>
<td>Cohort study</td>
<td>Compares a group with a given exposure or risk factor to a group without such exposure. Looks to see if exposure affects the likelihood of disease. Can be prospective (asks, “Who will develop disease?”) or historical (asks, “Who developed the disease [exposed vs nonexposed]?”)</td>
<td>Relative risk (RR). “Smokers had a higher risk of developing COPD than nonsmokers.”</td>
</tr>
<tr>
<td>Twin concordance study</td>
<td>Compares the frequency with which both monozygotic twins or both dizygotic twins develop the same disease.</td>
<td>Measures heritability and influence of environmental factors (“nature vs nurture”).</td>
</tr>
<tr>
<td>Adoption study</td>
<td>Compares siblings raised by biological vs adoptive parents.</td>
<td>Measures heritability and influence of environmental factors.</td>
</tr>
</tbody>
</table>

### 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.

<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.</td>
<td>“Is it safe?” Assesses safety, toxicity, pharmacokinetics, and pharmacodynamics.</td>
</tr>
<tr>
<td>Phase II</td>
<td>Small 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.</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. TP = true positive; FP = false positive; TN = true negative; FN = false negative.

Sensitivity and specificity are fixed properties of a test. PPV and NPV vary depending on disease prevalence.

**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.

Sensitivity = TP / (TP + FN) = 1 − false-negative rate

SN-N-OUT = highly Sensitive test, when Negative, rules OUT disease

If sensitivity is 100%, TP / (TP + FN) = 1, FN = 0, and 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.

Specificity = TN / (TN + FP) = 1 − false-positive rate

SP-P-IN = highly Specific test, when Positive, rules IN disease

If specificity is 100%, TN / (TN + FP) = 1, FP = 0, and all positives must be TPs

**Positive predictive value**

Proportion of positive test results that are true positive.

Probability that a person who has a positive test result actually has the disease.

PPV = TP / (TP + FP)

PPV varies directly with pretest probability (baseline risk, such as prevalence of disease): high pretest probability → high PPV

**Negative predictive value**

Proportion of negative test results that are true negative.

Probability that a person with a negative test result actually does not have the disease.

NPV = TN / (TN + FN)

NPV varies inversely with prevalence or pretest probability: high pretest probability → low NPV

**Possible Cutoff Values**

A = 100% sensitivity cutoff value

B = practical compromise between specificity and sensitivity

C = 100% specificity cutoff value

Lowering the cutoff point:

- Sensitivity ↑ NPV
- Specificity ↓ PPV

Raising the cutoff point:

- Specificity ↑ PPV
- Sensitivity ↓ NPV

**Incidence vs prevalence**

Incidence = # of new cases / # of people at risk (during a specified time period)

Prevalence = # of existing cases / Total # of people in a population (at a point in time)

Prevalence ≈ incidence for short duration disease (eg, common cold).

Prevalence > incidence for chronic diseases, due to large # of existing cases (eg, diabetes).

Incidence looks at new cases (incidents).

Prevalence looks at all current cases.

Prevalence = pretest probability.
Quantifying risk

Definitions and formulas are based on the classic 2 × 2 or contingency table.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Risk factor or intervention</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. Odds that the group with the disease (cases) was exposed to a risk factor (a/c) divided by the odds that the group without the disease (controls) was exposed (b/d).

\[ OR = \frac{a/c}{b/d} = \frac{ad}{bc} \]

### Relative risk
Typically used in cohort studies. Risk of developing disease in the exposed group divided by risk in the unexposed group (eg, if 21% of smokers develop lung cancer vs 1% of nonsmokers, RR = 21/1 = 21). If prevalence is low, OR ≈ RR.

\[ RR = \frac{a/(a + b)}{c/(c + d)} \]

### Attributable risk
The difference in risk between exposed and unexposed groups, or the proportion of disease occurrences that are attributable to the exposure (eg, if risk of lung cancer in smokers is 21% and risk in nonsmokers is 1%, then 20% of the lung cancer risk in smokers is attributable to smoking).

\[ AR = \frac{a}{a + b} - \frac{c}{c + d} \]

### 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).

\[ RRR = 1 - RR \]

### 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).

\[ ARR = \frac{c}{c + d} - \frac{a}{a + b} \]

### Number needed to treat
Number of patients who need to be treated for 1 patient to benefit.

\[ NNT = \frac{1}{ARR} \]

### Number needed to harm
Number of patients who need to be exposed to a risk factor for 1 patient to be harmed.

\[ NNH = \frac{1}{AR} \]
### Precision vs accuracy

<table>
<thead>
<tr>
<th><strong>Precision</strong></th>
<th><strong>Accuracy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>The consistency and reproducibility of a test</td>
<td>The trueness of test measurements (validity).</td>
</tr>
<tr>
<td>(reliability).</td>
<td>The absence of systematic error or bias in a test.</td>
</tr>
<tr>
<td>The absence of random variation in a test.</td>
<td></td>
</tr>
</tbody>
</table>

Random error ↓ precision in a test.  
↑ precision → ↓ standard deviation.  
↑ precision → ↑ statistical power \((1 - \beta)\).

<table>
<thead>
<tr>
<th><strong>Accurate, not precise</strong></th>
<th><strong>Precise, not accurate</strong></th>
<th><strong>Accurate and precise</strong></th>
<th><strong>Not accurate, not precise</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>![Accurate, not precise]</td>
<td>![Precise, not accurate]</td>
<td>![Accurate and precise]</td>
<td>![Not accurate, not precise]</td>
</tr>
</tbody>
</table>
### Bias and study errors

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DEFINITION</th>
<th>EXAMPLES</th>
<th>STRATEGY TO REDUCE BIAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruiting participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection bias</td>
<td>Error in assigning subjects to a study group resulting in an unrepresentative sample. Most commonly a sampling bias.</td>
<td>Berkson bias—study population selected from hospital is less healthy than general population. Healthy worker effect—study population is healthier than the 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>Performing study</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 HPV and cervical cancer not observed when using non-standardized classifications.</td>
<td>Use objective, standardized, and previously tested methods of data collection that are planned ahead of time.</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; self-fulfilling prophecy).</td>
<td>If observer expects treatment group to show signs of recovery, then he is more likely to document positive outcomes.</td>
<td></td>
</tr>
<tr>
<td>Interpreting results</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 → factor distorts or confuses effect of exposure on outcome.</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) Restriction Randomization</td>
</tr>
<tr>
<td>Lead-time bias</td>
<td>Early detection is confused with † survival.</td>
<td>Early detection makes it seem as though survival has increased, but the natural history of the disease has not changed</td>
<td>Measure “back-end” survival (adjust survival according to the severity of disease at the time of diagnosis)</td>
</tr>
</tbody>
</table>
**Statistical distribution**

<table>
<thead>
<tr>
<th>Measures of central tendency</th>
<th>Mean = (sum of values)/(total number of values).</th>
<th>Most affected by outliers (extreme values).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median = 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>
<td></td>
</tr>
<tr>
<td>Mode = most common value.</td>
<td>Least affected by outliers.</td>
<td></td>
</tr>
</tbody>
</table>

**Measures of dispersion**

| Standard deviation = how much variability exists from the mean in a set of values. | σ = SD; n = sample size. |
| Standard error of the mean = an estimate of how much variability exists between the sample mean and the true population mean. | SEM = σ/√n; SEM $\downarrow$ as n ↑. |

**Normal distribution**

Gaussian, also called bell-shaped.
Mean = median = mode.

**Nonnormal distributions**

- **Bimodal**
  Suggests two different populations (e.g., metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).

- **Positive skew**
  Typically, mean > median > mode.
  Asymmetry with longer tail on right.

- **Negative skew**
  Typically, mean < median < mode.
  Asymmetry with longer tail on left.

**Statistical hypotheses**

<table>
<thead>
<tr>
<th>Null (H₀)</th>
<th>Hypothesis of no difference or relationship (e.g., there is no association between the disease and the risk factor in the population).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative (H₁)</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>

<table>
<thead>
<tr>
<th>Reality</th>
<th>Study results support:</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₀</td>
<td>H₁</td>
</tr>
<tr>
<td>Power (1 - β)</td>
<td>α Type I error</td>
</tr>
<tr>
<td>β Type II error</td>
<td>Correct</td>
</tr>
</tbody>
</table>
### Outcomes of statistical hypothesis testing

<table>
<thead>
<tr>
<th><strong>Correct result</strong></th>
<th>Stating that there is an effect or difference when one exists (null hypothesis rejected in favor of alternative hypothesis).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stating that there is not an effect or difference when none exists (null hypothesis not rejected).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Incorrect result</strong></th>
<th>Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I error (α)</strong></td>
<td>α is the probability of making a type I error. p is judged against a preset α level of significance (usually 0.05). If p &lt; 0.05, then there is less than a 5% chance that the data will show something that is not really there.</td>
</tr>
<tr>
<td></td>
<td>Also known as false-positive error.</td>
</tr>
<tr>
<td></td>
<td>α = you “observed” a difference that did not exist. You can never “prove” the alternate hypothesis, but you can reject the null hypothesis as being very unlikely.</td>
</tr>
<tr>
<td><strong>Type II error (β)</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></td>
<td>β is the probability of making a type II error. β is related to statistical power (1 – β), which is the probability of rejecting the null hypothesis when it is false.</td>
</tr>
<tr>
<td></td>
<td>↑ power and ↓ β by:</td>
</tr>
<tr>
<td></td>
<td>* ↑ sample size</td>
</tr>
<tr>
<td></td>
<td>* ↑ expected effect size</td>
</tr>
<tr>
<td></td>
<td>* ↑ precision of measurement</td>
</tr>
<tr>
<td></td>
<td>Also known as false-negative error.</td>
</tr>
<tr>
<td></td>
<td>β = you were blinded by the truth. If you ↑ sample size, you ↑ power. There is power in numbers.</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 = mean ± Z(SEM).
- The 95% CI (corresponding to p = .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 H₀ is not rejected.
- If the 95% CI for odds ratio or relative risk includes 1, H₀ is not rejected.
- If the CIs between 2 groups do not overlap → statistically significant difference exists.
- If the CIs between 2 groups overlap → usually no significant difference exists.
**Common statistical tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>t-test</strong></td>
<td>Checks differences between means of 2 groups.</td>
<td>Example: comparing the mean blood pressure between men and women.</td>
</tr>
<tr>
<td><strong>ANOVA</strong></td>
<td>Checks differences between means of 3 or more groups.</td>
<td>Example: comparing the mean blood pressure between members of 3 different ethnic groups.</td>
</tr>
<tr>
<td><strong>Chi-square (χ²)</strong></td>
<td>Checks differences between 2 or more percentages or proportions of categorical outcomes (not mean values).</td>
<td>Example: comparing the percentage of members of 3 different ethnic groups who have essential hypertension.</td>
</tr>
</tbody>
</table>

**Pearson correlation coefficient (r)**

- $r$ 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 = $r^2$ (value that is usually reported).

---

**Core ethical principles**

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomy</strong></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><strong>Beneficence</strong></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 (eg, mandatory TB treatment). Traditionally, patient interest supersedes.</td>
</tr>
<tr>
<td><strong>Nonmaleficence</strong></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><strong>Justice</strong></td>
<td>To treat persons fairly and equitably. This does not always imply equally (eg, 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:
- Patient lacks decision-making capacity or is legally incompetent
- Implied consent in an emergency
- Therapeutic privilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity
- Waiver—patient explicitly waives the right of informed consent

Consent for minors

A minor is generally any person < 18 years old. Parental consent laws in relation to health care vary by state. In general, parental consent should be obtained unless emergent treatment is required (eg, blood transfusion) even if it opposes parental religious/cultural beliefs, or if a minor is legally emancipated (eg, is married, is self supporting, or is in the military).

Exceptions:
- Sex (contraception, STIs, pregnancy)
- Drugs (substance abuse)
- Rock and roll (emergency/trauma)

Physicians should always encourage healthy minor-guardian communication.

Decision-making capacity

Physician must determine whether the patient is psychologically and legally capable of making a particular health care decision.

Components:
- Patient is ≥ 18 years old or otherwise legally emancipated
- Patient makes and communicates a choice
- Patient is informed (knows and understands)
- Decision remains stable over time
- Decision is consistent with patient’s values and goals, not clouded by a mood disorder
- Decision is not a result of altered mental status (eg, delirium, psychosis, intoxication)
**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.

**Living will (written advance directive)**  
Describes treatments the patient wishes to receive or not receive if he/she loses decision-making capacity. Usually, patient directs physician to withhold or withdraw life-sustaining treatment if he/she develops a terminal disease or enters a persistent vegetative state.

**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.

**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 > adult siblings > other relatives.

**Confidentiality**  
Confidentiality respects patient privacy and autonomy. If patient is not present or is incapacitated, 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 exists 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:

- Reportable diseases (eg, STIs, TB, hepatitis, food poisoning)—physicians may have a duty to warn public officials, who will then notify people at risk
- The Tarasoff decision—California Supreme Court decision requiring physician to directly inform and protect potential victim from harm
- Child and/or elder abuse
- Impaired automobile drivers (eg, epileptics)
- Suicidal/homicidal patients
### Ethical situations

<table>
<thead>
<tr>
<th>SITUATION</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 or 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 or 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.</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 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 anesthetics 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.</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>
<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 that the boy is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).</td>
</tr>
</tbody>
</table>
Early developmental milestones

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>Infants</td>
<td>Parents</td>
<td>Start</td>
<td>Observing,</td>
</tr>
<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>Orients—first to voice (by 4 mo), then to name and gestures (by 9 mo)</td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Points to objects (by 12 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toddler</th>
<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>
<td>Words—200 words by age 2 (2 zeros), 2-word sentences</td>
</tr>
<tr>
<td>Climbs stairs (by 18 mo)</td>
<td>Rapprochement—moves away from and returns to mother (by 24 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cubes stacked—number = age (yr) × 3</td>
<td>Realization—core gender identity formed (by 36 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cultured—feeds self with fork and spoon (by 20 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kicks ball (by 24 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preschool</th>
<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>
<td>Language—1000 words by age 3 (3 zeros), uses complete sentences and prepositions (by 4 yr)</td>
</tr>
<tr>
<td>Drawings—copies line or circle, stick figure (by 4 yr)</td>
<td>Friends—cooperative play, has imaginary friends (by 4 yr)</td>
<td>Legends—can tell detailed stories (by 4 yr)</td>
<td></td>
</tr>
</tbody>
</table>
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 and ↑ early awakenings
- ↑ suicide rate
- ↓ vision, hearing, immune response, bladder control
- ↓ renal, pulmonary, GI function
- ↓ muscle mass, ↑ fat

Libido is stable in men but decreases in women after menopause.
Intelligence does not decrease.

Presbycusis—sensorineural hearing loss (often of higher frequencies) due to destruction of hair cells at the cochlear base (preserved low-frequency hearing at apex).

Disease prevention

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Prevent disease before it occurs (eg, HPV vaccination)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Screen early for and manage existing but asymptomatic disease (eg, Pap smear for cervical cancer)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Treatment to reduce complications from disease that is ongoing or has long-term effects (eg, chemotherapy)</td>
</tr>
<tr>
<td>Quaternary</td>
<td>Identifying patients at risk of unnecessary treatment, protecting from the harm of new interventions</td>
</tr>
</tbody>
</table>

Medicare and Medicaid

Medicare and Medicaid—federal 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 very low income.

Medicare is for Elderly.
Medicaid is for Destitute.

The 4 parts of Medicare:
- Part A: Hospital insurance
- Part B: Basic medical bills (eg, doctor’s fees, diagnostic testing)
- Part C: (Parts A+B) delivered by approved private companies
- Part D: Prescription drugs
Common causes of death (US) by age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;1 YR</th>
<th>1–14 YR</th>
<th>15–34 YR</th>
<th>35–44 YR</th>
<th>45–64 YR</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>Cancer</td>
<td>Heart disease</td>
<td></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

<table>
<thead>
<tr>
<th>Condition</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>

Readmission for any reason within 30 days of original admission.

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 [EMRs]). 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>Outcome</td>
<td>Impact on patients</td>
</tr>
<tr>
<td>Process</td>
<td>Performance of system as planned</td>
</tr>
<tr>
<td>Balancing</td>
<td>Impact on other systems/outcomes</td>
</tr>
</tbody>
</table>

Swiss cheese model

In complex organizations, flaws in multiple processes and systems may align to cause patient harm. Focuses on systems and conditions rather than an individual’s error.

Types of medical errors

May involve patient identification, diagnosis, monitoring, nosocomial infection, medications, procedures, devices, documentation, handoffs. Errors causing harmful outcomes must be disclosed to patients.

<table>
<thead>
<tr>
<th>Active error</th>
<th>Latent error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurs at level of frontline operator (eg, wrong IV pump dose programmed).</td>
<td>Occurs in processes indirect from operator but impacts patient care (eg, different types of IV pumps used within same hospital).</td>
</tr>
</tbody>
</table>

Medical error analysis

<table>
<thead>
<tr>
<th>Root cause analysis</th>
<th>Failure mode and effects analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses records and participant interviews to identify all the underlying problems that led to an error. Categories of causes include process, people (providers or patients), environment, equipment, materials, management.</td>
<td>Uses inductive reasoning to identify all the ways a process might fail and prioritize these by their probability of occurrence and impact on patients.</td>
</tr>
</tbody>
</table>

Retrospective approach applied after failure event to prevent recurrence. Plotted on fishbone (Ishikawa, cause-and-effect) diagram. Fix causes with corrective action plan. Forward-looking approach applied before process implementation to prevent failure occurrence.
HIGH-YIELD PRINCIPLES IN

Biochemistry

“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

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, immunoelectrophoresis, 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.
DNA exists in the condensed, chromatin form in order to fit into the nucleus. Negatively charged DNA loops twice around positively charged histone octamer to form nucleosome “beads on a string.” Histones are rich in the amino acids lysine and arginine. H1 binds to the nucleosome and to “linker DNA,” thereby stabilizing the chromatin fiber. In mitosis, DNA condenses to form chromosomes. DNA and histone synthesis occur during S phase.

<table>
<thead>
<tr>
<th>Chromatin structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA double helix</td>
</tr>
<tr>
<td>Nucleosome (H2A, H2B, H3, H4) x2</td>
</tr>
<tr>
<td>H1 histone (linker)</td>
</tr>
<tr>
<td>DNA exists in the condensed, chromatin form in order to fit into the nucleus. Negatively charged DNA loops twice around positively charged histone octamer to form nucleosome “beads on a string.” Histones are rich in the amino acids lysine and arginine. H1 binds to the nucleosome and to “linker DNA,” thereby stabilizing the chromatin fiber. In mitosis, DNA condenses to form chromosomes. DNA and histone synthesis occur during S phase.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heterochromatin</th>
<th>Condensed, appears darker on EM. Transcriptionally inactive, sterically inaccessible.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euchromatin</td>
<td>Less condensed, appears lighter on EM. Transcriptionally active, sterically accessible.</td>
</tr>
<tr>
<td>DNA methylation</td>
<td>Template strand cytosine and adenine are methylated in DNA replication, which allows mismatch repair enzymes to distinguish between old and new strands in prokaryotes. DNA methylation at CpG islands represses transcription.</td>
</tr>
<tr>
<td>Histone methylation</td>
<td>Usually reversibly represses DNA transcription, but can activate it in some cases depending on methylation location.</td>
</tr>
<tr>
<td>Histone acetylation</td>
<td>Relaxes DNA coiling, allowing for transcription.</td>
</tr>
</tbody>
</table>

HeteroChromatin = Highly Condensed. Barr bodies (inactive X chromosomes) are heterochromatin.

Euc = true, “truly transcribed.”

CpG Methylation Makes DNA Mute.

Histone Methylation Mostly Makes DNA Mute.

Histone Acetylation makes DNA Active.
Nucleotides

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

**PURines** (A,G)—2 rings.
**PYrimidines** (C,U,T)—1 ring.

Deamination of cytosine makes uracil.
Uracil found in RNA; thymine in DNA.

**PURe 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.

**GAG**—Amino acids necessary for purine synthesis:
Glycine
Aspartate
Glutamine

---

**De novo pyrimidine and purine synthesis**

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

**Disrupt pyrimidine synthesis:**
- Leflunomide: inhibits dihydroorotate dehydrogenase
- Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine: inhibit dihydrofolate reductase (4 deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, respectively
- 5-fluorouracil (5-FU): forms 5-F-dUMP, which inhibits thymidylate synthase (4 dTMP)

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

**Disrupts purine and pyrimidine synthesis:**
- Hydroxyurea: inhibits ribonucleotide reductase
Purine salvage deficiencies

- **Nucleic acids**
  - GMP
  - IMP
  - AMP

- **Nucleotides**
  - PRPP

- **Nucleosides**
  - Guanosine
  - Inosine
  - Adenosine

- **Free bases**
  - Guanine
  - Hypoxanthine
  - Xanthine

- **Ribose-5-phosphate**
  - PRPP synthetase

- **Degradation and salvage**
  - PRPP
  - Adenine
  - Xanthine oxidase
  - Allopurinol

**Adenosine deaminase deficiency**
- ADA is required for degradation of adenosine and deoxyadenosine. In ADA deficiency, dATP toxicity in lymphocytes.
- 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.
- Treatment: allopurinol or febuxostat (2nd line).

**Genetic code features**

- **Unambiguous**
  - Each codon specifies only 1 amino acid.

- **Degenerate/redundant**
  - Most amino acids are coded by multiple codons.
  - Exceptions: methionine and tryptophan encoded by only 1 codon (AUG and UGG, respectively).

- **Commaless, nonoverlapping**
  - Read from a fixed starting point as a continuous sequence of bases.
  - Exceptions: some viruses.

- **Universal**
  - Genetic code is conserved throughout evolution.
  - Exception in humans: mitochondria.
**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 and involves both continuous and discontinuous (Okazaki fragment) synthesis.

<table>
<thead>
<tr>
<th>Area of interest</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin of replication</strong></td>
<td>Particular consensus sequence of base pairs in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes). AT-rich sequences are found in promoters and origins of replication.</td>
</tr>
<tr>
<td><strong>Replication fork</strong></td>
<td>Y-shaped region along DNA template where leading and lagging strands are synthesized.</td>
</tr>
<tr>
<td><strong>Helicase</strong></td>
<td>Unwinds DNA template at replication fork.</td>
</tr>
<tr>
<td><strong>Single-stranded binding proteins</strong></td>
<td>Prevent strands from reannealing.</td>
</tr>
<tr>
<td><strong>DNA topoisomerases</strong></td>
<td>Create a single- or double-stranded break in the helix to add or remove supercoils. Topoisomerase inhibitors: fluoroquinolones—prokaryotic topoisomerase II [DNA gyrase] and topoisomerase IV; etoposide/teniposide—eukaryotic topoisomerase II.</td>
</tr>
<tr>
<td><strong>Primase</strong></td>
<td>Makes an RNA primer on which DNA polymerase III can initiate replication.</td>
</tr>
<tr>
<td><strong>DNA polymerase III</strong></td>
<td>Prokaryotic 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.</td>
</tr>
<tr>
<td><strong>DNA polymerase I</strong></td>
<td>Prokaryotic only. Degrades RNA primer; replaces it with DNA. Has same functions as DNA polymerase III but also excises RNA primer with 5′ → 3′ exonuclease.</td>
</tr>
<tr>
<td><strong>DNA ligase</strong></td>
<td>Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA (ie, joins Okazaki fragments).</td>
</tr>
</tbody>
</table>

**Telomerase**

An RNA-dependent DNA polymerase that adds DNA to 3′ ends of chromosomes to avoid loss of genetic material with every duplication. Eukaryotes only.

Often dysregulated in cancer cells, allowing unlimited replication.
**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. Usually results in nonfunctional protein.

**Stop the nonsense!**

**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.

**Duchenne muscular dystrophy, Tay-Sachs disease.**

**Splice site**

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

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

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**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 (adenyl cyclase) activity → ↑ generation of cAMP from ATP → activation of catabolite activator protein (CAP) → ↑ transcription.
- High lactose → unbinds repressor protein from repressor/operator site → ↑ transcription.
<table>
<thead>
<tr>
<th>DNA repair</th>
<th>Single strand</th>
</tr>
</thead>
</table>
| **Nucleotide excision repair** | Specific endonucleases release the oligonucleotides containing damaged bases; DNA polymerase and ligase fill and resel the gap, respectively. Repairs bulky helix-distorting lesions. Occurs in G1 phase of cell cycle. | Defective in xeroderma pigmentosum, which prevents repair of pyrimidine dimers because of ultraviolet light exposure.  
| **Base excision repair** | 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. | Important in repair of spontaneous/toxic deamination.  
| **Mismatch repair** | Newly synthesized strand is recognized, mismatched nucleotides are removed, and the gap is filled and ressealed. Occurs predominantly in G2 phase of cell cycle. | Defective in Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]).  
| **Double strand** |  
| **Nonhomologous end joining** | Brings together 2 ends of DNA fragments to repair double-stranded breaks. No requirement for homology. Some DNA may be lost. | Mutated in ataxia telangiectasia; Fanconi anemia.  

| DNA/RNA/protein synthesis direction | DNA and RNA are both synthesized 5' → 3'. The 5' end of the incoming nucleotide bears the triphosphate (energy source for bond). Protein synthesis is N-terminus to C-terminus. | mRNA is read 5' to 3'. The triphosphate bond is the target of the 3' hydroxyl attack. Drugs blocking DNA replication often have modified 3' OH, preventing addition of the next nucleotide (“chain termination”).  

| Start and stop codons |  
| --- | --- |  
| **mRNA start codons** | AUG (or rarely GUG). | AUG in AUGurates protein synthesis.  
| Eukaryotes | Codes for methionine, which may be removed before translation is completed. |  
| Prokaryotes | Codes for N-formylmethionine (fMet). | fMet stimulates neutrophil chemotaxis.  
| **mRNA stop codons** | UGA, UAA, UAG. | UGA = U Go Away. UAA = U Are Away. UAG = U Are Gone. |
Functional organization of a eukaryotic gene

Transcription start

<table>
<thead>
<tr>
<th>Coding strand: 5'</th>
<th>CAAT</th>
<th>TATAAT</th>
<th>Exon 1</th>
<th>GT</th>
<th>AG</th>
<th>Exon 2</th>
<th>GT</th>
<th>AG</th>
<th>Exon 3</th>
<th>AATAA AATAAA</th>
<th>3'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promoter</td>
<td>5'</td>
<td>UTR</td>
<td>Intron 1</td>
<td></td>
<td></td>
<td>Intron 2</td>
<td></td>
<td></td>
<td>3' UTR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**
Stretch of DNA that alters gene expression by binding transcription factors.
Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression it regulates.

**Silencer**
Site where negative regulators (repressors) bind.

RNA polymerases

**Eukaryotes**
RNA polymerase I makes rRNA (most numerous RNA, rampant).
RNA polymerase II makes mRNA (largest RNA, massive).
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: large ribosomal RNA, mRNA, then small RNAs.
α-amanitin, found in Amanita phalloides (death cap mushrooms), inhibits RNA polymerase II. Causes severe hepatotoxicity if ingested.
Rifampin inhibits RNA polymerase in prokaryotes. Actinomycin D inhibits RNA polymerase in both prokaryotes and eukaryotes.

**Prokaryotes**
1 RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.

RNA processing (eukaryotes)

Initial transcript is called heterogeneous nuclear RNA (hnRNA). hnRNA is then modified and becomes mRNA.
The following processes occur in the nucleus following transcription:
- 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 stored in P-bodies for future translation.
Poly-A polymerase does not require a template.
AAUAAA = polyadenylation signal.
**Splicing of pre-mRNA**

1. Primary transcript combines with small nuclear ribonucleoproteins (snRNPs) and other proteins to form spliceosome.
2. Lariat-shaped (looped) intermediate is generated.
3. Lariat is released to precisely remove intron and join 2 exons.

Antibodies to spliceosomal snRNPs (anti-Smith antibodies) are highly specific for SLE. Anti-U1 RNP antibodies are highly associated with mixed connective tissue disease (MCTD).

**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.

**microRNAs**

Small, noncoding RNA molecules that posttranscriptionally regulate protein expression. Introns can contain microRNA (miRNA) genes. They can have multiple mRNA targets, typically related to complementary base pairing. miRNA → degradation or inactivation of target mRNA → translation into protein. 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.

D-arm: contains dihydrouridine residues necessary for tRNA recognition by the correct 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.

**Wobble**
Accurate base pairing is usually required only in the first 2 nucleotide positions of an mRNA codon, so codons differing in the 3rd “wobble” position may code for the same tRNA/amino acid (as a result of degeneracy of genetic code).
Protein synthesis

Initiation
- Initiated by GTP hydrolysis; initiation factors (eukaryotic IFs) 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.

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

ATP—tRNA Activation (charging).
GTP—tRNA Gripping 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)
2. rRNA (“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
- Stop codon is recognized by release factor, and completed polypeptide is released from ribosome.

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). G_1 and G_0 are of variable duration.

Regulation of cell cycle

<table>
<thead>
<tr>
<th>CDKs</th>
<th>Constitutive and inactive.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclins</td>
<td>Regulatory proteins that control cell cycle events; phase specific; activate CDKs.</td>
</tr>
<tr>
<td>Cyclin-CDK complexes</td>
<td>Phosphorylate other proteins to coordinate cell cycle progression; must be activated and inactivated at appropriate times for cell cycle to progress.</td>
</tr>
<tr>
<td>Tumor suppressors</td>
<td>p53 induces p21, which inhibits CDKs → hypophosphorylation (activation) of Rb. Hypophosphorylated Rb binds to and inactivates transcription factor E2F → inhibition of G_1-S progression. Mutations in these genes result in unrestrained cell division (eg, Li-Fraumeni syndrome).</td>
</tr>
</tbody>
</table>

Cell types

| Permanent            | Remain in G_0, regenerate from stem cells. Neurons, skeletal and cardiac muscle, RBCs. |
| Stable (quiescent)   | Enter G_1 from G_0 when stimulated. Hepatocytes, lymphocytes. |
| Labile               | Never go to G_0, divide rapidly with a short G_1. 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 organellar 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-acetylgalactosaminyl-1-phosphotransferase → failure of the Golgi to phosphorylate mannose residues (ie, ↓ mannose-6-phosphate) on glycoproteins → proteins are secreted extracellularly rather than delivered to lysosomes. Results in coarse facial features, clouded corneas, restricted joint movement, 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).
Clathrin: trans-Golgi → lysosomes; plasma membrane → endosomes (receptor-mediated endocytosis [eg, LDL receptor activity]).

---

**Peroxisome**

Membrane-enclosed organelle involved in catabolism of very-long-chain fatty acids (through β-oxidation), branched-chain fatty acids, amino acids, and ethanol.

**Proteasome**

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>
</tr>
<tr>
<td>Intermediate filaments</td>
<td>Maintain cell structure</td>
<td>Vimentin, desmin, cytokeratin, lamins, glial fibrillary acid proteins (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>

**Immunohistochemical stains for intermediate filaments**

<table>
<thead>
<tr>
<th>STAIN</th>
<th>CELL TYPE</th>
<th>IDENTIFIES</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, and meningiomas)</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, oligodendroglia)</td>
<td>Astrocytoma, glioblastoma</td>
</tr>
<tr>
<td>Neurofilaments</td>
<td>Neurons</td>
<td>Neuronal tumors (eg, neuroblastoma)</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 (−→+).

**Kartagener syndrome (1° ciliary dyskinesia)**—immotile cilia due to a dynein arm defect. Results in male and female infertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; ↑ risk of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, and situs inversus (eg, dextrocardia on CXR).

**Cilia structure**

9 + 2 arrangement of microtubule doublets (arrows in A). The base of a cilium below the cell membrane, called the basal body, 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.
**Plasma membrane composition**
Asymmetric lipid bilayer. Contains cholesterol, phospholipids, sphingolipids, glycolipids, and proteins. Fungal membranes contain ergosterol.

**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).

Ouabain 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⁺] cell, → ↓ cardiac contractility.

**Collagen**

- **Type I**
  Most common (90%)—Bone (made by osteoblasts), Skin, Tendon, dentin, fascia, cornea, late wound repair.
  Type I: bone. ↓ production in osteogenesis imperfecta type I.

- **Type II**
  Cartilage (including hyaline), vitreous body, nucleus pulposus.
  Type II: cartilage.

- **Type III**
  Reticulin—skin, blood vessels, uterus, fetal tissue, granulation tissue.
  Type III: deficient in the uncommon, vascular type of Ehlers-Danlos syndrome (ThreE D).

- **Type IV**
  Basement membrane, basal lamina, lens.
  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 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.

5. **Proteolytic processing**—cleavage of disulfide-rich terminal regions of procollagen → insoluble tropocollagen.

6. **Cross-linking**—reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by copper-containing lysyl oxidase) to make collagen fibrils. Problems with cross-linking → Ehlers-Danlos syndrome, Menkes disease.
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
- Hearing loss (abnormal ossicles)
- Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)

May be confused with child abuse.

Ehlers-Danlos syndrome

Faulty collagen synthesis causing hyperextensible skin, tendency to bleed (easy bruising), and hypermobile joints. 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.
Vascular type (vascular and organ rupture): deficient type III collagen.

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). Results in brittle, “kinky” hair, growth retardation, and hypotonia.
**Elastin**

Stretchie 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.

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.

**Marfan syndrome**—caused by a defect in fibrillin, a glycoprotein that forms a sheath around elastin.

**Emphysema**—can be caused by α₁-antitrypsin deficiency, resulting in excess elastase activity.

Wrinkles of aging are due to collagen and elastin production.

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**Polymerase chain reaction**

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

Steps:

1. Denaturation (T= 95°C)
   - DNA is denatured by heating to separate the strands.

2. Annealing (T= 55°C)
   - During cooling, excess DNA primers anneal to a specific sequence on each strand to be amplified.

3. Elongation (T= 72°C)
   - Heat-stable DNA polymerase replicates the DNA sequence following each primer.

DNA primer
Nucleotide triphosphate
Double-stranded DNA
Repeted cycles
### Blotting procedures

<table>
<thead>
<tr>
<th>Blot Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| **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. Confirmatory test for HIV after ⊕ ELISA. |
| **Southwestern blot** | Identifies DNA-binding proteins (e.g., 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 $\odot$ for both CD8 and CD3.
- Cells in right lower quadrant $\oplus$ for CD8. (Right lower quadrant is empty because all CD8-expressing cells also express CD3.)
- Cells in left upper quadrant $\odot$ for CD3.
- Cells in right upper quadrant $\oplus$ for CD8 and CD3 (red + blue $\rightarrow$ 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 (eg, color change). Major ELISA variations include direct, sandwich, and competitive. Can have high sensitivity and specificity.

**Karyotyping**

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

**Fluorescence in situ hybridization**

Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes. 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 outside the original chromosome
- Duplication—extra site of fluorescence on one chromosome relative to its homologous chromosome

**Cloning methods**

Cloning is the production of a recombinant DNA molecule that is self-perpetuating.

Steps:
1. Isolate eukaryotic mRNA (post-RNA processing steps) of interest.
2. Expose mRNA to reverse transcriptase to produce cDNA (lacks introns).
3. Insert cDNA fragments into bacterial plasmids containing antibiotic resistance genes.
4. Transform 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.

**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.

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**Genetic terms**

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Codominance</strong></td>
<td>Both alleles contribute to the phenotype of the heterozygote.</td>
<td>Blood groups A, B, AB; α₁-antitrypsin deficiency.</td>
</tr>
<tr>
<td><strong>Variable expressivity</strong></td>
<td>Phenotype varies among individuals with same genotype.</td>
<td>2 patients with neurofibromatosis type 1 (NF1) may have varying disease severity.</td>
</tr>
<tr>
<td><strong>Incomplete penetrance</strong></td>
<td>Not all individuals with a mutant genotype show the mutant phenotype.</td>
<td>BRCA1 gene mutations do not always result in breast or ovarian cancer.</td>
</tr>
<tr>
<td><strong>Pleiotropy</strong></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><strong>Anticipation</strong></td>
<td>Increased severity or earlier onset of disease in succeeding generations.</td>
<td>Trinucleotide repeat diseases (eg, Huntington disease).</td>
</tr>
<tr>
<td><strong>Loss of heterozygosity</strong></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 (HNPPCC), Li-Fraumeni syndrome.</td>
</tr>
<tr>
<td><strong>Dominant negative mutation</strong></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><strong>Linkage disequilibrium</strong></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>
</table>
| Mosaicism                    | 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.                                                                                           | McCune-Albright syndrome—due to mutation affecting G-protein signaling. Presents with unilateral café-au-lait spots, polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities. Lethal if mutation occurs before fertilization (affecting all cells), but survivable in patients with mosaicism. |
| Locus heterogeneity          | Mutations at different loci can produce a similar phenotype.                                                                                                                                                                                                                                 | Albinism.                                                                                         |
| Allelic heterogeneity        | Different mutations in the same locus produce the same phenotype.                                                                                                                                                                                                                   | β-thalassemia.                                                                                   |
| Heteroplasmy                 | Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrially inherited disease.                                                                                                                                                                  |                                                                                                   |
| Uniparental disomy           | Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent. Heterodisomy (heterozygous) indicates a meiosis I error. Isodisomy (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. | Uniparental is eUloid (correct number of chromosomes), not aneuploid. Most occurrences of UPD → normal phenotype. Consider UPD in an individual manifesting a recessive disorder when only one parent is a carrier. |

Hardy-Weinberg population genetics

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

If a population is in Hardy-Weinberg equilibrium and if p and q are the frequencies of separate alleles, then:  
p^2 + 2pq + q^2 = 1  
p + q = 1, which implies that:  
p^2 = frequency of homozygosity for allele p  
q^2 = frequency of homozygosity for allele q  
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 = q^2.  

Hardy-Weinberg law assumptions include:  
• No mutation occurring at the locus  
• Natural selection is not occurring  
• Completely random mating  
• No net migration

Imprinting

At some loci, only one allele is active; the other is inactive (imprinted/inactivated by methylation). With one allele inactivated, deletion of the active allele → disease.  
Both Prader-Willi and Angelman syndromes are due to mutation or deletion of genes on chromosome 15.

Prader-Willi syndrome  
Maternal imprinting; gene from mom is normally silent and maternal gene is deleted/mutated. Results in hyperphagia, obesity, intellectual disability, hypogonadism, and hypotonia.  
25% of cases due to maternal uniparental disomy (two maternally imprinted genes are received; no paternal gene received).

AngelMan syndrome  
Paternal imprinting; gene from dad is normally silent and paternal gene is deleted/mutated. Results in inappropriate laughter (“happy puppet”), seizures, ataxia, and severe intellectual disability.  
5% of cases due to paternal uniparental disomy (two paternally imprinted genes are received; no maternal gene received).
**Modes of inheritance**

**Autosomal dominant**
- Often due to defects in structural genes. Many generations, both male and female, 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, \( \frac{1}{2} \) 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: \( \frac{1}{4} \) of children will be affected (homozygous), \( \frac{1}{2} \) of children will be carriers, and \( \frac{1}{4} \) 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: Rett syndrome, 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 encephalopathy, lactic acidosis, and stroke-like episodes). 2° to failure in oxidative phosphorylation. Muscle biopsy often shows “ragged red fibers.”

\( \square = \) unaffected male; \( \square = \) affected male; \( \bigcirc = \) unaffected female; \( \bullet = \) affected female.
Autosomal dominant diseases

**Achondroplasia**
Mutation of fibroblast growth factor receptor 3 (FGFR3) inhibits chondrocyte proliferation. Most common cause of dwarfishness; limb length affected more than head or torso size. Full penetrance.

**Autosomal dominant polycystic kidney disease**
Bilateral, massive enlargement of kidneys due to multiple large cysts. 85% of cases are due to mutation in *PKD1* (chromosome 16; 16 letters in “polycystic kidney”); remainder due to mutation in *PKD2* (chromosome 4).

**Familial adenomatous polyposis**
Colon becomes covered with adenomatous polyps after puberty. Progresses to colon cancer unless colon is resected. Mutations on chromosome 5q (*APC* gene; 5 letters in “polyp.”)

**Familial hypercholesterolemia**
Elevated LDL due to defective or absent LDL receptor. Leads to severe atherosclerotic disease early in life, corneal arcus, tendon xanthomas (classically in the Achilles tendon).

**Hereditary hemorrhagic telangiectasia**
Inherited disorder of blood vessels. Findings: branching skin lesions (telangiectasias), recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria. Also known as Osler-Weber-Rendu syndrome.

**Hereditary spherocytosis**
Spheroid erythrocytes due to spectrin or ankyrin defect; hemolytic anemia; ↑ MCHC, ↑ RDW. Treatment: splenectomy.

**Huntington disease**

**Li-Fraumeni syndrome**
Abnormalities in *TP53* → multiple malignancies at an early age. Also known as SBLA cancer syndrome (sarcoma, breast, leukemia, adrenal gland).

**Marfan syndrome**
*FBN1* gene mutation on chromosome 15 → defective fibrillin (scaffold for elastin) → connective tissue disorder affecting skeleton, heart, and eyes. Findings: tall with long extremities, pectus excavatum, hypermobile joints, and 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.

**Multiple endocrine neoplasias (MEN)**
Several distinct syndromes (1, 2A, 2B) characterized by familial tumors of endocrine glands, including those of the pancreas, parathyroid, pituitary, thyroid, and adrenal medulla. MEN 1 is associated with *MEN1* gene, MEN 2A and 2B are associated with *RET* gene.

**Neurofibromatosis type 1 (von Recklinghausen disease)**
Neurocutaneous disorder characterized by café-au-lait spots, cutaneous neurofibromas, optic gliomas, pheochromocytomas, Lisch nodules (pigmented iris hamartomas). 100% penetrance, variable expression. Caused by mutations in the *NF1* gene on chromosome 17; 17 letters in “von Recklinghausen.”

**Neurofibromatosis type 2**
Findings: bilateral acoustic schwannomas, juvenile cataracts, meningiomas, and ependymomas. *NF2* gene on chromosome 22; type 2 = 22.

**Tuberous sclerosis**
Neurocutaneous disorder with multi-organ system involvement, characterized by numerous benign hamartomas. Variable expression.

**von Hippel-Lindau disease**
Disorder characterized by development of numerous tumors, both benign and malignant. Associated with deletion of *VHL* gene (tumor suppressor) on chromosome 3 (3p). Von Hippel-Lindau = 3 words for chromosome 3.
Autosomal recessive diseases

Albinism, autosomal recessive polycystic kidney disease (ARPKD), cystic fibrosis, 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 (> 60 mEq/L) in sweat 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.

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. Pancreatic enzymes for insufficiency.

X-linked recessive disorders


Female carriers can be variably affected depending on the percentage inactivation of the X chromosome carrying the mutant vs normal gene.

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

**Duchenne**
X-linked disorder typically due to **frameshift** or nonsense mutations → truncated dystrophin protein → inhibited muscle regeneration.
Weakness begins in pelvic girdle muscles and progresses superiority. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle. Gower maneuver—patients use upper extremities to help them stand up. Waddling gait. Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.

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

**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.

**Fragile X syndrome**
X-linked dominant inheritance. Trinucleotide repeat in **FMR1** gene → methylation → † expression. The 2nd most common cause of genetic intellectual disability (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 diseases**
**Huntington disease, myotonic dystrophy, Friedreich ataxia, fragile X syndrome.**
Fragile X syndrome = (CGG)n.
Friedreich ataxia = (GAA)n.
Huntington disease = (CAG)n.
Myotonic dystrophy = (CTG)n.

Try (trinucleotide) **hunting** for my fried eggs (X).
X-Girlfriend’s First Aid Helped Ace My Test. May show genetic anticipation (disease severity † and age of onset ‡ in successive generations).
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. 1% of cases due to mosaicism (no maternal association; post-fertilization 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; ↓ serum PAPP-A, ↑ free β-hCG.

Second-trimester quad screen shows ↓ α-fetoprotein, ↑ β-hCG, ↓ estriol, ↑ inhibin A.

**Edwards syndrome** (trisomy 18)

Findings: severe intellectual disability, rocker-bottom feet, micrognathia (small jaw), low-set Ears, clenched hands with overlapping fingers, prominent occiput, congenital heart disease. Death usually occurs within 1 year of birth.

Incidence 1:8000.

**Election age (18).**

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

PAPP-A and free β-hCG are ↓ in first trimester.

Quad screen shows ↓ α-fetoprotein, ↑ β-hCG, ↓ estriol, ↓ or normal inhibin A.

**Patau syndrome** (trisomy 13)

Findings: severe intellectual disability, rocker-bottom feet, microphthalmia, microcephaly, cleft lip/Palate, holoProsencephaly, Polydactyly, congenital heart disease, cutis aplasia. Death usually occurs within 1 year of birth.

Incidence 1:15,000.

**Puberty (13).**

First-trimester pregnancy screen shows ↓ free β-hCG, ↓ PAPP-A.
### 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</td>
</tr>
<tr>
<td>11</td>
<td>Wilms tumor, β-globin gene defects (eg, sickle cell disease, β-thalassemia)</td>
</tr>
<tr>
<td>13</td>
<td>Patau syndrome, Wilson disease, retinoblastoma (RBI), 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)</td>
</tr>
<tr>
<td>17</td>
<td>Neurofibromatosis type 1, BRCA1</td>
</tr>
<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 microdeletion of short arm of chromosome 5 (46,XX or XY, 5p−). Findings: microcephaly, moderate to severe intellectual disability, high-pitched crying, 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 (1 sensitivity to vitamin D), well-developed verbal skills, extreme friendliness with strangers, cardiovascular problems.
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 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, such as cystic fibrosis and sprue, 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 (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 AML subtype M5. | **DEFICIENCY** | Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); corneal degeneration (keratomalacia); Bitot spots 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** | 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 (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 | **DEFICIENCY** | Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. Wernicke-Korsakoff syndrome and beriberi. Seen in malnutrition and alcoholism (2° to malnutrition and malabsorption). Diagnosis made by ↑ in RBC transketolase activity following vitamin B₁ administration. |
| **DEFICIENCY** | 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—polyneuritis, symmetrical muscle wasting. Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema. |
### Vitamin B<sub>2</sub> (riboflavin)

<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>Component of flavins FAD and FMN, used as cofactors in redox reactions, e.g., the succinate dehydrogenase reaction in the TCA cycle.</th>
<th>FAD and FMN are derived from riboflavin (B&lt;sub&gt;2&lt;/sub&gt; ≈ 2 ATP).</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFICIENCY</td>
<td>Cheilosis (inflammation of lips, scaling and fissures at the corners of the mouth), Corneal vascularization.</td>
<td>The 2 C's of B&lt;sub&gt;2&lt;/sub&gt;.</td>
</tr>
</tbody>
</table>

### Vitamin B<sub>3</sub> (niacin)

<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>Constituent of NAD&lt;sup&gt;+&lt;/sup&gt;, NADP&lt;sup&gt;+&lt;/sup&gt; (used in redox reactions). Derived from tryptophan. Synthesis requires vitamins B&lt;sub&gt;2&lt;/sub&gt; and B&lt;sub&gt;6&lt;/sub&gt;. Used to treat dyslipidemia; lowers levels of VLDL and raises levels of HDL.</th>
<th>NAD derived from niacin (B&lt;sub&gt;3&lt;/sub&gt; ≈ 3 ATP).</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFICIENCY</td>
<td>Glossitis. Severe deficiency leads to pellagra, which can be caused by Hartnup disease, malignant carcinoid syndrome (↑ tryptophan metabolism), and isoniazid (↓ vitamin B&lt;sub&gt;6&lt;/sub&gt;). Symptoms of pellagra: Diarrhea, Dementia (also hallucinations), Dermatitis (C3/C4 dermatome circumferential “broad collar” rash [Casal necklace], hyperpigmentation of sun-exposed limbs [A]).</td>
<td>The 3 D's of B&lt;sub&gt;3&lt;/sub&gt;. Hartnup disease—autosomal recessive. Deficiency of neutral amino acid (e.g., tryptophan) transporters in proximal renal tubular cells and on enterocytes → neutral aminoaciduria and ↓ absorption from the gut → ↓ tryptophan for conversion to niacin → pellagra-like symptoms. Treat with high-protein diet and nicotinic acid.</td>
</tr>
<tr>
<td>EXCESS</td>
<td>Facial flushing (induced by prostaglandin, not histamine; can avoid by taking aspirin with niacin), hyperglycemia, hyperuricemia.</td>
<td></td>
</tr>
</tbody>
</table>

### Vitamin B<sub>5</sub> (pantothenic acid)

<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>Essential component of coenzyme A (CoA, a cofactor for acyl transfers) and fatty acid synthase.</th>
<th>B&lt;sub&gt;5&lt;/sub&gt; is “pento”thenic acid.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFICIENCY</td>
<td>Dermatitis, enteritis, alopecia, adrenal insufficiency.</td>
<td></td>
</tr>
</tbody>
</table>

### Vitamin B<sub>6</sub> (pyridoxine)

<table>
<thead>
<tr>
<th>FUNCTION</th>
<th>Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (e.g., ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of cystathionine, heme, niacin, histamine, and neurotransmitters including serotonin, epinephrine, norepinephrine (NE), dopamine, and GABA.</th>
<th>Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by isoniazid and oral contraceptives), sideroblastic anemias due to impaired hemoglobin synthesis and iron excess.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFICIENCY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Vitamin B7 (biotin)

**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)

“Avidin in egg whites avidly binds biotin.”

**DEFICIENCY**

- Relatively rare. Dermatitis, alopecia, enteritis.
- Caused by antibiotic use or excessive ingestion of raw egg whites.

### Vitamin B9 (folate)

**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. Most common vitamin deficiency in the United States. Seen in alcoholism and pregnancy.

- Deficiency can be caused by several drugs (eg, phenytoin, sulfonamides, methotrexate).
  - Supplemental maternal folic acid in early pregnancy ↓ risk of neural tube defects.
**Vitamin B<sub>12</sub> (cobalamin)**

**FUNCTION**
Cofactor for methionine synthase (transfers \( \text{CH}_3 \) groups as methylcobalamin) and methylmalonyl-CoA mutase.

**DEFICIENCY**
Macrocytic, megaloblastic anemia; hypersegmented PMNs; 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. Prolonged deficiency → irreversible nerve damage.

Vitamin B<sub>12</sub> is 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*), lack of intrinsic factor (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.

**Vitamin C (ascorbic acid)**

**FUNCTION**
Antioxidant; also facilitates iron absorption by reducing it to Fe<sup>2+</sup> state. Necessary for hydroxylation of proline and lysine in collagen synthesis. Necessary for dopamine \( \beta \)-hydroxylase, which converts dopamine to NE.

**DEFICIENCY**
Scurvy—swollen gums, bruising, petechiae, hemorrhathrosis, 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 ↑ risk of iron toxicity in predisposed individuals (eg, those with transfusions, hereditary hemochromatosis).

---

[Diagram of vitamin B<sub>12</sub> and vitamin C metabolism and deficiencies]
### Vitamin D

| D₂ | ergocalciferol—ingested from plants. |
| D₃ | cholecalciferol—consumed in milk, formed in sun-exposed skin (stratum basale). |
| 25-OH D₃ | storage form. |
| 1,25-(OH)₂ D₃ | calcitriol = active form. |

**Function**

- ↑ intestinal absorption of calcium and phosphate, ↑ bone mineralization at low levels, ↑ bone resorption at higher levels.

**Deficiency**

- Rickets **A** in children (bone pain and deformity), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany. Breastfed infants should receive oral vitamin D. Deficiency is exacerbated by low sun exposure, pigmented skin, prematurity.

**Excess**

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

### Vitamin E (tocopherol/tocotrienol)

**Function**

- Antioxidant (protects RBCs and membranes from free radical damage).
- Can enhance 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.

### Vitamin K (phytomenadione, phyloquinone, phytonadione)

**Function**

- Cofactor for the γ-carboxylation of glutamic acid residues on various proteins required for blood clotting. Synthesized by intestinal flora.

**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**

<table>
<thead>
<tr>
<th>Function</th>
<th>Mineral essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>Delayed wound healing, hypogonadism, adult hair (axillary, facial, pubic), dysgeusia, anosmia, acrodermatitis enteropathica. May predispose to alcoholic cirrhosis.</td>
</tr>
</tbody>
</table>

**Malnutrition**

<table>
<thead>
<tr>
<th>Kwashiorkor</th>
<th>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. Kwashiorkor results from a protein-deficient MEAL: Malnutrition Edema Anemia Liver (fatty).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marasmus</td>
<td>Total calorie malnutrition resulting in emaciation (tissue and muscle wasting, loss of subcutaneous fat); +/- edema. Marasmus results in Muscle wasting.</td>
</tr>
</tbody>
</table>
**Ethanol metabolism**

Fomepizole—inhibits alcohol dehydrogenase and is an antidote for methanol or ethylene glycol poisoning.

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

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)

End result is clinical picture seen in chronic alcoholism.

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.

<table>
<thead>
<tr>
<th><strong>Kinase</strong></th>
<th>Catalyzes transfer of a phosphate group from a high-energy molecule (usually ATP) to a substrate (eg, phosphofructokinase).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phosphorylase</strong></td>
<td>Adds inorganic phosphate onto substrate without using ATP (eg, glycogen phosphorylase).</td>
</tr>
<tr>
<td><strong>Phosphatase</strong></td>
<td>Removes phosphate group from substrate (eg, fructose-1,6-bisphosphatase).</td>
</tr>
<tr>
<td><strong>Dehydrogenase</strong></td>
<td>Catalyzes oxidation-reduction reactions (eg, pyruvate dehydrogenase).</td>
</tr>
<tr>
<td><strong>Hydroxylase</strong></td>
<td>Adds hydroxyl group (−OH) onto substrate (eg, tyrosine hydroxylase).</td>
</tr>
<tr>
<td><strong>Carboxylase</strong></td>
<td>Transfers CO₂ groups with the help of biotin (eg, pyruvate carboxylase).</td>
</tr>
<tr>
<td><strong>Mutase</strong></td>
<td>Relocates a functional group within a molecule (eg, vitamin B₁₂–dependent methylmalonyl-CoA mutase).</td>
</tr>
</tbody>
</table>

### Rate-determining enzymes of metabolic processes

<table>
<thead>
<tr>
<th>Process</th>
<th>Enzyme</th>
<th>Regulators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycolysis</strong></td>
<td>Phosphofructokinase-1 (PFK-1)</td>
<td>AMP ⊕, fructose-2,6-bisphosphate ⊕, ATP ⊕, citrate ⊕</td>
</tr>
<tr>
<td><strong>Gluconeogenesis</strong></td>
<td>Fructose-1,6-bisphosphatase</td>
<td>AMP ⊖, fructose-2,6-bisphosphate ⊖</td>
</tr>
<tr>
<td><strong>TCA cycle</strong></td>
<td>Isocitrate dehydrogenase</td>
<td>ADP ⊕, ATP ⊕, NADH ⊕</td>
</tr>
<tr>
<td><strong>Glycogenesis</strong></td>
<td>Glycogen synthase</td>
<td>Glucose-6-phosphate ⊖, insulin ⊖, cortisol ⊖, Epinephrine ⊖, glucagon ⊖</td>
</tr>
<tr>
<td><strong>Glycogenolysis</strong></td>
<td>Glycogen phosphorylase</td>
<td>Epinephrine ⊖, glucagon ⊖, AMP ⊖, Glucose-6-phosphate ⊖, insulin ⊖, ATP ⊖</td>
</tr>
<tr>
<td><strong>HMP shunt</strong></td>
<td>Glucose-6-phosphate dehydrogenase (G6PD)</td>
<td>NADP⁺ ⊖</td>
</tr>
<tr>
<td><strong>De novo pyrimidine synthesis</strong></td>
<td>Carbamoyl phosphate synthetase II</td>
<td>ATP ⊖, PRPP ⊖</td>
</tr>
<tr>
<td><strong>De novo purine synthesis</strong></td>
<td>Glutamine-phosphoribosylpyrophosphate (PRPP) amidotransferase</td>
<td>AMP ⊖, inosine monophosphate (IMP) ⊖, GMP ⊖</td>
</tr>
<tr>
<td><strong>Urea cycle</strong></td>
<td>Carbamoyl phosphate synthetase I</td>
<td>N-acetylglutamate ⊖</td>
</tr>
<tr>
<td><strong>Fatty acid synthesis</strong></td>
<td>Acetyl-CoA carboxylase (ACC)</td>
<td>Insulin ⊖, citrate ⊖, Glucagon ⊖, palmitoyl-CoA ⊖</td>
</tr>
<tr>
<td><strong>Fatty acid oxidation</strong></td>
<td>Carnitine acyltransferase I</td>
<td>Malonyl-CoA ⊖</td>
</tr>
<tr>
<td><strong>Ketogenesis</strong></td>
<td>HMG-CoA synthase</td>
<td>Insulin ⊖, thyroxine ⊖, Glucagon ⊖, cholesteryl ⊖</td>
</tr>
<tr>
<td><strong>Cholesterol synthesis</strong></td>
<td>HMG-CoA reductase</td>
<td></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-bisphosphatase
9. Fructokinase (essential fructosuria)
10. Aldolase B (fructose intolerance)
11. Aldolase B (liver), A (muscle)
12. Pyruvate kinase
13. Pyruvate dehydrogenase
14. HMG-CoA reductase
15. Pyruvate carboxylase
16. PEP carboxykinase
17. Citrate synthase
18. Isocitrate dehydrogenase
19. α-ketoglutarate dehydrogenase
20. Ornithine transcarbamylase
21. Propionyl-CoA carboxylase

1. Requires biotin cofactor
2. Requires thiamine cofactor (TPP)
3. Irreversible, important point of regulation

Glycolysis

- 1. Glucose
- 2. Glucose-6-phosphate
- 3. 6-phosphogluconolactone
- 4. Fructose-6-phosphate
- 5. Ribulose-5-phosphate

Gluconeogenesis

- 1. Glucose-6-phosphate
- 2. Fructose-1,6-bisphosphate
- 3. DHAP
- 4. Glycerolphosphate
- 5. 1,3-bisphosphoglycerate
- 6. 3-phosphoglycerate
- 7. 2-phosphoglycerate
- 8. Phosphoenolpyruvate (PEP)
- 9. Pyruvate
- 10. Acetyl-CoA

TCA cycle

- 1. Citrate
- 2. Oxaloacetate
- 3. α-Ketoglutarate
- 4. Malate
- 5. Fumarate
- 6. Succinate
- 7. Succinyl-CoA

Ketogenesis

- 1. Acetoacetate
- 2. β-Hydroxybutyrate
- 3. Odd-chain fatty acids, branched-chain amino acids, methionine, and threonine

Protein metabolism

- 1. Methylenalcohol-CoA
- 2. Propionyl-CoA

Galactose metabolism

- 1. Galactose
- 2. Galactose-1-phosphate

Urea cycle

- 1. NH₃ + CO₂
- 2. Argininosuccinate
- 3. Citrulline
- 4. Aspartate
- 5. Ornithine
- 6. Arginase
- 7. Urea
- 8. H₂O
ATP production

Aerobic metabolism of glucose 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⁺ from vitamin B₃, NADP⁺) 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 (steroid and fatty acid synthesis) as a supply of reducing equivalents.

NADPH is a product of the HMP shunt.

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

Hexokinase vs glucokinase

Phosphorylation of glucose to yield glucose-6-phosphate serves as the 1st committed step of glycolysis (also serves as the 1st step of glycogen synthesis in the liver). Reaction is catalyzed by either hexokinase or glucokinase, depending on the tissue. At low glucose concentrations, hexokinase sequesters glucose in the tissue. At high glucose concentrations, excess glucose is stored in the 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>
<tr>
<td>Gene mutation associated with maturity-onset diabetes of the young (MODY)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**Glycolysis regulation, key enzymes**

Net glycolysis (cytoplasm):

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

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

**REQUIRE ATP**

\[
\begin{align*}
\text{Glucose} & \rightarrow \text{Glucose-6-P} \\
\text{Fructose-6-P} & \rightarrow \text{Fructose-1,6-BP}
\end{align*}
\]

Glucose-6-P $\ominus$ hexokinase.
Fructose-6-P $\ominus$ glucokinase.

**PRODUCE ATP**

\[
\begin{align*}
\text{1,3-BPG} & \rightarrow \text{3-PG} \\
\text{Fructose-1,6-bisphosphate} & \rightarrow \text{Pyruvate}
\end{align*}
\]

Fructose-1,6-bisphosphate $\oplus$.
ATP $\ominus$, alanine $\ominus$.

**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, ↓ PFK-2, less glycolysis, more gluconeogenesis.

**Fed state:**

↓ insulin → ↓ cAMP → ↓ protein kinase A → ↓ FBPase-2, ↑ PFK-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).

Reaction: pyruvate + NAD$^+$ + CoA $\rightarrow$ 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$_5$, pantothenic acid)
4. FAD (B$_2$, riboflavin)
5. NAD (B$_3$, 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 $\rightarrow$ succinyl-CoA (TCA cycle).

TLC For Nancy.
Arsenic inhibits lipoic acid. Findings: vomiting, rice-water stools, 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).

Lysine and Leucine—the only purely ketogenic amino acids.

---

**Pyruvate metabolism**

Functions of different pyruvate metabolic pathways (and their associated cofactors):

1. Alanine aminotransferase (B6): alanine carries amino groups to the liver from muscle
2. Pyruvate carboxylase (biotin): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
3. Pyruvate dehydrogenase (B1, B2, B3, B5, lipoic acid): transition from glycolysis to the TCA cycle
4. Lactic acid dehydrogenase (B3): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

---

**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/acytetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria. 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. FADH₂ 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.

![Electron transport chain diagram]

**ATP PRODUCED VIA ATP SYNTHASE**

1 NADH → 2.5 ATP; 1 FADH₂ → 1.5 ATP.

**OXIDATIVE PHOSPHORYLATION POISONS**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP synthase inhibitors</td>
<td>Directly inhibit mitochondrial ATP synthase, causing an ↑ proton gradient. No ATP is produced because electron transport stops.</td>
<td>Oligomycin.</td>
</tr>
<tr>
<td>Uncoupling agents</td>
<td>↑ permeability of membrane, causing a ↓ proton gradient and ↑ O₂ consumption. ATP synthesis stops, but electron transport continues. Produces heat.</td>
<td>2,4-Dinitrophenol (used illicitly for weight loss), aspirin (fevers often occur after aspirin overdose), thermogenin in brown fat.</td>
</tr>
</tbody>
</table>

**Gluconeogenesis, irreversible enzymes**

**Pathway** Produces Fresh Glucose.

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

**REACTIONS**

<table>
<thead>
<tr>
<th>Oxidative (irreversible)</th>
<th>Key Enzymes</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-6-P</td>
<td>NADP⁺</td>
<td>2 NADPH</td>
</tr>
<tr>
<td>Glucose-6-P dehydrogenase</td>
<td></td>
<td>CO₂, Ribulose-5-Pᵢ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonoxidative (reversible)</th>
<th>Key Enzymes</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribulose-5-P</td>
<td>Phosphopentose isomerase, transketolases</td>
<td>Glyceroldehyde-3-phosphate Fructose-6-P</td>
</tr>
<tr>
<td>Requires B₁</td>
<td></td>
<td></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, primaquine, 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 Hemoglobin precipitates 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, since fructose is not trapped in cells. Symptoms: fructose appears in blood and urine. Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.

**Fructose intolerance**
Hereditary deficiency of aldolase B. Autosomal recessive. Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be ⊗ (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: ↓ intake of both fructose and sucrose (glucose + fructose).

Fructose metabolism (liver)

Disorders of galactose metabolism

**Galactokinase deficiency**
Hereditary deficiency of galactokinase. Galactitol accumulates if galactose is present in diet. Relatively mild condition. Autosomal recessive.
Symptoms develop when infant begins feeding (lactose present in breast milk and routine formula).
Symptoms: galactose appears in blood (galactosemia) and urine (galactosuria); infantile cataracts. May present as failure to track objects or to develop a social smile.

**Classic galactosemia**
Absence of galactose-1-phosphate uridyltransferase. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye). Symptoms: failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can lead to *E. coli* sepsis in neonates.
Treatment: exclude galactose and lactose (galactose + glucose) from diet.

Galactose metabolism

Fructose is to Aldolase B as Galactose is to UridylT transferase (FAB GUT).
The more serious defects lead to PO₄³⁻ depletion.
Sorbitol

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, called 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 for intracellular sorbitol accumulation, causing osmotic damage (eg, 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.

Lactase deficiency

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the brush border to digest lactose (in human and cow milk) 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 brush border due to gastroenteritis (eg, 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

Glucogenic: methionine (Met), valine (Val), histidine (His).

Glucogenic/ketogenic: isoleucine (Ile), phenylalanine (Phe), threonine (Thr), tryptophan (Trp).

Ketogenic: leucine (Leu), lysine (Lys).

All essential amino acids need to be supplied in the diet.

Acidic

Aspartic acid (Asp) and glutamic acid (Glu).

Negatively charged at body pH.

Basic

Arginine (Arg), lysine (Lys), histidine (His).

Arg is most basic.

His has no charge at body pH.

Arg and His are required during periods of growth. Arg and Lys are + in histones, which bind negatively charged DNA.
**Urea cycle**

Amino acid catabolism results in the formation of common metabolites (e.g., pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen (NH₃) generated by this process is converted to urea and excreted by the kidneys. Ordinarily, Careless Crappers Are Also Frivolous About Urination.

\[
\begin{align*}
\text{Urea} & \rightarrow \text{NH}_2 + \text{NH}_3 \\
\text{CO}_2 & \rightarrow \text{C} = \text{O} \\
\text{Aspartate} & \rightarrow \text{NH}_2
\end{align*}
\]

**Transport of ammonia by alanine and glutamate**

Can be acquired (e.g., liver disease) or hereditary (e.g., urea cycle enzyme deficiencies). Results in excess NH₃, which depletes α-ketoglutarate, leading to inhibition of TCA cycle.

Treatment: limit protein in diet.

May be given to ↓ ammonia levels:
- Lactulose to acidify the GI tract and trap NH₄⁺ for excretion.
- Rifaximin to ↓ colonic ammoniogenic bacteria.
- Benzoate, phenylacetate, or phenylbutyrate to bind to NH₄⁺ and lead to excretion.

**Hyperammonemia**

Ammonia accumulation—tremor (asterixis), slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.
**N-acetylglutamate synthase deficiency**

Required cofactor for carbamoyl phosphate synthetase I. Absence of N-acetylglutamate → hyperammonemia.  
 Presents in neonates as poorly regulated respiration and body temperature, poor feeding, developmental delay, intellectual disability (identical to presentation of carbamoyl phosphate synthetase I deficiency).

---

**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**

![Amino acid derivatives diagram](image-url)
Catecholamine synthesis/tyrosine catabolism

Phenylalanine
\[ \text{BH}_4 \rightarrow \text{Phenylalanine hydroxylase} \]

Tyrosine
\[ \text{BH}_4 \rightarrow \text{Tyrosine hydroxylase} \]

DOPA (Dihydroxyphenylalanine)
\[ \text{DOPA decarboxylase} \]

B6

Vitamin C

Dopamine
\[ \text{B} \_6 \text{ decarboxylase} \]

Melanin

Tyrosinase

Homogentisate oxidase

Maleylacetoacetic acid

Fumarate

TCA cycle

Carbidopa

Phenylalanine hydroxylase

Phenylketonuria
Due to \( \uparrow \) phenylalanine hydroxylase or \( \uparrow \) tetrahydrobiopterin cofactor (malignant PKU). Tyrosine becomes essential.

\( \uparrow \) phenylalanine \( \rightarrow \) excess phenylketones in urine.

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

Treatment: \( \downarrow \) phenylalanine and \( \uparrow \) tyrosine in diet, tetrahydrobiopterin supplementation.


Maple syrup urine disease
Blocked degradation of branched amino acids (Isoleucine, Leucine, Valine) due to \( \downarrow \) branched-chain \( \alpha \)-ketoacid dehydrogenase (B1). Causes \( \uparrow \) \( \alpha \)-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 \( \approx \) 1:10,000.

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

Phenylketones—phenylacetate, phenyllactate, and phenylpyruvate.

Disorder of aromatic amino acid metabolism \( \rightarrow \) musty body odor.

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

Autosomal recessive.

Presentation: vomiting, poor feeding, urine smells like maple syrup/burnt sugar.

I Love Vermont maple syrup from maple trees (with B1 branches).
**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 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, ↑ 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.

Findings: ↑ homocysteine in urine, intellectual disability, osteoporosis, marfanoid habitus, kyphosis, lens subluxation (downward and inward), thrombosis, and atherosclerosis (stroke and MI).

**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 A.

Treatment: urinary alkalinization (eg, potassium citrate, acetazolamide) and chelating agents (eg, penicillamine) ↑ solubility of cystine stones; good hydration.

Autosomal recessive. Common (1:7000).

Urinary cyanide-nitroprusside test is diagnostic.

Cystine is made of 2 cysteines connected by a disulfide bond.
Glycogen regulation by insulin and glucagon/epinephrine

- **Epinephrine (liver and muscle)**
- **Insulin (liver and muscle)**
- **Glucagon receptor**
- **ATP**
- **β Receptor**
- **α Receptor**
- **Glucagon (liver)**
- **Adenylate cyclase**
- **cAMP**
- **Protein kinase A**
- **Glycogen phosphorylase kinase**
- **Glycogen synthase**
- **Calcium-calmodulin complex**
- **Calcium**
- **Protein kinase A**
- **Glucagon receptor**
- **Glucagon (liver)**
- **Receptor Tyrosine kinase dimer receptor**
- **Endoplasmic reticulum**
- **Glycogen**
- **Glucose**
- **Protein phosphatase**

**Reactions:**
- Glucagon activates adenylate cyclase, leading to cAMP production.
- cAMP activates protein kinase A, which phosphorylates glycogen phosphorylase kinase.
- Calcium-calmodulin complex is released during muscle contraction.
- Insulin activates protein kinase A, which inhibits glycogen phosphorylase and activates glycogen synthase.

**Key Terms:**
- **Adenylate cyclase:** Produces cAMP from ATP.
- **Glycogen phosphorylase kinase:** Activated by cAMP and protein kinase A.
- **Protein kinase A:** Activated by cAMP.
- **Glucagon:** Stimulates glycogen breakdown.
- **Insulin:** Promotes glycogen synthesis.
- **Calcium-calmodulin:** Regulates enzyme activity.
- **Protein phosphatase:** Inhibits phosphorylation reactions.
Glycogen

Branches have $\alpha$-(1,6) bonds; linkages have $\alpha$-(1,4) bonds.

Skeletal muscle

Glycogen undergoes glycogenolysis $\rightarrow$ glucose-1-phosphate $\rightarrow$ glucose-6-phosphate, which is rapidly metabolized during exercise.

Hepatocytes

Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels. Glycogen phosphorylase liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then $4\alpha$-d-glucanotransferase (debranching enzyme 5) moves 3 molecules of glucose-1-phosphate from the branch to the linkage. Then $\alpha$-1,6-glucosidase (debranching enzyme 6) 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.

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

12 types, 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.

Very Poor Carbohydrate Metabolism. Types I, II, III, and V are autosomal recessive.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>FINDINGS</th>
<th>DEFICIENT ENZYME</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Von Gierke disease</strong> (type I)</td>
<td>Severe fasting hypoglycemia,†† Glycogen in liver, † blood lactate, † triglycerides, † uric acid (Gout), and hepatomegaly.</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><strong>Pompe disease</strong> (type II)</td>
<td>Cardiomegaly, hypertrophic cardiomyopathy, exercise intolerance, and systemic finds leading to early death.</td>
<td>Lysosomal α-1,4-glucosidase with α-1,6-glucosidase activity (acid maltase)</td>
<td>Pompe trashes the Pump (heart, liver, and muscle)</td>
</tr>
<tr>
<td><strong>Cori disease</strong> (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><strong>McArdle disease</strong> (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>Blood glucose levels typically unaffected McArdle = Muscle</td>
</tr>
</tbody>
</table>
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>Fabry disease</td>
<td>Early: Triad of episodic peripheral neuropathy, angiokeratomas A, hypohidrosis. Late: progressive renal failure, cardiovascular disease.</td>
<td>α-galactosidase A</td>
<td>Ceramide trihexoside</td>
<td>XR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, aseptic necrosis of femur, bone crises, Gaucher cells (lipid-laden macrophages resembling crumpled tissue paper).</td>
<td>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 D</td>
<td>Sphingomyelinase</td>
<td>Sphingomyelin</td>
<td>AR</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Progressive neurodegeneration, developmental delay, “cherry-red” spot on macula D, lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick).</td>
<td>Hexosaminidase A</td>
<td>GM₂ ganglioside</td>
<td>AR</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>Peripheral neuropathy, developmental delay, optic atrophy, globoid cells.</td>
<td>Galactocerebrosidase</td>
<td>Galactocerebroside, psychosine</td>
<td>AR</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Central and peripheral demyelination with ataxia, dementia.</td>
<td>Arylsulfatase A</td>
<td>Cerebroside sulfate</td>
<td>AR</td>
</tr>
<tr>
<td>Mucopolysaccharidoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 sulfatase</td>
<td>Heparan sulfate, dermatan sulfate</td>
<td>XR</td>
</tr>
</tbody>
</table>

No man picks (Niemann-Pick) his nose with his sphing (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 (palmitate, a 16C FA)
- Malonyl-CoA
- Acetyl-CoA
- CO₂ (biotin)
- ATP citrate lyase
- Citrate shuttle
- Citrate
- 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.

"SYrate" = SYnthesis.
CARnitine = CARnage of fatty acids.

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

Medium-chain acyl-CoA dehydrogenase deficiency
- Autosomal recessive disorder of fatty acid oxidation. Ability to break down fatty acids into acetyl-CoA → accumulation of 8- to 10-carbon fatty acyl carnitines in the blood and hypoketotic hypoglycemia. May present in infancy or early childhood with vomiting, lethargy, seizures, coma, and liver dysfunction.

Minor illness can lead to sudden death. 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 and FFA 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.
### Metabolic fuel use

<table>
<thead>
<tr>
<th>Duration of exercise</th>
<th>% Maximal energy by source</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 sec</td>
<td>Stored ATP</td>
</tr>
<tr>
<td>10 sec</td>
<td>Creatine phosphate</td>
</tr>
<tr>
<td>1 min</td>
<td>Anaerobic metabolism</td>
</tr>
<tr>
<td>2 hr</td>
<td>Aerobic metabolism</td>
</tr>
<tr>
<td></td>
<td>Overall performance</td>
</tr>
</tbody>
</table>

1 g protein or carbohydrate = 4 kcal.
1 g fat = 9 kcal.
1 g alcohol = 7 kcal.

### Fasting and starvation

<table>
<thead>
<tr>
<th>State</th>
<th>Metabolism</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fed state (after a meal)</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>Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor).</td>
<td>Glucagon and epinephrine stimulate use of fuel reserves.</td>
</tr>
<tr>
<td>Starvation days 1–3</td>
<td>Blood glucose levels maintained by:</td>
<td>Glycogen reserves depleted after day 1. RBCs lack mitochondria and therefore cannot use ketones.</td>
</tr>
<tr>
<td></td>
<td>* Hepatic glycogenolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* Adipose release of FFA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* Muscle and liver, which shift fuel use from glucose to FFA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* 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)</td>
<td></td>
</tr>
<tr>
<td>Starvation after day 3</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

### Cholesterol synthesis

Cholesterol needed to maintain cell membrane integrity and to synthesize bile acid, steroids, and vitamin D. Rate-limiting step catalyzed by HMG-CoA reductase (induced by insulin), which converts HMG-CoA to mevalonate. 2/3 of plasma cholesterol esterified by lecithin-cholesterol acyltransferase (LCAT).

Statins (eg, atorvastatin) competitively and reversibly inhibit HMG-CoA reductase.
Lipid transport, key enzymes

Pancreatic lipase—degradation of dietary triglycerides (TGs) in small intestine. Lipoprotein lipase (LPL)—degradation of TGs circulating in chylomicrons and VLDLs. Found on vascular endothelial surface. Hepatic TG lipase (HL)—degradation of TGs remaining in IDL. Hormone-sensitive lipase—degradation of TGs stored in adipocytes.

LCAT—catalyzes esterification of cholesterol. Cholesterol ester transfer protein (CETP)—mediates transfer of cholesterol esters to other lipoprotein particles.

### Major apolipoproteins

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Function</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</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>
</tr>
<tr>
<td>C-II</td>
<td>Lipoprotein lipase cofactor</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-48</td>
<td>Mediates chylomicron secretion</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-100</td>
<td>Binds LDL receptor</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.**

### Chylomicron

Delivers dietary TGs to peripheral tissue. 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.

<table>
<thead>
<tr>
<th>Familial dyslipidemias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPE</strong></td>
</tr>
<tr>
<td>I—Hyperchylomicronemia</td>
</tr>
<tr>
<td>IIa—Familial hypercholesterolemia</td>
</tr>
<tr>
<td>IV—Hypertriglyceridemia</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

This high-yield material covers the basic concepts of microbiology. The emphasis in previous examinations has been approximately 40% bacteriology (20% basic, 20% quasi-clinical), 25% immunology, 25% virology (10% basic, 15% quasi-clinical), 5% parasitology, and 5% mycology.

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.
### Microbiology—Basic Bacteriology

#### 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>
<tr>
<td>Spore</td>
<td>Keratin-like coat; dipicolinic acid; peptidoglycan, DNA.</td>
<td>Gram ⊕ only. Survival: resist dehydration, heat, chemicals.</td>
</tr>
<tr>
<td>Cell envelope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule</td>
<td>Organized, discrete polysaccharide layer (except poly-d glutamate on B anthracis).</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>Gram ⊕ only. 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 [PBP]) 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 and IL-1.</td>
</tr>
</tbody>
</table>

#### Cell walls

[Diagram showing unique and common structures to gram-positive and gram-negative bacteria]
### Bacterial taxonomy

<table>
<thead>
<tr>
<th>MORPHOLOGY</th>
<th>Gram examples</th>
<th>Gram examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical (coccus)</td>
<td>Staphylococcus (clusters)</td>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td></td>
<td>Streptococcus (chains or pairs)</td>
<td>Neisseria</td>
</tr>
<tr>
<td>Rod (bacillus)</td>
<td>Bacillus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clostridium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corynebacterium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gardnerella (gram variable)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactobacillus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Listeria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycobacterium (acid fast)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propionibacterium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacteroides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Campylobacter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E. coli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enterobacter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Helicobacter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Klebsiella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proteus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudomonas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salmonella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serratia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vibrio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yersinia</td>
<td></td>
</tr>
<tr>
<td>Respiratory:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bordetella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkholderia cepacia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemophilus (pleomorphic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Legionella (silver stain)</td>
<td></td>
</tr>
<tr>
<td>Zoonotic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bartonella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brucella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Francisella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pasteurella</td>
<td></td>
</tr>
<tr>
<td>Branching filamentous</td>
<td>Actinomyces</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nocardia (weakly acid fast)</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>Chlamydiae (Giemsa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rickettsiae (Giemsa)</td>
<td></td>
</tr>
<tr>
<td>Spiral</td>
<td>Spirochetes:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borrelia (Giemsa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leptospira</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treponema</td>
<td></td>
</tr>
<tr>
<td>No cell wall</td>
<td>Mycoplasma, Ureaplasma (contain sterols, which do not Gram stain)</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.

<table>
<thead>
<tr>
<th>Bug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treponema, Leptospira</td>
</tr>
<tr>
<td>Mycobacteria</td>
</tr>
<tr>
<td>Mycoplasma, Ureaplasma</td>
</tr>
<tr>
<td>Legionella, Rickettsia, Chlamydia, Bartonella, Ehrlichia, Anaplasma</td>
</tr>
</tbody>
</table>

These microorganisms may lack real color.

**Giemsa stain**

Chlamydia, Borrelia, Rickettsia, Trypanosomes, Plasmodium

Certain bugs really try my patience.

**Periodic acid–Schiff stain**

Stains glycogen, mucopolysaccharides; used to diagnose Whipple disease (Tropheryma whippelii)

Paß the sugar.

**Ziehl-Neelsen stain (carbol fuchs)***

Acid-fast bacteria, eg, Mycobacteria (stains mycolic acid in cell wall), Nocardia, protozoa, eg, Cryptosporidium oocysts

Alternative is auramine-rhodamine stain for screening (inexpensive, more sensitive but less specific).

**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 confirming 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 (different) 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</em>, <em>N. meningitidis</em></td>
<td>Thayer-Martin agar</td>
<td>Selectively favors growth of Neisseria by inhibiting growth of gram ⊕ organisms with Vancomycin, gram ⊖ organisms except Neisseria with Trimethoprim and Colistin, and fungi with Nystatin</td>
</tr>
<tr>
<td><em>B. pertussis</em></td>
<td>Bordet-Gengou agar (Bordet for Bordetella)</td>
<td>Potato</td>
</tr>
<tr>
<td></td>
<td>Regan-Lowe medium</td>
<td>Charcoal, blood, and antibiotic</td>
</tr>
<tr>
<td><em>C. diphtheriae</em></td>
<td>Tellurite agar, Löffler medium</td>
<td></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.

**Anaerobes**

Examples include *Clostridium*, *Bacteroides*, *Fusobacterium*, and *Actinomyces*. 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.
Intracellular bugs

<table>
<thead>
<tr>
<th>Obligate intracellular</th>
<th>Facultative intracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stay inside (cells) when it is really <em>Chilly</em> and <em>Cold</em>.</td>
<td>Some nasty bugs may live facultatively.</td>
</tr>
</tbody>
</table>

Encapsulated bacteria

Examples are *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus Influenzae* type B, *Neisseria meningitidis*, *Escherichia coli*, *Salmonella*, *Klebsiella pneumoniae*, and group B *Strept*. 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.

Pneumococcal vaccine: PCV (pneumococcal conjugate vaccine, ie, Prevnar); PPSV (pneumococcal polysaccharide vaccine with no conjugated protein, ie, Pneumovax) *H influenzae* type B (conjugate vaccine) Meningococcal vaccine (conjugate vaccine)

Urease-positive organisms


Pee CHUNKSS.

Catalase-positive organisms

Catalase degrades H₂O₂ into H₂O and bubbles of O₂ before it can be converted to microbicidal 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*.

Cats need PLACESS to belch their hairballs.
### Pigment-producing bacteria

- **Actinomyces israelii**—yellow “sulfur” granules, which are composed of filaments of bacteria.  
  - Israel has yellow sand.
- **S. aureus**—yellow pigment.  
  - *Aureus* (Latin) = gold.
- **P. aeruginosa**—blue-green pigment.  
  - *Aerugula* is green.
- **Serratia marcescens**—red pigment.  
  - *Serratia marcescens*—think red maraschino cherries.

### In vivo biofilm-producing bacteria

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

### Bacterial virulence factors

- **Protein A**  
  - Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by *S. aureus*.
- **IgA protease**  
  - Enzyme that cleaves IgA. Secreted by *S. pneumoniae*, *H. influenzae* type B, and *Neisseria (SHiN)* in order to colonize respiratory mucosa.
- **M protein**  
  - 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.

### Type III secretion system

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

#### Transformation
Ability to take up naked DNA (ie, from cell lysis) from environment (also known as “competence”). A feature of many bacteria, especially *S. pneumoniae*, *H. influenzae* type B, and *Neisseria* (SHiN). Any DNA can be used. Adding deoxyribonuclease to environment will degrade naked DNA in medium → no transformation seen.

#### Conjugation

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F&lt;sup&gt;+&lt;/sup&gt; × F&lt;sup&gt;-&lt;/sup&gt;</td>
<td>F&lt;sup&gt;+&lt;/sup&gt; plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed F&lt;sup&gt;-&lt;/sup&gt;. Sex pilus on F&lt;sup&gt;+&lt;/sup&gt; bacterium contacts F&lt;sup&gt;-&lt;/sup&gt; bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge (“mating bridge”). No transfer of chromosomal DNA.</td>
</tr>
<tr>
<td>Hfr × F&lt;sup&gt;-&lt;/sup&gt;</td>
<td>F&lt;sup&gt;+&lt;/sup&gt; plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Replication of incorporated plasmid DNA may include some flanking chromosomal DNA. Transfer of plasmid and chromosomal genes.</td>
</tr>
</tbody>
</table>

#### Transposition
Segment of DNA (eg, transposon) that can “jump” (excision and reintegration) from one location to another, can transfer genes from plasmid to chromosome and vice versa. When excision occurs, may include some flanking chromosomal DNA, which can be incorporated into a plasmid and transferred to another bacterium (eg, vanA gene from vancomycin-resistant *Enterococcus* to *S. aureus*).

#### Transduction

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>A “packaging” event. 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.</td>
</tr>
</tbody>
</table>
| 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 |

### Spore-forming bacteria
Some bacteria can form spores at the end of the stationary phase when nutrients are limited. Spores are highly resistant to heat and chemicals. Have dipicolinic acid in their core. Have no metabolic activity. Must autoclave to potentially kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes.

<table>
<thead>
<tr>
<th>Species</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. anthracis</em></td>
<td>Anthrax</td>
</tr>
<tr>
<td><em>B. cereus</em></td>
<td>Food poisoning</td>
</tr>
<tr>
<td><em>C. botulinum</em></td>
<td>Botulism</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td><em>C. perfringens</em></td>
<td>Gas gangrene</td>
</tr>
<tr>
<td><em>C. tetani</em></td>
<td>Tetanus</td>
</tr>
</tbody>
</table>
### Main features of exotoxins and endotoxins

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>Exotoxin</th>
<th>Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOURCE</strong></td>
<td>Certain species of gram ‡ and gram ⊝ bacteria</td>
<td>Outer cell membrane of most gram ⊝ bacteria</td>
</tr>
<tr>
<td><strong>SECRETED FROM CELL</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>CHEMISTRY</strong></td>
<td>Polypeptide</td>
<td>Lipid A component of LPS (structural part of bacteria; released when lysed)</td>
</tr>
<tr>
<td><strong>LOCATION OF GENES</strong></td>
<td>Plasmid or bacteriophage</td>
<td>Bacterial chromosome</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></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><strong>CLINICAL EFFECTS</strong></td>
<td>Various effects (see following pages)</td>
<td>Fever, shock (hypotension), DIC</td>
</tr>
<tr>
<td><strong>MODE OF ACTION</strong></td>
<td>Various modes (see following pages)</td>
<td>Induces TNF, IL-1, and IL-6</td>
</tr>
<tr>
<td><strong>ANTIGENICITY</strong></td>
<td>Induces high-titer antibodies called antitoxins</td>
<td>Poorly antigenic</td>
</tr>
<tr>
<td><strong>VACCINES</strong></td>
<td>Toxoids used as vaccines</td>
<td>No toxoids formed and no vaccine available</td>
</tr>
<tr>
<td><strong>HEAT STABILITY</strong></td>
<td>Destroyed rapidly at 60°C (except staphylococcal enterotoxin)</td>
<td>Stable at 100°C for 1 hr</td>
</tr>
<tr>
<td><strong>TYPICAL DISEASES</strong></td>
<td>Tetanus, botulism, diphtheria</td>
<td>Meningococcemia; sepsis by gram ⊝ rods</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Toxin</td>
<td>Mechanism</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td><strong>Corynebacterium diphtheriae</strong></td>
<td>Diphtheria toxin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Inactivate elongation factor (EF-2)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Exotoxin A&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><em>Shigella</em> spp.</td>
<td>Shiga toxin (ST)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Inactivate 60S ribosome by removing adenine from tRNA</td>
</tr>
<tr>
<td><em>Enterohemorrhagic E. coli</em> (EHEC)</td>
<td>Shiga-like toxin (SLT)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

### Increase fluid secretion

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Toxin</th>
<th>Mechanism</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterotoxigenic E. coli</em> (ETEC)</td>
<td>Heat-labile toxin (LT)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Overactivates adenylate cyclase (1 cAMP) → 1 Cl&lt;sup&gt;-&lt;/sup&gt; secretion in gut and H&lt;sub&gt;2&lt;/sub&gt;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 (1 cGMP) → 4 resorption of NaCl and H&lt;sub&gt;2&lt;/sub&gt;O in gut</td>
<td>Voluminous “rice-water” diarrhea</td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td>Edema toxin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mimics the adenylate cyclase enzyme (1 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&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Overactivates adenylate cyclase (1 cAMP) by permanently activating G&lt;sub&gt;i&lt;/sub&gt; → 1 Cl&lt;sup&gt;-&lt;/sup&gt; secretion in gut and H&lt;sub&gt;2&lt;/sub&gt;O efflux</td>
<td>Voluminous “rice-water” diarrhea</td>
</tr>
</tbody>
</table>

### Inhibit phagocytic ability

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Toxin</th>
<th>Mechanism</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bordetella pertussis</em></td>
<td>Pertussis toxin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Overactivates adenylate cyclase (1 cAMP) by disabling G&lt;sub&gt;i&lt;/sub&gt;, 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>
</tbody>
</table>

### Inhibit release of neurotransmitter

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Toxin</th>
<th>Mechanism</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium tetani</em></td>
<td>Tetanospasmin&lt;sup&gt;a&lt;/sup&gt;</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>Spastic paralysis, risus sardonicus, and “lockjaw”; toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Botulinum toxin&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Flaccid paralysis, floppy baby; toxin prevents release of stimulatory (ACh) signals at neuromuscular junctions → flaccid paralysis</td>
</tr>
</tbody>
</table>

<sup>a</sup>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><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>Binds to MHC II and TCR outside of antigen binding site to cause 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 (enterotoxin)</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Exotoxin A</td>
<td></td>
<td>Toxic shock syndrome: fever, rash, shock</td>
</tr>
</tbody>
</table>

### Endotoxin

LPS found in outer membrane of gram-negative 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), complement activation, and tissue factor activation.

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

![Diagram of endotoxin effects](image)
Gram-positive lab algorithm

**Gram-positive cocci antibiotic tests**

<table>
<thead>
<tr>
<th>Staphylococci</th>
<th>NO</th>
<th><strong>S</strong>. <em>pneumoniae</em> is Resistant; <em>E. epidermidis</em> is Sensitive.</th>
<th>On the office’s “staph” retreat, there was NO StRESs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococci</td>
<td>Optochin—<strong>Viridans</strong> is Resistant; <em>P. pneumoniae</em> is Sensitive.</td>
<td>OVRPS (overpass).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bactarin—group B strep are Resistant; group A strep are Sensitive.</td>
<td>B-BRAS.</td>
<td></td>
</tr>
</tbody>
</table>

Important tests are in **bold**. Important pathogens are in **bold italics**.

Note: Enterococcus is either α- or γ-hemolytic.
**α-hemolytic bacteria**

Gram + cocci. Partial reduction of hemoglobin causes greenish or brownish color without clearing around growth on blood agar. Include the following organisms:
- *Streptococcus pneumoniae* (catalase + and optochin sensitive)
- Viridans streptococci (catalase + and optochin resistant)

**β-hemolytic bacteria**

Gram + 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 + and bacitracin sensitive)
- *Streptococcus agalactiae*—group B strep (catalase + and bacitracin resistant)

**Staphylococcus aureus**

Gram +, β-hemolytic, catalase +, coagulase + cocci in clusters. Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares.

Causes:
- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).
- MRSA (methicillin-resistant *S. aureus*) infection—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) presents as 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.

**Staph** make catalase because they have more “staff.” Bad staph *(aureus)* make coagulase and toxins. Forms fibrin clot around self → abscess.

**Staphylococcus epidermidis**

Gram +, catalase +, coagulase +, urease + cocci in clusters. Novobiocin sensitive.

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 cause 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 splenectomy. No virulence without capsule.

**Viridans group streptococci**

Gram +, α-hemolytic cocci. They are normal flora of the oropharynx that cause dental caries (*Streptococcus mutans and S. mitis*) and subacute bacterial endocarditis at damaged heart valves (*S. sanguinis*). Resistant to optochin, differentiating them from *S. pneumoniae*, which is α-hemolytic but is optochin sensitive.

*Sanguinis = blood*. Think, “there is lots of blood in the heart” (endocarditis). *S. sanguinis* makes dextran, which bind to fibrin-platelet aggregates on damaged heart valves. Viridans group strep live in the mouth because they are not afraid of-the-chin (op-to-chin resistant).

**Streptococcus pyogenes (group A streptococci)**

Gram + cocci. Group A strep cause:
- Pyogenic—pharyngitis, cellulitis, impetigo, erysipelas
- Toxigenic—scarlet fever, toxic shock-like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive, β-hemolytic, pyrrolidonyl arylamidase (PYR) +. Antibodies to M protein enhance host defenses against *S. pyogenes* but can give rise to rheumatic fever. ASO titer detects recent *S. pyogenes* infection.

J♥NES (major criteria for acute rheumatic fever):
- Joints—polyarthritis
- ♥—carditis
- Nodules (subcutaneous)
- Erythema marginatum
- Sydenham chorea

Pharyngitis can result in rheumatic “pfever” and glomerulonephritis. Impetigo usually precedes 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 ⊕ cocci, 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. Patients with ⊕ culture receive intrapartum penicillin prophylaxis.

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

**Enterococci**
Gram ⊕ cocci. 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).

**Cutaneous anthrax**
Painless papule surrounded by vesicles → ulcer with black eschar (았다) (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.
### Bacillus cereus

| Spores survive cooking rice. 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)

<table>
<thead>
<tr>
<th>Gram ⊕, spore-forming, obligate anaerobic rods.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C tetani</strong> 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). Prevent with tetanus vaccine. Treat with antitoxin +/- vaccine booster, diazepam (for muscle spasms), and wound debridement.</td>
</tr>
<tr>
<td>Tetanus is tetanic paralysis.</td>
</tr>
<tr>
<td><strong>C botulinum</strong> 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 antitoxin.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td><strong>C perfringens</strong> Produces α toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene) and hemolysis. Spores can survive in undercooked food; when ingested, bacteria release heat-labile enterotoxin → food poisoning.</td>
</tr>
<tr>
<td>Perfringens perforates a gangrenous leg.</td>
</tr>
<tr>
<td><strong>C difficile</strong> Produces 2 toxins. Toxin A, enterotoxin, binds to the brush border of the gut. Toxin B, cytotoxin, causes cytoskeletal disruption via actin depolymerization → diarrhea → pseudomembranous colitis. Often 2º to antibiotic use, especially clindamycin or ampicillin; associated with PPI use. Diagnosed by detecting one or both toxins in stool by PCR.</td>
</tr>
<tr>
<td>Difficile causes diarrhea. Treatment: metronidazole or oral vancomycin. For recurrent cases, consider repeating prior regimen, fidaxomicin, or fecal microbiota transplant.</td>
</tr>
</tbody>
</table>
**Corynebacterium diphtheriae**

Gram \(\oplus\) rod. Causes diphtheria via exotoxin encoded by \(\beta\)-prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2.

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

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

Toxoid vaccine prevents diphtheria.

**Listeria monocytogenes**

Gram \(\oplus\), facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, via transplacental transmission, or by vaginal transmission during birth.

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 infantiseptica; neonatal meningitis; meningitis in immunocompromised patients; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin in infants, immunocompromised, and the elderly as empirical treatment of meningitis.

**Nocardia vs Actinomyces**

Both are gram \(\oplus\) 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)</td>
<td>Not acid fast</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 (\oplus) PPD); cutaneous infections after trauma in immunocompetent</td>
<td>Causes oral/facial abscesses that drain through sinus tracts, 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— <em>Nocardia</em>; Penicillin— <em>Actinomyces</em></td>
<td></td>
</tr>
</tbody>
</table>

*Coryne = club shaped.*

Black colonies on cystine-tellurite agar.

**ABCDEFG:**
- ADP-ribosylation
- \(\beta\)-prophage
- *Corynebacterium*
- *Diphtheriae*
- Elongation Factor 2
- Granules
Primary and secondary tuberculosis

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).

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; inhibits macrophage maturation and induces release of TNF-α. Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

Mycobacterium tuberculosis

PPD ⊕ if current infection or past exposure. PPD ⊖ if no infection and in sarcoidosis.

Interferon-γ release assay (IGRA) has fewer false positives from BCG vaccination.

Caseating granulomas A with central necrosis (upper left) and Langerhans giant cells (arrow) 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. Reservoir in United States: armadillos.

Hansen disease has 2 forms:
- **Lepromatous**—presents diffusely over the skin, with leonine (lion-like) facies, and is communicable; characterized by low cell-mediated immunity with a humoral Th2 response. Lepromatous form can be lethal.
- **Tuberculoid**—limited to a few hypoesthetic, hairless plaques; characterized by high cell-mediated immunity with a largely Th1-type immune response.

Treatment: dapsone and rifampin for tuberculoid form; clofazimine is added for lepromatous form.

Gram-negative lab algorithm

Important tests are in **bold**. Important pathogens are in **bold italics.**
### Lactose-fermenting enteric bacteria

Fermentation of lactose → pink colonies on MacConkey agar. Examples include *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 MacConkey’s agar.
- EMB—lactose fermenters grow as purple/black colonies. *E. coli* grows colonies with a green sheen.

### Neisseria

Gram − diplococci. Metabolize glucose and produce IgA proteases. *N. gonorrhoeae* is often intracellular (within neutrophils). *

**Menin**
- Gonococci ferment maltose and glucose.
- Gonococci ferment glucose.

<table>
<thead>
<tr>
<th><strong>Gonococci</strong></th>
<th><strong>Meningococci</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No polysaccharide capsule</td>
<td>Polysaccharide capsule</td>
</tr>
<tr>
<td>No maltose metabolized</td>
<td>Maltose fermentation</td>
</tr>
<tr>
<td>No vaccine due to antigenic variation of pilus proteins</td>
<td>Vaccine (type B vaccine not widely available)</td>
</tr>
<tr>
<td>Sexually or perinatally transmitted</td>
<td>Transmitted via respiratory and oral secretions</td>
</tr>
<tr>
<td>Causes gonorrhea, septic arthritis, neonatal conjunctivitis, pelvic inflammatory disease (PID), and Fitz-Hugh–Curtis syndrome</td>
<td>Causes meningococcemia with petechial hemorrhages and gangrene of toes, meningitis, Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC, shock) syndrome</td>
</tr>
<tr>
<td>Condoms ↓ sexual transmission, erythromycin eye ointment prevents neonatal blindness</td>
<td>Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts</td>
</tr>
<tr>
<td>Treatment: ceftriaxone + (azithromycin or doxycycline) for possible chlamydial coinfection</td>
<td>Treatment: ceftriaxone or penicillin G</td>
</tr>
</tbody>
</table>

### 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 through the hemolysis of RBCs. *HaEMOPhilus* causes epiglottitis (endoscopic appearance in A can be “cherry red” in children; “thumbprint sign” on 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 and PRP (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 \( \Theta \), aerobic coccobacillus. Virulence factors include pertussis toxin (disables \( \text{G}_{\text{as}} \)) and tracheal cytotoxin. Causes whooping cough. Prevented by Tdap, DTaP vaccines. May be mistaken as viral infection due to lymphocytic infiltrate resulting from immune response.

**Legionella pneumophila**


Think of a French *legionnaire* (soldier) with his silver helmet, sitting around a campfire (charcoal) with his iron dagger—he is no sissy (cysteine).

**Pseudomonas aeruginosa**

Aerobic, motile, gram \( \Theta \) rod. Non-lactose fermenting, oxidase \( \Theta \). Produces pyocyanin (blue-green pigment [A]); has a grape-like odor. Produces endotoxin (fever, shock), exotoxin A (inactivates EF-2), phospholipase C (degrades cell membranes), and pyocyanin (generates reactive oxygen species). **PSEUDOMONAS** is associated with:

- Pneumonia, pyocyanin
- Sepsis
- Ecthyma gangrenosum
- UTIs
- Diabetes, drug use
- Osteomyelitis (eg, puncture wounds)
- Mucoid polysaccharide capsule
- Otitis externa (swimmer’s ear)
- Nosocomial infections (catheters, equipment)
- exotoxin A
- Skin infections (hot tub folliculitis)

Treatments include “CAMPFIRE” drugs:

- Carbapenems
- Aminoglycosides
- Monobactams
- Polymyxins (eg, polymyxin B, colistin)
- Fluoroquinolones (eg, ciprofloxacin, levofloxacin)
- Thirde- and fourth-generation cephalosporins (eg, ceftazidime, cefepime)
- Extended-spectrum penicillins (eg, piperacillin, ticarcillin)

**Aeruginosa**—aerobic. Mucoid polysaccharide capsule may contribute to chronic pneumonia in cystic fibrosis patients due to biofilm formation. Can cause wound infection in burn victims. Frequently found in water \( \mapsto \) hot tub folliculitis. **Ecthyma gangrenosum**—rapidly progressive, necrotic cutaneous lesion [B] caused by *Pseudomonas* bacteremia. Typically seen in immunocompromised patients.
**E. coli**

Gram − 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>EIEC</td>
<td>Microbe invades intestinal mucosa and causes necrosis and inflammation.</td>
<td>Invasive; dysentery. Clinical manifestations similar to <em>Shigella</em>.</td>
</tr>
<tr>
<td>ETEC</td>
<td>Produces heat-labile and heat-stable enterotoxins. No inflammation or invasión.</td>
<td>Travelers’ diarrhea (watery).</td>
</tr>
<tr>
<td>EPEC</td>
<td>No toxin produced. Adheres to apical surface, flattens villi, prevents absorption.</td>
<td>Diarrhea, usually in children (<em>Pediatrics</em>).</td>
</tr>
<tr>
<td>EHEC</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 (distinguishes EHEC from other <em>E. coli</em>). <strong>Hemorrhagic, Hamburgers, Hemolytic-uremic syndrome.</strong></td>
</tr>
</tbody>
</table>

**Klebsiella**

Gram − 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.

**4 A’s of Klebsiella**:  
Aspiration pneumonia  
Abscess in lungs and liver  
Alcoholics  
diabetes

**Campylobacter jejuni**

Gram − comma or S shaped (with polar flagella), oxidase −, 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.
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>Reservoirs</th>
<th>Salmonella typhi</th>
<th>Salmonella spp. (except S typhi)</th>
<th>Shigella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans only</td>
<td>Humans and animals</td>
<td>Humans only</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spread</th>
<th>Can disseminate hemogenously</th>
<th>Can disseminate hemogenously</th>
<th>Cell to cell; no hematogenous spread</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>H₂S Production</th>
<th>Yes</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Flagella</th>
<th>Yes (salmon swim)</th>
<th>Yes (salmon swim)</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Virulence Factors</th>
<th>Endotoxin; Vi capsule</th>
<th>Endotoxin</th>
<th>Endotoxin; Shiga toxin (enterotoxin)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Infectious Dose (ID₅₀)</th>
<th>High—large inoculum required because organism inactivated by gastric acids</th>
<th>High</th>
<th>Low—very small inoculum required; resistant to gastric acids</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Effect of Antibiotics on Fecal Excretion</th>
<th>Prolongs duration</th>
<th>Prolongs duration</th>
<th>Shortens duration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Immune Response</th>
<th>Primarily monocytes</th>
<th>PMNs in disseminated disease</th>
<th>Primarily PMN infiltration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>GI Manifestations</th>
<th>Constipation, followed by diarrhea</th>
<th>Diarrhea (possibly bloody)</th>
<th>Bloody diarrhea (bacillary dysentery)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Oral vaccine contains live attenuated S typhi</th>
<th>No vaccine</th>
<th>No vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM vaccine contains Vi capsular polysaccharide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unique Properties</th>
<th>Causes typhoid fever (rose spots on abdomen, constipation, abdominal pain, fever); treat with ceftriaxone or fluoroquinolone</th>
<th>Poultry, eggs, pets, and turtles are common sources</th>
<th>Antibiotics not indicated</th>
<th>Gastroenteritis is usually caused by non-typhoidal Salmonella</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carrier state with gallbladder colonization</td>
<td></td>
<td></td>
<td>Four F’s: Fingers, Flies, Food, Feces</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In order of decreasing severity (less toxin produced): S dysenteriae, S flexneri, S boydii, S sonnei</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Invasion is the key to pathogenicity; organisms that produce little toxin can cause disease due to invasion</td>
</tr>
</tbody>
</table>

Vibrio cholerae

Gram negative, flagellated, comma shaped. oxidase positive, grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates Gₛ₁, cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high ID₅₀) unless host has low gastric acidity. Prompt oral rehydration is necessary.

Yersinia enterocolitica

Gram negative rod. Usually transmitted from pet feces (eg, puppies), contaminated milk, or pork. Causes acute diarrhea or pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis).
**Helicobacter pylori**

Curved, terminally flagellated, gram-negative rod that is triple-positive for 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 *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.

---

**Leptospira interrogans**

Spirochete found in water contaminated with animal urine, causes 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.

---

**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. Mice are important to tick life cycle. Common in northeastern United States.

Stage 1—early localized: erythema migrans, flu-like symptoms.

Stage 2—early disseminated: secondary lesions, carditis, AV block, facial nerve (Bell) palsy, migratory myalgias/transient arthritis.

Stage 3—late disseminated: encephalopathies, chronic arthritis.

A Key Lyme pie to the FACE:

- Facial nerve palsy (typically bilateral)
- Arthritis
- Cardiac block
- Erythema migrans
Syphilis

Caused by spirochete *Treponema pallidum*.

**Primary syphilis**
Localized disease presenting with painless chancre. If available, use dark-field microscopy to visualize treponemes in fluid from chancre. VDRL in ~ 80%.

**Secondary syphilis**
Disseminated disease with constitutional symptoms, maculopapular rash (including palms and soles), condylomata lata (smooth, moist, 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 (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), snuffles (nasal discharge, red arrow), saddle nose, notched (Hutchinson) teeth, 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. Inexpensive, widely available test for syphilis, quantitative, sensitive but not specific.

False-positive results on VDRL with:
- 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.
### Zoonotic bacteria

Zoonosis: infectious disease transmitted between animals and humans.

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>DISEASE</th>
<th>TRANSMISSION AND SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Anaplasma spp.</em></td>
<td>Anaplasmosis</td>
<td><em>Ixodes</em> ticks (live on deer and mice)</td>
</tr>
<tr>
<td><em>Bartonella spp.</em></td>
<td>Cat scratch disease, bacillary angiomatosis</td>
<td>Cat scratch</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Lyme disease</td>
<td><em>Ixodes</em> ticks (live on deer and mice)</td>
</tr>
<tr>
<td><em>Borrelia recurrentis</em></td>
<td>Relapsing fever</td>
<td>Louse (recurrent due to variable surface antigens)</td>
</tr>
<tr>
<td><em>Brucella spp.</em></td>
<td>Brucellosis/undulant fever</td>
<td>Unpasteurized dairy</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Bloody diarrhea</td>
<td>Feces from infected pets/animals; contaminated meats/foods/hands</td>
</tr>
<tr>
<td><em>Chlamydia psittaci</em></td>
<td>Psittacosis</td>
<td>Parrots, other birds</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>Q fever</td>
<td>Aerosols of cattle/sheep amniotic fluid</td>
</tr>
<tr>
<td><em>Ehrlichia chaffeensis</em></td>
<td>Ehrlichiosis</td>
<td><em>Amblyomma</em> (Lone Star tick)</td>
</tr>
<tr>
<td><em>Francisella tularensis</em></td>
<td>Tularemia</td>
<td>Ticks, rabbits, deer flies</td>
</tr>
<tr>
<td><em>Leptospiira spp.</em></td>
<td>Leptospirosis</td>
<td>Animal urine in water; recreational water use</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>Leprosy</td>
<td>Humans with lepromatous leprosy; armadillo (rare)</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>Cellulitis, osteomyelitis</td>
<td>Animal bite, cats, dogs</td>
</tr>
<tr>
<td><em>Rickettsia prowazekii</em></td>
<td>Epidemic typhus</td>
<td>Human to human via human body louse</td>
</tr>
<tr>
<td><em>Rickettsia rickettsii</em></td>
<td>Rocky Mountain spotted fever</td>
<td><em>Dermacentor</em> (dog tick)</td>
</tr>
<tr>
<td><em>Rickettsia typhi</em></td>
<td>Endemic typhus</td>
<td>Fleas</td>
</tr>
<tr>
<td><em>Salmonella spp.</em></td>
<td>Diarrhea (which may be bloody), vomiting, fever, abdominal cramps</td>
<td>Reptiles and poultry</td>
</tr>
<tr>
<td>(except <em>S typhi</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Plague</td>
<td>Fleas (rats and prairie dogs are reservoirs)</td>
</tr>
</tbody>
</table>

### 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.

I don’t have a clue why I smell fish in the *vagina garden*! Amine whiff test—mixing discharge with 10% KOH enhances fishy odor.
### Rickettsial diseases and vector-borne illnesses

**Rash common**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Classic triad</th>
<th>Palms and soles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em>, 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.</td>
<td>Headache, fever, rash (vasculitis).</td>
<td>Palms and soles rash is seen in Coxsackievirus A infection (hand, foot, and mouth disease). Rocky Mountain spotted fever, and 2° Syphilis (you drive CARS using your palms and soles).</td>
</tr>
<tr>
<td>Typhus</td>
<td>Endemic (fleas)—R typhi. Epidemic (human body louse)—R prowazekii. Rash starts centrally and spreads out, sparing palms and soles.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rash rare**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>MEGA berry</th>
<th>Granulocytes = Anaplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrlichiosis</td>
<td><em>Ehrlichia</em>, vector is tick. Monocytes with morulae (mulberry-like inclusions) in cytoplasm.</td>
<td>Monocytes = Ehrlichiosis</td>
<td>Granulocytes = Anaplasmosis</td>
</tr>
<tr>
<td>Anaplasmosis</td>
<td><em>Anaplasma</em>, vector is tick. Granulocytes with morulae in cytoplasm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q fever</td>
<td><em>Coxiella burnetii</em>, no arthropod vector. Spores inhaled as aerosols from cattle/sheep amniotic fluid. Presents as pneumonia. Most common cause of culture endocarditis.</td>
<td>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 <em>Rickettsia</em> genus, but closely related.</td>
<td></td>
</tr>
</tbody>
</table>
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; Regenerates into elementary bodies.

*Chlamydia trachomatis* causes reactive arthritis (Reiter syndrome), follicular conjunctivitis, nongonococcal urethritis, and PID.

*Chlamydophila pneumoniae* and *Chlamydophila psittaci* cause atypical pneumonia; transmitted by aerosol.

Treatment: azithromycin (favored because one-time treatment) or doxycycline.

---

**Chlamydia trachomatis** serotypes

| Types A, B, and C | Chronic infection, cause blindness due to follicular conjunctivitis in Africa. | ABC = Africa, Blindness, Chronic infection. |
| Types L1, L2, and L3 | Lymphogranuloma venereum—small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (buboes). Treat with doxycycline. | |

---

**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 or lyse 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.

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. The only exception is coccidioidomycosis, which is a spherule (not yeast) in tissue. Treatment: fluconazole or itraconazole for local infection; amphotericin B for systemic infection. Systemic mycoses can form granulomas (like TB) but cannot be transmitted person-to-person (unlike TB).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endemic Location and Pathologic Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasmosis</td>
<td>Mississippi and Ohio River valleys. Macrophage filled with <em>Histoplasma</em> (smaller than RBC) A.</td>
<td>Histo hides within macrophages. Bird (e.g., starlings) or bat droppings.</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Eastern United States and Central America. Causes inflammatory lung disease and can disseminate to skin and bone. Forms granulomatous nodules. Broad-base budding (same size as RBC) B.</td>
<td>Blasto buds broadly.</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>Southwestern United States, California. Causes pneumonia and meningitis; can disseminate to skin and bone. Case rate ↑ after earthquakes (spores in dust thrown into air → inhaled → spherules in lung). Spherule (much larger than RBC) filled with endospores C.</td>
<td>Coccidio crowds endospores. &quot;(San Joaquin) Valley fever&quot; &quot;Desert bumps&quot; = erythema nodosum &quot;Desert rheumatism&quot; = arthralgias</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td>Latin America. Budding yeast with &quot;captain's wheel&quot; formation (much larger than RBC) D.</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>Tinea (dermatophytes)</th>
<th>Tinea is the clinical name given to dermatophyte (cutaneous fungal) infections. Dermatophytes include <em>Microsporum</em>, <em>Trichophyton</em>, and <em>Epidermophyton</em>. Branching septate hyphae visible on KOH preparation with blue fungal stain.</th>
</tr>
</thead>
<tbody>
<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 (&quot;ringworm&quot;) 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: most common  
  - 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 and/or pink patches. 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** | alba = white. Dimorphic; forms pseudo hyphae 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 (to any organ), chronic mucocutaneous candidiasis.
Treatment: topical azole for vaginal; nystatin, fluconazole, or caspofungin for oral/esophageal; fluconazole, caspofungin, or amphotericin B for systemic. |
| **Aspergillus fumigatus** | Septate hyphae that branch at 45° Acute Angle. Produces conidia in radiating chains at end of conidiophore.
Causes invasive aspergillosis, especially in immunocompromised and those with chronic granulomatous disease.
Can cause aspergillomas in pre-existing lung cavities, especially after TB infection.
Some species of *Aspergillus* produce aflatoxins, which are associated with hepatocellular carcinoma.
Allergic bronchopulmonary aspergillosis (ABPA): hypersensitivity response associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia. |
| **Cryptococcus neoformans** | 5–10 μm with narrow budding. Heavily encapsulated yeast. Not dimorphic.
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. |
| **Mucor and Rhizopus spp.** | Irregular, broad, nonseptate hyphae branching at wide angles.
Mucormycosis. Causes disease mostly in ketoacidotic diabetic and/or neutropenic patients (eg, leukemia). 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. |
**Pneumocystis jirovecii**

Causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia. Yeast-like fungus (originally classified as protozoan). Inhaled. Most infections are asymptomatic. Immunosuppression (eg, AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on CXR/CT. 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.

“Plant a rose in the pot.”
### Protozoa—GI 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>Giardia lamblia</strong></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 or cysts in stool</td>
<td>Metronidazole</td>
</tr>
<tr>
<td><strong>Entamoeba histolytica</strong></td>
<td><strong>Amebiasis</strong>—bloody diarrhea (dysentery), liver abscess (“anchovy paste” exudate), RUQ pain; histology shows flask-shaped ulcer</td>
<td>Cysts in water</td>
<td>Serology and/or trophozoites (with engulfed RBCs in the cytoplasm) or cysts with up to 4 nuclei in stool</td>
<td>Metronidazole; iodoquinol for asymptomatic cyst passers</td>
</tr>
<tr>
<td><strong>Cryptosporidium</strong></td>
<td>Severe diarrhea in AIDS Mild disease (watery diarrhea) in immunocompetent hosts</td>
<td>Oocysts in water</td>
<td>Oocysts on acid-fast stain</td>
<td>Prevention (by filtering city water supplies); nitazoxanide in immunocompetent hosts</td>
</tr>
</tbody>
</table>

![Images of protozoa](image-url)
**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><em>Toxoplasma gondii</em></td>
<td>Congenital toxoplasmosis = classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications; reactivation in AIDS → brain abscess seen as ring-enhancing lesions on MRI</td>
<td>Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant women should avoid cats)</td>
<td>Serology, biopsy (tachyzoite)</td>
<td>Sulfadiazine + pyrimethamine</td>
</tr>
<tr>
<td><em>Naegleria fowleri</em></td>
<td>Rapidly fatal meningoencephalitis</td>
<td>Swimming in fresh water lakes (think Nalgene bottle filled with fresh water containing <em>Naegleria</em>); enters via cribriform plate</td>
<td>Amoebas in spinal fluid</td>
<td>Amphotericin B has been effective for a few survivors</td>
</tr>
<tr>
<td><em>Trypanosoma brucei</em></td>
<td>African sleeping sickness—enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma Two subspecies: <em>Trypanosoma brucei rhodesiense</em>, <em>Trypanosoma brucei gambiense</em></td>
<td>Tsetse fly, a painful bite Trypomastigote in blood smear</td>
<td>Suramin for blood-borne disease or melarsoprol for CNS penetration (&quot;it sure is nice to go to sleep&quot;); melatonin helps with sleep</td>
<td></td>
</tr>
<tr>
<td>Protozoa—hematologic infections</td>
<td>Disease</td>
<td>Organism</td>
<td>Transmission</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>----------</td>
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</tr>
<tr>
<td>Plasmodium</td>
<td>Malaria—fever, headache, anemia, splenomegaly</td>
<td>Anopheles mosquito</td>
<td>Blood smear: trophozoite ring form within RBC, schizont containing merozoites; red granules (Schüffner stippling) throughout RBC cytoplasm seen with P vivax/ovale</td>
<td>Chloroquine (for sensitive species), which blocks Plasmodium heme polymerase; if resistant, use mefloquine or atovaquone/proguanil If life-threatening, use intravenous quinidine or artemisinin (test for G6PD deficiency) For P vivax/ovale, add primaquine for hypnozoite (test for G6PD deficiency)</td>
</tr>
<tr>
<td>P vivax/ovale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P falciparum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P malariae</td>
<td>Babesia—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>
<tr>
<td>Babesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Protozoa**

**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)

**Babesia**
- 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)

**Transmission**
- *Anopheles* mosquito
- *Ixodes* tick

**Diagnosis**
- Blood smear
- PCR

**Treatment**
- Chloroquine (for sensitive species), which blocks *Plasmodium* heme polymerase; if resistant, use mefloquine or atovaquone/proguanil If life-threatening, use intravenous quinidine or artemisinin (test for G6PD deficiency) For *P. vivax/ovale*, add primaquine for hypnozoite (test for G6PD deficiency)
| Protozoa—others | |
|---|---|---|---|---|---|
| **Visceral infections** | **DISEASE** | **TRANSMISSION** | **DIAGNOSIS** | **TREATMENT** |
| Trypanosoma cruzi | Chagas disease—dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America | Reduviid bug (“kissing bug”) feces, deposited in a painless bite (much like a kiss) | Trypomastigote in blood smear | Benznidazole or nifurtimox; Cruzing in my Benz, with a fur coat on |
| Leishmania donovani | Visceral leishmaniasis (kala-azar)—spiking fevers, hepatosplenomegaly, pancytopenia | Sandfly | Macrophages containing amastigotes | Amphotericin B, sodium stibogluconate |
| | Cutaneous leishmaniasis—skin ulcers | | | |

| **Sexually transmitted infections** | **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 | You’ll get sick if you EATT these! |
| | Cutaneous—Strongyloides, Ancylostoma, Necator | These get into your feet from the SANd. |
| | Bites—Loa loa, Onchocerca volvulus, Wuchereria bancrofti | Lay LOW to avoid getting bitten. |

| **Immune response to helminths** | Eosinophils act by type I and type II hypersensitivity reactions in responding to helminths. Type I—neutralization of histamine and leukotrienes. Type II—eosinophils attach to surface of helminths via IgE and release cytotoxins (eg, major basic protein) contained in their granules. |
### 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>Intestinal infection causing anal pruritus (diagnosed by seeing egg via the tape test)</td>
<td>Fecal-oral</td>
<td>Bendazoles (because worms are bendy)</td>
</tr>
<tr>
<td><em>Ascaris lumbricoides</em> (giant roundworm)</td>
<td>Intestinal infection with possible obstruction at ileocecal valve</td>
<td>Fecal-oral; eggs visible in feces under microscope</td>
<td>Bendazoles</td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em> (threadworm)</td>
<td>Intestinal infection causing vomiting, diarrhea, epigastric pain (may mimic peptic ulcer)</td>
<td>Larvae in soil penetrate the skin</td>
<td>Ivermectin or bendazoles</td>
</tr>
<tr>
<td><em>Ancylostoma duodenale, Necator americanus</em> (hookworms)</td>
<td>Intestinal infection causing anemia by sucking blood from intestinal wall. <strong>Cutaneous larva migrans</strong>—pruritic, serpiginous rash from walking barefoot on contaminated beach.</td>
<td>Larvae penetrate skin</td>
<td>Bendazoles or pyrantel pamoate</td>
</tr>
<tr>
<td><em>Trichinella spiralis</em></td>
<td>Intestinal infection; larvae enter bloodstream and encyst in striated muscle cells → inflammation of muscle. <strong>Trichinosis</strong>—fever, vomiting, nausea, periorbital edema, myalgia.</td>
<td>Fecal-oral; undercooked meat (especially pork)</td>
<td>Bendazoles</td>
</tr>
<tr>
<td><strong>Tissue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Toxocara canis</em></td>
<td>Visceral larva migrans—nematodes migrate to blood through intestinal wall causing inflammation and damage. Organs frequently affected include the heart (myocarditis), liver, and CNS (seizures, coma).</td>
<td>Fecal-oral</td>
<td>Bendazoles</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>Skin changes, loss of elastic fibers, and river blindness (black flies, black skin nodules, <strong>black sight</strong>); allergic reaction to microfilaria possible.</td>
<td>Female blackfly</td>
<td>Ivermectin (ivermectin for river blindness)</td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td>Swelling in skin, worm in conjunctiva</td>
<td>Deer fly, horse fly, mango fly</td>
<td>Diethylcarbamazine</td>
</tr>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td><strong>Elephantiasis</strong>—worms invade lymph nodes and cause inflammation, which can block lymphatic vessels, takes 9 mo–1 yr after bite to become symptomatic.</td>
<td>Female mosquito</td>
<td>Diethylcarbamazine</td>
</tr>
</tbody>
</table>
### Cestodes (tapeworms)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Taenia solium</em> A</td>
<td>Intestinal tapeworm</td>
<td>Ingestion of larvae encysted in undercooked pork</td>
<td>Praziquantel</td>
</tr>
<tr>
<td></td>
<td>Cysticercosis, neurocysticercosis B</td>
<td>Ingestion of eggs contaminated with human feces</td>
<td>Praziquantel; albendazole for neurocysticercosis</td>
</tr>
<tr>
<td><em>Diphyllobothrium latum</em></td>
<td>Vitamin $B_{12}$ deficiency</td>
<td>Ingestion of larvae from raw freshwater fish</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Echinococcus granulosus</em> C</td>
<td>Hydatid cysts in liver E, causing anaphylaxis if antigens released (hydatid cyst injected with ethanol or hypertonic saline to kill daughter cysts before removal)</td>
<td>Ingestion of eggs from dog feces Sheep are an intermediate host</td>
<td>Albendazole</td>
</tr>
</tbody>
</table>

### Trematodes (flukes)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Schistosoma</em> A</td>
<td>Liver and spleen enlargement ((S \text{ mansoni}, \text{ egg with lateral spine }A), \text{ fibrosis, and inflammation})</td>
<td>Snails are host; cercariae penetrate skin of humans</td>
<td>Praziquantel</td>
</tr>
<tr>
<td></td>
<td>Chronic infection with ((S \text{ haematobium}, \text{ egg with terminal spine }B)) can lead to squamous cell carcinoma of the bladder (painless hematuria) and pulmonary hypertension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *Clonorchis sinensis* | Biliary tract inflammation \(\rightarrow\) pigmented gallstones
Associated with cholangiocarcinoma | Undercooked fish | Praziquantel                                   |
### Parasite hints

<table>
<thead>
<tr>
<th>Association</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary tract disease, cholangiocarcinoma</td>
<td>Clonorchis sinensis</td>
</tr>
<tr>
<td>Brain cysts, seizures</td>
<td>Taenia solium (neurocysticercosis)</td>
</tr>
<tr>
<td>Hematuria, squamous cell bladder cancer</td>
<td>Schistosoma haematobium</td>
</tr>
<tr>
<td>Liver (hydatid) cysts</td>
<td>Echinococcus granulosus</td>
</tr>
<tr>
<td>Microcytic anemia</td>
<td>Ancylostoma, Necator</td>
</tr>
<tr>
<td>Myalgias, periorbital edema</td>
<td>Trichinella spiralis</td>
</tr>
<tr>
<td>Perianal pruritus</td>
<td>Enterobius</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>Schistosoma mansoni, Schistosoma japonicum</td>
</tr>
<tr>
<td>Vitamin B₁₂ deficiency</td>
<td>Diphyllobothrium latum</td>
</tr>
</tbody>
</table>

### Ectoparasites

#### Scabies

*Scabies (Sarcoptes scabiei)*

Mites that burrow into the stratum corneum and cause pruritis. Causes serpiginous burrows (lines) in webspace of hands and feet. Common in children, crowded populations (jails, nursing homes); transmission through fomites. Treatment: permethrin cream, washing/drying all clothing/bedding, treat close contacts.

#### Lice

*Pediculus humanus/Phthirius pubis*

Blood-sucking insects that prefer to live on clothing. Cause intense pruritis, pink macules and papules commonly in intertriginous regions. Can transmit *Rickettsia prowazekii* (typhus), *Borrelia recurrentis* (relapsing fever), *Bartonella quintana* (trench fever). Treatment includes pyrethroids, malathion, or ivermectin lotion, and nit combing. Children with head lice can be treated at home without interrupting school.
### Viral structure—general features

<table>
<thead>
<tr>
<th>Naked virus with icosahedral capsid</th>
<th>Enveloped virus with icosahedral capsid</th>
<th>Enveloped virus with helical capsid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsid</td>
<td>Surface protein</td>
<td>Surface protein</td>
</tr>
<tr>
<td>Nucleic acid</td>
<td>Lipid bilayer</td>
<td>Lipid bilayer</td>
</tr>
<tr>
<td></td>
<td>Capsid</td>
<td>Capsid</td>
</tr>
<tr>
<td></td>
<td>Nucleic acid</td>
<td>Nucleic acid</td>
</tr>
</tbody>
</table>

### Viral genetics

<table>
<thead>
<tr>
<th><strong>Recombination</strong></th>
<th>Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reassortment</strong></td>
<td>When viruses with segmented genomes (e.g., 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.</td>
</tr>
<tr>
<td><strong>Complementation</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Phenotypic mixing</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

### Viral vaccines

| **Live attenuated vaccines** | Induce humoral and cell-mediated immunity but have reverted to virulence on rare occasions. **Live attenuated:** smallpox, yellow fever, rotavirus, chickenpox (VZV), Sabin polio virus, MMR, Influenza (intranasal). | No booster needed for live attenuated vaccines. Dangerous to give live vaccines to immunocompromised patients. Close contacts may be vaccinated with live vaccines (except live polio or influenza). **“Live! One night only! See small yellow rotating chickens get vaccinated with Sabin and MMR! It’s incredible!”** MMR = measles, mumps, rubella; live attenuated vaccine that can be given to HIV + patients who do not show signs of immunodeficiency. |
| **Killed** | Rabies, Influenza (injected), Salk Polio, and HAV vaccines. Killed/inactivated vaccines induce only humoral immunity but are stable. | SalK = Killed. RIP Always. |
| **Subunit** | HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18). | |
### DNA viral genomes

All DNA viruses except the Paroviridae are dsDNA. All are linear except papilloma-, polyoma-, and hepadnaviruses (circular).

All are dsDNA (like our cells), except “part-of-a-virus” (parvovirus) is ssDNA. *Parvus* = small.

### RNA viral genomes

All RNA viruses except Reoviridae are ssRNA. ⊕ 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 (like our mRNA), except “*repeato-virus*” (reovirus) is dsRNA.

### Naked viral genome infectivity

Purified nucleic acids of most dsDNA (except poxviruses and HBV) and ⊗ strand ssRNA (= mRNA) viruses are infectious. Naked nucleic acids of ⊗ strand ssRNA and dsRNA viruses are not infectious. They require polymerases contained in the complete virion.

### Viral replication

**DNA viruses**

All replicate in the nucleus (except pox virus).

**RNA viruses**

All replicate in the cytoplasm (except influenza virus and retroviruses).

### Viral envelopes

**Naked** (nonenveloped) viruses include Papillomavirus, Adenovirus, Parovirus, Polyomavirus, Calicivirus, Picornavirus, Reovirus, and Hepatitis virus. Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.

Give PAPP smears and CPR to a naked hippie (hepevirus). DNA = PAPP; RNA = CPR and 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>VIRAL FAMILY</td>
<td>ENVELOPE</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</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

<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, herpes labialis, herpetic whitlow on finger, temporary lobe encephalitis.</td>
<td>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, neonatal herpes.</td>
<td>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, shingles), encephalitis, pneumonia.</td>
<td>Latent in dorsal root or trigeminal ganglia.</td>
</tr>
<tr>
<td>Epstein-Barr virus (HHV-4)</td>
<td>Respiratory secretions, saliva; aka “kissing disease,” (common in teens, young adults)</td>
<td>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.</td>
<td>Infects 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.</td>
</tr>
<tr>
<td>Cytomegalovirus (HHV-5)</td>
<td>Congenital transfusion, sexual contact, saliva, urine, transplant</td>
<td>Mononucleosis (⊕ Monospot) in immunocompetent patients; infection in immunocompromised patients, especially pneumonia in transplant patients; AIDS retinitis (&quot;sightomegalovirus&quot;): hemorrhage, cotton-wool exudates, vision loss. Congenital CMV</td>
<td>Infected cells have characteristic “owl eye” inclusions. Latent in mononuclear cells.</td>
</tr>
<tr>
<td>Human herpesviruses 6 and 7</td>
<td>Saliva</td>
<td>Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash. HHV-7—less common cause of roseola.</td>
<td></td>
</tr>
<tr>
<td>Human herpesvirus 8</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.</td>
<td>Can also affect GI and lungs.</td>
</tr>
</tbody>
</table>
**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.
Intranuclear inclusions also seen with HSV-1, HSV-2, VZV.
**Tzanck** heavens I do not have herpes.

<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>Rabies</td>
<td>Nicotinic AChR</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>VIRAL FAMILY</td>
<td>ENVELOPE</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>Reoviruses</td>
<td>No</td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>No</td>
</tr>
<tr>
<td>Hepevirus</td>
<td>No</td>
</tr>
<tr>
<td>Caliciviruses</td>
<td>No</td>
</tr>
<tr>
<td>Flaviviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Togaviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Retroviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Coronaviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Orthomyxoviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Paramyxoviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Rhabdoviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Filoviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Arenaviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Bunyaviruses</td>
<td>Yes</td>
</tr>
<tr>
<td>Delta virus</td>
<td>Yes</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 \(\ominus\) strand to \(\oplus\). 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 (fecal-oral spread) except rhinovirus.

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

Rotavirus, the most important global cause of infantile gastroenteritis, is a segmented dsRNA virus (a reovirus). 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.
**Influenza viruses**

Orthomyxoviruses. Enveloped, ssRNA viruses with 8-segment genome. Contain hemagglutinin (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.

**Genetic shift/antigenic shift**

Causes pandemics. Reassortment of viral genome segments, such as when segments of human flu A virus re assort with swine flu A virus.

Sudden shift is more deadly than gradual drift.

**Rubella virus**

A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, confluent rash that starts on face and spreads centrifugally to involve trunk and extremities. Causes mild disease in children but serious congenital disease (a ToRCHiS 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: seal-like barking cough), mumps, and measles as well as RSV, 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.
Croup (acute laryngotracheobronchitis)  
Caused by parainfluenza viruses (paramyxovirus). 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. SSPE (subacute sclerosing panencephalitis, occurring years later), encephalitis (1:2000), and giant cell pneumonia (rarely, in immunosuppressed) are possible sequelae.

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 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 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 (eg, 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.

**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 → 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>FAMILY</td>
<td>RNA picornavirus</td>
<td>DNA hepadnavirus</td>
<td>RNA flavivirus</td>
<td>RNA deltavirus</td>
<td>RNA hepevirus</td>
</tr>
<tr>
<td>TRANSMISSION</td>
<td>Fecal-oral (shellfish, travelers, day care)</td>
<td>Parenteral (Blood), sexual (Babymaking), perinatal (Birthing)</td>
<td>Primarily blood (IVDU, post-transfusion)</td>
<td>Parenteral, sexual, perinatal</td>
<td>Fecal-oral, especially waterborne</td>
</tr>
<tr>
<td>INCUBATION</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>CLINICAL COURSE</td>
<td>Asymptomatic (usually), Acute</td>
<td>Initially like serum sickness (fever, arthralgias, rash); may progress to cirrhosis or carcinoma</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>PROGNOSIS</td>
<td>Good</td>
<td>Most adults have full resolution, minority have chronic infection</td>
<td>Majority develop stable, chronic hepatitis C</td>
<td>Superinfection → worse prognosis</td>
<td>High mortality in pregnant women</td>
</tr>
<tr>
<td>HCC RISK</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>LIVER BIOPSY</td>
<td>Hepatocyte swelling, monocyte infiltration, Councilman bodies</td>
<td>Granulat 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>NOTES</td>
<td>No carrier state (“Alone”)</td>
<td>Carrier state common</td>
<td>Carrier state common</td>
<td>Defective virus, depends on HBV</td>
<td>Enteric, Epidemic, no carrier state</td>
</tr>
</tbody>
</table>
**Hepatitis serologic markers**

<table>
<thead>
<tr>
<th>Test</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.</td>
</tr>
<tr>
<td><strong>HBeAg</strong></td>
<td>Secreted by infected hepatocyte into circulation. Not part of mature HBV virion. Indicates active</td>
</tr>
<tr>
<td></td>
<td>viral replication and therefore high transmissibility.</td>
</tr>
<tr>
<td><strong>Anti-HBe</strong></td>
<td>Antibody to HBeAg; indicates low transmissibility.</td>
</tr>
<tr>
<td><strong>Anti-HBc</strong></td>
<td>Antibody to HBcAg; IgM = acute/recent infection; IgG = prior exposure or chronic infection. IgM</td>
</tr>
<tr>
<td></td>
<td>anti-HBc may be the sole marker of infection during window period.</td>
</tr>
</tbody>
</table>

### Important diagnostic tests

- **HBsAg**: Early, Prodrome, acute disease
- **Anti-HBc**: Anti-HBc (anti-HBc)
- **Anti-HBs**: Anti-HBs (anti-HBc)
- **HBeAg**: Convalescence
- **Anti-HBe**: Early, Prodrome, acute disease
- **Anti-HBc**: Window period

### Relative concentration of reactants

- **HBsAg**, **DNA polymerase**, **HBcAg**
- **HBeAg**, **Anti-HBs**, **Anti-HBc**
- **ALT**↑

### Level of detection

- **Months after exposure**: 1, 2, 3, 4, 5, 6, 7, 8

### Symptomatology

- **Early**: Incubation period
- **Prodrome**: Acute disease
- **Convalescence**: Late
- **Window period**: Anti-HBc

### Disease states

<table>
<thead>
<tr>
<th>State</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></td>
</tr>
<tr>
<td>Immunized</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HIV

Envelope proteins acquired through budding from host cell plasma membrane.

- gp120
- gp41

Docking glycoprotein

Transmembrane glycoprotein

- gp120
- gp41

 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.

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.

HIV diagnosis

Presumptive diagnosis made with ELISA (sensitive, high false rate and low threshold, rule out test); results are then confirmed with Western blot assay (specific, low false rate and high threshold, rule in test).

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.

AIDS diagnosis ≤ 200 CD4+ cells/mm³ (normal: 500–1500 cells/mm³). HIV⊕ with AIDS-defining condition (eg, Pneumocystis pneumonia) or CD4+ percentage < 14%.

ELISA/Western blot tests look for antibodies to viral proteins; these tests often are falsly in the first 1–2 months of HIV infection and falsely initially in babies born to infected mothers (anti-gp120 crosses placenta).
Four stages of untreated infection:
1. Flu-like (acute)
2. Feeling fine (latent)
3. Falling count
4. Final crisis

During latent phase, virus replicates in lymph nodes.

Red line = CD4+ T cell count (cells/mm³); blue line = HIV RNA copies/mL plasma.

Blue boxes on vertical 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.
**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>PATHGEN</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><em>Candida albicans</em></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><em>Bartonella henselae</em></td>
<td>Bacillary angiomatosis</td>
<td>Biopsy with neutrophilic inflammation</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi sarcoma</td>
<td>Biopsy with lymphocytic inflammation</td>
</tr>
<tr>
<td><em>Cryptosporidium spp.</em></td>
<td>Chronic, watery diarrhea</td>
<td>Acid-fast oocysts in stool</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>HIV</td>
<td>Dementia</td>
<td></td>
</tr>
<tr>
<td><em>JC virus (reactivation)</em></td>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Nonenhancing areas of demyelination on MRI</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em></td>
<td><em>Pneumocystis pneumonia</em></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><em>Aspergillus fumigatus</em></td>
<td>Hemoptysis, pleuritic pain</td>
<td>Cavitation or infiltrates on chest imaging</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Meningitis</td>
<td>Encapsulated yeast on India ink stain or capsular antigen ⊕</td>
</tr>
<tr>
<td><em>Candida albicans</em></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>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><em>Histoplasma capsulatum</em></td>
<td>Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea</td>
<td>Oval yeast cells within macrophages</td>
</tr>
<tr>
<td><em>Mycobacterium avium–intracellulare, Mycobacterium avium complex</em></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 (PrPc) to a β-pleated form (PrPsc), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). PrPsc resists protease degradation and facilitates the conversion of still more PrPc to PrPsc. Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of PrPsc results in spongiform encephalopathy and dementia, ataxia, and death.

Creutzfeldt-Jakob disease—rapidly progressive dementia, typically sporadic (some familial forms).

Bovine spongiform encephalopathy (BSE)—also known as “mad cow disease.”

Kuru—acquired prion disease noted in tribal populations practicing human cannibalism.

Normal flora: dominant

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>MICROORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>S epidermidis</td>
</tr>
<tr>
<td>Nose</td>
<td>S epidermidis; colonized by S aureus</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Viridans group streptococci</td>
</tr>
<tr>
<td>Dental plaque</td>
<td>S mutans</td>
</tr>
<tr>
<td>Colon</td>
<td>B fragilis &gt; E coli</td>
</tr>
<tr>
<td>Vagina</td>
<td>Lactobacillus, colonized by E coli and group B strep</td>
</tr>
</tbody>
</table>

Neonates delivered by C-section have no flora but are rapidly colonized after birth.

Bugs causing food poisoning

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>B cereus</td>
<td>Reheated rice. “Food poisoning from reheated rice? Be serious!” (B cereus)</td>
</tr>
<tr>
<td>C botulinum</td>
<td>Improperly canned foods (toxins), raw honey (spores)</td>
</tr>
<tr>
<td>C perfringens</td>
<td>Reheated meat</td>
</tr>
<tr>
<td>E. coli O157:H7</td>
<td>Undercooked meat</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Poultry, meat, and eggs</td>
</tr>
<tr>
<td>S aureus</td>
<td>Meats, mayonnaise, custard, preformed toxin</td>
</tr>
<tr>
<td>V parahaemolyticus and V vulnificus*</td>
<td>Contaminated seafood</td>
</tr>
</tbody>
</table>

*V vulnificus can also cause wound infections from contact with contaminated water or shellfish.
### Bugs causing diarrhea

<table>
<thead>
<tr>
<th>Bloody diarrhea</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Campylobacter</strong></td>
<td>Comma- or S-shaped organisms; growth at 42°C</td>
</tr>
<tr>
<td><strong>E histolytica</strong></td>
<td>Protozoan; amebic dysentery; liver abscess</td>
</tr>
<tr>
<td><strong>Enterohemorrhagic E coli</strong></td>
<td>O157:H7; can cause HUS; makes Shiga-like toxin</td>
</tr>
<tr>
<td><strong>Enteroinvasive E coli</strong></td>
<td>Invades colonic mucosa</td>
</tr>
<tr>
<td><strong>Salmonella</strong></td>
<td>Lactose ; flagellar motility; has animal reservoir, especially poultry and eggs</td>
</tr>
<tr>
<td><strong>Shigella</strong></td>
<td>Lactose ; very low ID₅₀; produces Shiga toxin (human reservoir only); bacillary dysentery</td>
</tr>
<tr>
<td><strong>Y enterocolitica</strong></td>
<td>Day care outbreaks, pseudoappendicitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Watery diarrhea</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C difficile</strong></td>
<td>Pseudomembranous colitis; caused by antibiotics; occasionally bloody diarrhea</td>
</tr>
<tr>
<td><strong>C perfringens</strong></td>
<td>Also causes gas gangrene</td>
</tr>
<tr>
<td><strong>Enterotoxigenic E coli</strong></td>
<td>Travelers’ diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins</td>
</tr>
<tr>
<td><strong>Protozoon</strong></td>
<td>Giardia, Cryptosporidium</td>
</tr>
<tr>
<td><strong>V cholerae</strong></td>
<td>Comma-shaped organisms; rice-water diarrhea; often from infected seafood</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>Rotavirus, norovirus, adenovirus</td>
</tr>
</tbody>
</table>

### Common causes of pneumonia

<table>
<thead>
<tr>
<th>Neonates (&lt; 4 WK)</th>
<th>Children (4 WK–18 YR)</th>
<th>Adults (18–40 YR)</th>
<th>Adults (40–65 YR)</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group B streptococci</strong></td>
<td>Viruses (RSV)</td>
<td>Mycoplasma</td>
<td>S pneumoniae</td>
<td>S pneumoniae</td>
</tr>
<tr>
<td><strong>E coli</strong></td>
<td>Mycoplasma</td>
<td>C pneumoniae</td>
<td>H influenzae</td>
<td>Influenza virus</td>
</tr>
<tr>
<td></td>
<td><strong>C trachomatis</strong></td>
<td>S pneumoniae</td>
<td>Anaerobes</td>
<td>Anaerobes</td>
</tr>
<tr>
<td>(infants–3 yr)</td>
<td></td>
<td>Viruses (eg, influenza)</td>
<td>Viruses</td>
<td>H influenzae</td>
</tr>
<tr>
<td></td>
<td><strong>C pneumoniae</strong></td>
<td></td>
<td>Mycoplasma</td>
<td>Gram rods</td>
</tr>
<tr>
<td>(school-aged children)</td>
<td></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 My 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

<table>
<thead>
<tr>
<th>Alcoholic</th>
<th>Klebsiella, anaerobes (eg, Peptostreptococcus, Fusobacterium, Prevotella, Bacteroides)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV drug users</td>
<td><strong>S pneumoniae, S aureus</strong></td>
</tr>
<tr>
<td>Aspiration</td>
<td>Anaerobes</td>
</tr>
<tr>
<td>Atypical</td>
<td>Mycoplasma, Legionella, Chlamydia</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Pseudomonas, S aureus, S pneumoniae, Burkholderia cepacia</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td><strong>S aureus</strong>, enteric gram rods, fungi, viruses, P jirovecii (with HIV)</td>
</tr>
<tr>
<td>Nosocomial (hospital acquired)</td>
<td><strong>S aureus</strong>, Pseudomonas, other enteric gram rods</td>
</tr>
<tr>
<td>Postviral</td>
<td><strong>S pneumoniae, S aureus, H influenzae</strong></td>
</tr>
</tbody>
</table>
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>
</tbody>
</table>

Give ceftriaxone and vancomycin empirically (add ampicillin if *Listeria* is suspected).
Viral causes of meningitis: enteroviruses (especially coxsackievirus), 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 decreased with introduction of the conjugate *H. influenzae* vaccine in last 10–15 years. Today, cases are usually seen in unimmunized children.

<table>
<thead>
<tr>
<th>CSF findings in meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPENING PRESSURE</strong></td>
</tr>
<tr>
<td>Bacterial</td>
</tr>
<tr>
<td>Fungal/TB</td>
</tr>
<tr>
<td>Viral</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.

<table>
<thead>
<tr>
<th>Osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISK FACTOR</strong></td>
</tr>
<tr>
<td>Assume if no other information is available</td>
</tr>
<tr>
<td>Sexually active</td>
</tr>
<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Prosthetic joint replacement</td>
</tr>
<tr>
<td>Vertebral involvement</td>
</tr>
<tr>
<td>Cat and dog bites</td>
</tr>
<tr>
<td>IV drug abuse</td>
</tr>
</tbody>
</table>

Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate common but nonspecific. MRI is best for detecting acute infection and detailing anatomic involvement. Radiographs are insensitive early but can be useful in chronic osteomyelitis.
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. Males—infants with congenital defects, vesicoureteral reflux. Elderly—enlarged prostate. 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.

UTI bugs

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>FEATURES</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| *Escherichia coli*             | Leading cause of UTI. Colonies show green metallic sheen on EMB 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, *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; produces urease; 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>Bacterial vaginosis</th>
<th><em>Trichomonas vaginitis</em></th>
<th><em>Candida vulvovaginitis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>SIGN AND SYMPTOMS</td>
<td>No inflammation</td>
<td>Inflammation (&quot;strawberry cervix&quot;)</td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>Thin, white discharge with fishy odor</td>
<td>Frothy, yellow-green, foul-smelling discharge</td>
<td>Thick, white, &quot;cottage cheese&quot; discharge</td>
</tr>
<tr>
<td>LAB FINDINGS</td>
<td>Clue cells pH &gt; 4.5</td>
<td>Motile trichomonads pH &gt; 4.5</td>
<td>Pseudohyphae pH normal (4.0–4.5)</td>
</tr>
<tr>
<td>TREATMENT</td>
<td>Metronidazole</td>
<td>Metronidazole</td>
<td>-azoles</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><em>Toxoplasma gondii</em></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, 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>Encephalitis, herpetic (vesicular) lesions</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Sexual contact</td>
<td>Chancre (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, 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 (rubeola)</td>
<td>Beginning at head and moving down; rash is 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 (can cause hydrops fetalis in pregnant women)</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Rubella (German measles)</td>
<td>Pink coalescing macules begin at head and move down; fine desquamating truncal rash; postauricular lymphadenopathy</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Scarlet fever</td>
<td>Erythematous, sandpaper-like rash with fever and sore throat</td>
</tr>
<tr>
<td>Varicella-Zoster virus</td>
<td>Chickenpox</td>
<td>Vesicular rash begins on trunk; spreads to face and extremities with lesions of different stages</td>
</tr>
</tbody>
</table>

![Image A](image1.png)  ![Image B](image2.png)  ![Image C](image3.png)
### 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>Hepatitis B</td>
<td>Jaundice</td>
<td>HBV</td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
<td>Infection of lymphatics; painful 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, tabes 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. Cervical motion tenderness (chandelier sign), 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 **Fitz-Hugh–Curtis syndrome**—infection of the liver capsule and “violin string” adhesions of peritoneum to liver.
### Nosocomial Infections

<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,</td>
<td>Polymicrobial, gram ⊗ bacteria, often</td>
<td>Right lower lobe infiltrate or right upper/middle lobe (patient recumbent); purulent</td>
</tr>
<tr>
<td>old age)</td>
<td>anaerobes</td>
<td>malodorous sputum</td>
</tr>
<tr>
<td>Decubitus ulcers, surgical wounds, drains</td>
<td><em>S aureus</em> (including MRSA), gram ⊗ anaerobes</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></td>
<td>Erythema, induration, tenderness, drainage from access sites</td>
</tr>
<tr>
<td></td>
<td>(long term), <em>Enterobacter</em></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation, endotracheal intubation</td>
<td>Late onset: <em>P aeruginosa</em>, <em>Klebsiella</em>,</td>
<td>New infiltrate on CXR, ↑ sputum production; sweet odor (<em>Pseudomonas</em>)</td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em>, <em>S aureus</em></td>
<td></td>
</tr>
<tr>
<td>Renal dialysis unit, needlestick</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>Urinary catheterization</td>
<td><em>E coli</em>, <em>Klebsiella</em>, <em>Proteus</em> spp.</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 (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 diphtheriae</em> (elaborates toxin that causes necrosis in pharynx, cardiac, and CNS tissue)</td>
</tr>
</tbody>
</table>

### Bug hints (if all else fails)

<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 <em>SHiN</em> (<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</td>
<td><em>Borreli burgdorferi</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 (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>Coxackie A virus, <em>Treponema pallidum</em>, <em>Rickettsia rickettsi</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, gram - cocci, and spirochetes. Penicillinase sensitive.

**ADVERSE EFFECTS**

Hypersensitivity reactions, direct Coombs + hemolytic anemia.

**RESISTANCE**

Penicillinase in bacteria (a type of β-lactamase) cleaves β-lactam ring.
### Penicillinase-sensitive penicillins

**Amoxicillin, ampicillin; aminopenicillins.**

| MECHANISM | Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by β-lactamase. | AMinoPenicillins are AMPed-up penicillin. AmOxicillin has greater Oral bioavailability than ampicillin. |
| ADVERSE EFFECTS | Hypersensitivity reactions; rash; pseudomembranous colitis. | |
| MECHANISM OF RESISTANCE | Penicillinase in bacteria (a type of β-lactamase) cleaves β-lactam ring. | |

### Penicillinase-resistant penicillins

**Dicloxacillin, nafcillin, oxacillin.**

| 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; resistant because of altered penicillin-binding protein target site). “Use naf (nafcillin) for staph.” | |
| ADVERSE EFFECTS | Hypersensitivity reactions, interstitial nephritis. | |

### Antipseudomonal penicillins

**Piperacillin, ticarcillin.**

| MECHANISM | Same as penicillin. Extended spectrum. | |
| CLINICAL USE | Pseudomonas spp. and gram ⊥ rods; susceptible to penicillinase; use with β-lactamase inhibitors. | |
| ADVERSE EFFECTS | Hypersensitivity reactions. | |

### β-lactamase inhibitors

Include Clavulanic Acid, Sulbactam, Tazobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β-lactamase (penicillinase).

CAST.
### Cephalosporins (generations I–V)

| MECHANISM | Organisms typically not covered by 1st–4th generation cephalosporins are **LAME**: Listeria, Atypicals (*Chlamydia, Mycoplasma*), MRSA, and Enterococci. Exception: ceftaroline (5th generation cephalosporin) covers MRSA.
| **β-lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinas. Bactericidal.** |
| CLINICAL USE | 1st generation (cefazolin, cephalexin)—gram **⊕** cocci, *Proteus mirabilis, E. coli, Klebsiella pneumoniae*. Cefazolin used prior to surgery to prevent *S. aureus* wound infections. |
| | 2nd generation (cefaclor, cefoxitin, cefuroxime)—gram **⊕** cocci, *H inflenzae, Enterobacter aerogenes, Neisseria spp., Serratia marcescens, Proteus mirabilis, E. coli, Klebsiella pneumoniae*. |
| | 3rd generation (ceftriaxone, cefotaxime, ceftazidime)—serious gram **⊖** infections resistant to other β-lactams. |
| | 4th generation (cefpime)—gram **⊖** organisms, with **↑** activity against *Pseudomonas* and gram **⊕** organisms. |
| | 5th generation (ceftaroline)—broad gram **⊕** and gram **⊖** organism coverage, including MRSA; does not cover *Pseudomonas*. |
| ADVERSE EFFECTS | Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Exhibit cross-reactivity with penicillins. **↑** nephrotoxicity of aminoglycosides. |
| MECHANISM OF RESISTANCE | Structural change in penicillin-binding proteins (transpeptidases). |
### Carbapenems

**Mechanism**

Imipenem is a broad-spectrum, \( \beta \)-lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to prevent inactivation of drug in renal tubules.

**Clinical Use**

Gram \(^{+}\) cocci, gram \(^{-}\) rods, and anaerobes. Wide spectrum, but significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a higher risk of seizures and is stable to dehydropeptidase I.

**Adverse Effects**

GI distress, skin rash, and CNS toxicity (seizures) at high plasma levels.

### Monobactams

**Ampicillin**

Less susceptible to \( \beta \)-lactamases. Prevents peptidoglycan cross-linking by binding to penicillin-binding protein 3. Synergistic with aminoglycosides. No cross-allergenicity with penicillins.

**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 \( \beta \)-lactamases.

**Clinical Use**

Gram \(^{-}\) bugs only—serious, multidrug-resistant organisms, including MRSA, \( S \) epidermidis, sensitive \( E \)nterococcus species, and \( C \)lostridium difficile (oral dose for pseudomembranous colitis).

**Adverse Effects**

Well tolerated in general—but NOT trouble free. Nephrotoxicity, Ototoxicity, Thrombophlebitis, diffuse flushing—red man syndrome (can largely prevent by pretreatment with antihistamines and slow infusion rate).

**Mechanism of Resistance**

Occurs in bacteria via amino acid modification of D-ala D-ala to D-ala D-lac. “Pay back 2 D-ala (dollars) for vandalizing (vancomycin).”
Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

### 30S inhibitors

- **A** = Aminoglycosides [bactericidal]
- **T** = Tetracyclines [bacteriostatic]

### 50S inhibitors

- **C** = Chloramphenicol, Clindamycin [bacteriostatic]
- **E** = Erythromycin (macrolides) [bacteriostatic]
- **L** = Linezolid [variable]

“Buy AT 30, CCEL (sell) at 50.”

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**Protein synthesis inhibitors**

- Aminoglycosides (30S) also cause misreading of mRNA.
- Tetracyclines (30S) block initiation complex formation.
- Chloramphenicol (50S) specifically targets peptidyl transferase.
- Macrolides (e.g., erythromycin) and clindamycin (50S) specifically target ribosome translocation.

---

**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 blocks 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

**Mechanism:** Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA; limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk (Ca²⁺), antacids (Ca²⁺ or Mg²⁺), 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.

**Adverse Effects:** GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. Contraindicated in pregnancy.

**Mechanism of Resistance:** ↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps.

---

### Chloramphenicol

**Mechanism:** Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic.

**Clinical Use:** Meningitis (*Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae*) and Rocky Mountain spotted fever (*Rickettsia rickettsii*). Limited use owing to toxicities 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-glucuronyl transferase).

**Mechanism of Resistance:** Plasmid-encoded acetyltransferase inactivates the drug.

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### 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

**Linezolid.**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Inhibit protein synthesis by binding to 50S subunit and preventing formation of the initiation complex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Gram $\oplus$ species including MRSA and VRE.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Bone marrow suppression (especially thrombocytopenia), peripheral neuropathy, serotonin syndrome.</td>
</tr>
<tr>
<td>MECHANISM OF RESISTANCE</td>
<td>Point mutation of ribosomal RNA.</td>
</tr>
</tbody>
</table>

### Macrolides

**Azithromycin, clarithromycin, erythromycin.**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Inhibit protein synthesis by blocking translocation (“macrolides”); bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Atypical pneumonias (Mycoplasma, Chlamydia, Legionella), STIs (Chlamydia), gram $\oplus$ cocci (streptococcal infections in patients allergic to penicillin), and B pertussis.</td>
</tr>
<tr>
<td>MECHANISM OF RESISTANCE</td>
<td>Methylation of 23S rRNA-binding site prevents binding of drug.</td>
</tr>
</tbody>
</table>
**Sulfonamides**  
Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazone.

**MECHANISM**  
Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).

**CLINICAL USE**  
Gram−, gram +, Nocardia, Chlamydia. SMX for simple UTI.

**ADVERSE EFFECTS**  
Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, 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.

**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. (May alleviate with supplemental 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*, *Neisseria*, some gram + organisms).

**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.

**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 membrane of gram + cocci.

**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*). Used with a proton pump inhibitor and clarithromycin for “triple therapy” against *H pylori*. GET GAP on the Metro with metronidazole! Treats anaerobic infection below the diaphragm vs clindamycin (anaerobic infections above diaphragm).

**ADVERSE EFFECTS**
Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.
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><strong>Rifampin, Isoniazid, Pyrazinamide,</strong> 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

- **MYCOLIC ACID SYNTHESIS**
  - Isoniazid

- **ARABINOGLYCAN SYNTHESIS** (arabinosyl transferase)
  - Ethambutol

- **mRNA SYNTHESIS** (DNA-dependent RNA polymerase)
  - Rifabutin
  - Rifampin

- **INTRACELLULAR** (unclear mechanism)
  - Pyrazinamide

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 chemophrophylaxis in contacts of children with *Haemophilus 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**

- **4** 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, vitamin B₆ deficiency (peripheral neuropathy, sideroblastic anemia). Administer with pyridoxine (B₆).

**Mechanism of Resistance**

- Mutations leading to underexpression of KatG.

**INH Injures Neurons and Hepatocytes.**

### 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 <em>S. aureus</em></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>CELL COUNT</th>
<th>PROPHYLAXIS</th>
<th>INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 200 cells/mm³</td>
<td>TMP-SMX</td>
<td><em>Pneumocystis</em> pneumonia</td>
</tr>
<tr>
<td>CD4 &lt; 100 cells/mm³</td>
<td>TMP-SMX</td>
<td><em>Pneumocystis</em> pneumonia and toxoplasmosis</td>
</tr>
<tr>
<td>CD4 &lt; 50 cells/mm³</td>
<td>Azithromycin or clarithromycin</td>
<td><em>Mycobacterium avium</em> complex</td>
</tr>
</tbody>
</table>

Treatment of highly resistant bacteria

| MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline. VRE: linezolid and streptogramins (quinupristin, dalfopristin). Multidrug-resistant *P. aeruginosa*, multidrug-resistant *Acinetobacter baumannii*: polymyxins B and E (colistin). |

Antifungal therapy

[Diagram of fungal cell and antifungal drugs]
### Amphotericin B

**MECHANISM**
Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes.

**CLINICAL USE**

**ADVERSE EFFECTS**
Fever/chills ("shake and bake"), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis ("amphoterrible"). 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, 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. Flucytosine 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.

**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**
Dermatophytoses (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, ↑ cytochrome P-450 and warfarin metabolism.

### Antiprotozoan Therapy
- **Pyrimethamine** (toxoplasmosis), suramin and melarsoprol (*Trypanosoma brucei*), nifurtimox (*T cruzi*), sodium stibogluconate (leishmaniasis).

### Anti-mite/lice Therapy
- **Permethrin** (blocks Na⁺ channels → neurotoxicity), malathion (acetylcholinesterase inhibitor), lindane (blocks GABA channels → neurotoxicity). Used to treat scabies (*Sarcoptes scabiei*) and lice (*Pediculus* and *Pthirus*).
- **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 artesunate/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
- **Mebendazole** (microtubule inhibitor), pyrantel pamoate, ivermectin, diethylcarbamazine, praziquantel.
Antiviral therapy

**HIV ANTIVIRAL THHERAPY**

- **NRTIs**
  - Abacavir (ABC)
  - Didanosine (ddI)
  - Emtricitabine (FTC)
  - Lamivudine (3TC)
  - Stavudine (d4T)
  - Tenofovir (TDF)
- **NNRTIs**
  - Delavirdine
  - Efavirenz
  - Nevirapine

**OTHER ANTIVIRAL THERAPY**

- **Protease Inhibitors**
  - Atazanavir
  - Darunavir
  - Fosamprenavir
  - Indinavir
  - Lopinavir
  - Ritonavir
  - Saquinavir

**INTEGRASE**

- Dolutegravir
- Elvitegravir

**GUANOSINE SYNTHESIS**

- Acyclovir, famciclovir, valacyclovir
- Guanosine analogs
- Ganciclovir (CMV)
  - Viral DNA polymerase inhibitors
  - Cidofovir
  - Foscarnet

**NUCLEIC ACID SYNTHESIS**

- Ribavirin (RSV, HCV)
- Guanine nucleotide synthesis inhibitors
  - Foscarnet

**PROTEIN SYNTHESIS**

- Interferon-α (HBV, HCV)

**RELEASE OF PROGENY VIRUS**

- Neuraminidase inhibitors
  - Oseltamivir
  - Zanamivir

**FUSION**

- Enfuvirtide

**ATTACHMENT**

- Maraviroc

**UNCOATING**

- Amantadine
- Rimantadine (no longer used for influenza due to resistance)

**REVERSE TRANSSCRIPTASE**

- NRTIs
  - Abacavir (ABC)
  - Didanosine (ddI)
  - Emtricitabine (FTC)
  - Lamivudine (3TC)
  - Stavudine (d4T)
  - Tenofovir (TDF)
  - Zidovudine (3TC, formerly AZT)

- NNRTIs
  - Delavirdine
  - Efavirenz
  - Nevirapine

**PENETRATION**

- Reverse transcription

**INTEGRASE**

- Dolutegravir
- Elvitegravir

**ENVELOPE**

- Enfuvirtide

**RECEPTOR BINDING**

- Maraviroc

**BIND**

- Release

**UNCOATING**

- Uncoating

**ENDOCYTOSIS**

- Endocytosis

**DNA INTEGRATION**

- Integration

**TRANSCRIPTION**

- Transcription

**TRANSLATION**

- Translation

**PROTEOLYTIC PROCESSING**

- Proteolytic processing

**DNA INTEGRATION**

- Integration

**VIRION ASSEMBLY**

- Virion assembly

**PACKAGING AND ASSEMBLY**

- Packaging and assembly

**BUDDING**

- Budding

**RELEASE**

- Release

**OSELTAMIVIR, ZANAMIVIR**

**MECHANISM**

Inhibit influenza neuraminidase → release of progeny virus.

**CLINICAL USE**

Treatment and prevention of both influenza A and B.

**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 reduce 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 and 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). Abacavir contraindicated if patient has HLA-B*5701 mutation.</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (ZDV, formerly AZT)</td>
<td>Have you dined (vudine) with my nuclear (nucleosides) family?</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 (indinavir). Rifampin (a potent CYP/UGT inducer) contraindicated with protease inhibitors because it can decrease protease inhibitor concentration.</td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td></td>
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<tr>
<td>Darunavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navir (never)</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>t creatine kinase.</td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fusion inhibitors</strong></td>
<td>Binds gp41, inhibiting viral entry.</td>
<td>Skin reaction at injection sites.</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maravirocin</td>
<td>Binds CCR-5 on surface of T cells/macrophages, inhibiting interaction with gp120.</td>
<td></td>
</tr>
</tbody>
</table>
Interferons

**MECHANISM**
Glycoproteins normally synthesized by virus-infected cells, exhibiting a wide range of antiviral and antitumoral properties.

**CLINICAL USE**
- IFN-β: multiple sclerosis.
- IFN-γ: chronic granulomatous disease.

**ADVERSE EFFECTS**
Flu-like symptoms, depression, neutropenia, myopathy.

---

**Hepatitis C therapy**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>Inhibits synthesis of guanine nucleotides by competitively inhibiting inosine monophosphate dehydrogenase.</td>
<td>Chronic HCV; also used in RSV (palivizumab preferred in children) Adverse effects: hemolytic anemia; severe teratogen.</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Inhibits HCV RNA-dependent RNA polymerase acting as a chain terminator.</td>
<td>Chronic HCV in combination with ribavirin, +/- peginterferon alfa. Adverse effects: fatigue, headache, nausea.</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>HCV protease inhibitor; prevents viral replication.</td>
<td>Chronic HCV in combination with ledipasvir (NS5A inhibitor). Do not use as monotherapy. Adverse effects: photosensitivity reactions, rash.</td>
</tr>
</tbody>
</table>

---

**Infection control techniques**
Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of self-propagating biological entities (sterilization).

- **Autoclave**: Pressurized steam at > 120°C. May be sporicidal.
- **Alcohols**: Denature proteins and disrupt cell membranes. Not sporicidal.
- **Chlorhexidine**: Denatures proteins and disrupts cell membranes. Not sporicidal.
- **Hydrogen peroxide**: Free radical oxidation. Sporicidal.
- **Iodine and iodophors**: Halogenation of DNA, RNA, and proteins. May be sporicidal.

---

**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>Otoxicity</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Cartilage damage</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Embryotoxic</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.**
Mastery of the basic principles and facts in the immunology section will be useful for the Step 1 exam. Cell surface markers are important to know because they are clinically useful (eg, in identifying specific types of immunodeficiency or cancer) and are functionally critical to the jobs immune cells carry out. By spending a little extra effort here, it is possible to turn a traditionally difficult subject into one that is high yield.
# IMMUNOLOGY—LYMPHOID STRUCTURES

## 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).

### Lymph drainage

<table>
<thead>
<tr>
<th>LYMPH NODE CLUSTER</th>
<th>AREA OF BODY Drained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Head and neck</td>
</tr>
<tr>
<td>Hilar</td>
<td>Lungs</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>Trachea and esophagus</td>
</tr>
<tr>
<td>Axillary</td>
<td>Upper limb, breast, skin above umbilicus</td>
</tr>
<tr>
<td>Celiac</td>
<td>Liver, stomach, spleen, pancreas, upper duodenum</td>
</tr>
<tr>
<td>Superior mesenteric</td>
<td>Lower duodenum, jejunum, ileum, colon to splenic flexure</td>
</tr>
<tr>
<td>Inferior mesenteric</td>
<td>Colon from splenic flexure to upper rectum</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate</td>
</tr>
<tr>
<td>Para-aortic</td>
<td>Testes, ovaries, kidneys, uterus</td>
</tr>
<tr>
<td>Superficial inguinal</td>
<td>Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva</td>
</tr>
<tr>
<td>Popliteal</td>
<td>Dorsolateral foot, posterior calf</td>
</tr>
</tbody>
</table>

Right lymphatic duct drains right side of body above diaphragm. Thoracic duct drains everything else into junction of left subclavian and internal jugular veins.
**Sinusoids of spleen**

Long, vascular channels in red pulp (red arrow in A) with fenestrated “barrel hoop” basement membrane.
- T cells are found in the periarteriolar lymphatic sheath (PALS) within the white pulp (white arrow 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. Macrophages found nearby in spleen remove encapsulated bacteria.

**Splenic dysfunction (eg, postsplenectomy, sickle cell disease):**
- IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms (Please SHINE my SKiS):
  - *Pseudomonas aeruginosa*
  - *Streptococcus pneumoniae*
  - *Haemophilus Influenzae* type b
  - *Neisseria meningitidis*
  - *Escherichia coli*
  - *Salmonella* spp.
  - *Klebsiella pneumoniae*
  - Group B *Streptococci*

**Post-splenectomy:**
- Howell-Jolly bodies (nuclear remnants)
- Target cells
- Thrombocytosis (loss of sequestration and removal)
- Lymphocytosis (loss of sequestration)

**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.

T cells = Thymus
B cells = Bone marrow
Hypoplastic in DiGeorge syndrome and severe combined immunodeficiency (SCID).
Enlarged in myasthenia gravis.
### 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</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&lt;br&gt;Occurs rapidly (minutes to hours)</td>
<td>Highly specific, refined over time&lt;br&gt;Develops over long periods; memory response is faster and more robust</td>
</tr>
<tr>
<td><strong>Physical Barriers</strong></td>
<td>Epithelial tight junctions, mucus</td>
<td>—</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). Examples of PAMPs include LPS (gram $\oplus$ bacteria), flagellin (bacteria), nucleic acids (viruses).</td>
<td>Memory cells: activated B and T cells;&lt;br&gt;subsequent exposure to a previously encountered antigen $\rightarrow$ stronger, quicker immune response</td>
</tr>
</tbody>
</table>

### MHC I and II

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

<table>
<thead>
<tr>
<th>MHC I (1 letter)</th>
<th>MHC II (2 letters)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOC</strong></td>
<td>HLA-A, HLA-B, HLA-C</td>
</tr>
<tr>
<td><strong>Binding</strong></td>
<td>TCR and CD8</td>
</tr>
<tr>
<td><strong>Expression</strong></td>
<td>Expressed on all nucleated cells&lt;br&gt;Not expressed on RBCs</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Present endogenously synthesized antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells</td>
</tr>
<tr>
<td><strong>Antigen Loading</strong></td>
<td>Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing)</td>
</tr>
<tr>
<td><strong>Associated Proteins</strong></td>
<td>$\beta_2$-microglobulin</td>
</tr>
</tbody>
</table>

![Diagram of MHC I and II](image-url)
**HLA subtypes associated with diseases**

<table>
<thead>
<tr>
<th>HLA Subtype</th>
<th>Associated Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A3</strong></td>
<td>Hemochromatosis.</td>
</tr>
<tr>
<td><strong>B8</strong></td>
<td>Addison disease, myasthenia gravis.</td>
</tr>
<tr>
<td><strong>B27</strong></td>
<td>Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis (formerly Reiter syndrome). <strong>PAIR</strong>. Also known as seronegative arthropathies.</td>
</tr>
<tr>
<td><strong>DQ2/DQ8</strong></td>
<td>Celiac disease. I ate (8) too (2) much gluten at Dairy Queen.</td>
</tr>
<tr>
<td><strong>DR2</strong></td>
<td>Multiple sclerosis, hay fever, SLE, Goodpasture syndrome.</td>
</tr>
<tr>
<td><strong>DR3</strong></td>
<td>Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease.</td>
</tr>
<tr>
<td><strong>DR4</strong></td>
<td>Rheumatoid arthritis, diabetes mellitus type 1, Addison disease. There are 4 walls in a &quot;rheum&quot; (room).</td>
</tr>
<tr>
<td><strong>DR5</strong></td>
<td>Pernicious anemia → vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency, Hashimoto thyroiditis.</td>
</tr>
</tbody>
</table>

**Natural killer cells**

Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells. Lymphocyte member of innate immune system. 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 class I MHC 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-cell functions**

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-cell functions**

CD4<sup>+</sup> T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes. CD8<sup>+</sup> 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

**Bone marrow**

**Thymus**

**Lymph node**

<table>
<thead>
<tr>
<th>T-cell precursor</th>
<th>CD4+CD8+ T cell</th>
<th>CD4+ T cell</th>
<th>CD8+ T cell</th>
</tr>
</thead>
</table>

**Cytotoxic T cell**
- Kills virus-infected, neoplastic, and donor graft cells
- CD8+ T cell

**Helper T cell**
- CD4+ T cell

**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.
- Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (AIRE); deficiency leads to autoimmune polyendocrine syndrome I.

**Helper T cells**

<table>
<thead>
<tr>
<th><strong>Th1 cell</strong></th>
<th><strong>Th2 cell</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretes IFN-γ</td>
<td>Secretes IL-4, IL-5, IL-10, IL-13</td>
</tr>
<tr>
<td>Activates macrophages and cytotoxic T cells</td>
<td>Recruits eosinophils for parasite defense and promotes IgE production by B cells</td>
</tr>
<tr>
<td>Differentiation induced by IFN-γ and IL-12</td>
<td>Differentiation induced by IL-4</td>
</tr>
<tr>
<td>Inhibited by IL-4 and IL-10 (from Th2 cell)</td>
<td>Inhibited by IFN-γ (from Th1 cell)</td>
</tr>
</tbody>
</table>

**Macrophage-lymphocyte interaction—**
- Macrophages and other APCs release IL-12, which stimulates T cells to differentiate into Th1 cells.
- Th1 cells release IFN-γ to stimulate macrophages.
- Helper T cells have CD4, which binds to MHC II on APCs.

**Cytotoxic T cells**
- Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis.
- Release cytotoxic granules containing preformed proteins (e.g., 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 produce anti-inflammatory cytokines (e.g., IL-10, TGF-β).
T- and B-cell activation

APCs: B cells, macrophages, dendritic cells.
Two signals are required for T-cell activation, B-cell activation, and class switching.

Naive T-cell activation

1. Dendritic cell (specialized APC) samples and processes antigen.
2. Dendritic cell migrates to the draining lymph node.
3. T-cell activation (signal 1): antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous antigen is presented on MHC I to Tc (CD8+) cell.
4. Proliferation and survival (signal 2): costimulatory signal via interaction of B7 proteins (CD80/86) and CD28.
5. 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 idiotype: 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; mediated by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.

IgG

Main antibody in 2° (delayed) response to an antigen. Most abundant isotype in serum. Fixes complement, crosses the placenta (provides infants with passive immunity), opsonizes bacteria, neutralizes bacterial toxins and viruses.

IgA

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, Giardia). 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.

IgM

Produced in the 1° (immediate) response to an antigen. Fixes complement but does not 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.

IgD

Unclear function. Found on surface of many B cells and in serum.

IgE

Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Mediates immunity to worms by activating eosinophils. Lowest concentration in serum.

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 (CD40–CD40L interaction).
### Acute-phase reactants
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.

<table>
<thead>
<tr>
<th><strong>Acute-phase reactants</strong></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C-reactive protein</strong></td>
<td>Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a sign of ongoing inflammation.</td>
</tr>
<tr>
<td><strong>Ferritin</strong></td>
<td>Binds and sequesters iron to inhibit microbial iron scavenging.</td>
</tr>
<tr>
<td><strong>Fibrinogen</strong></td>
<td>Coagulation factor; promotes endothelial repair; correlates with ESR.</td>
</tr>
<tr>
<td><strong>Hepcidin</strong></td>
<td>↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.</td>
</tr>
<tr>
<td><strong>Serum amyloid A</strong></td>
<td>Prolonged elevation can lead to amyloidosis.</td>
</tr>
</tbody>
</table>

**POSITIVE (UPREGULATED)**

<table>
<thead>
<tr>
<th><strong>Factor</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

**NEGATIVE (DOWNREGULATED)**

<table>
<thead>
<tr>
<th><strong>Factor</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Reduction conserves amino acids for positive reactants.</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Internalized by macrophages to sequester iron.</td>
</tr>
</tbody>
</table>
**Complement**

System of hepatically synthesized plasma proteins that play a role in innate immunity and inflammation. Membrane attack complex (MAC) defends against gram $\oplus$ bacteria.

### Activation

- **Classic pathway**—IgG or IgM mediated.
- **Alternative pathway**—microbe surface molecules.
- **Lectin pathway**—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 $1^\circ$ 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 pathway diagram](image)

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

### Complement disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</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. ACE inhibitors are contraindicated.</td>
</tr>
<tr>
<td><strong>C3 deficiency</strong></td>
<td>Increases risk of severe, recurrent pyogenic sinus and respiratory tract infections; $\uparrow$ susceptibility to type III hypersensitivity reactions.</td>
</tr>
<tr>
<td><strong>C5–C9 deficiencies</strong></td>
<td>Terminal complement deficiency increases susceptibility to recurrent <em>Neisseria</em> bacteremia.</td>
</tr>
<tr>
<td><strong>DAF (GPI-anchored enzyme) deficiency</strong></td>
<td>Causes complement-mediated lysis of RBCs and paroxysmal nocturnal hemoglobinuria.</td>
</tr>
</tbody>
</table>
## Important Cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Secreted By</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-1</strong></td>
<td>Macrophages</td>
<td>Also called osteoclast-activating factor. Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“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.</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td></td>
<td>Causes fever and stimulates production of acute-phase proteins.</td>
</tr>
<tr>
<td><strong>IL-8</strong></td>
<td></td>
<td>Major chemotactic factor for neutrophils. “Clean up on aisle 8.” Neutrophils are recruited by IL-8 to clear infections.</td>
</tr>
<tr>
<td><strong>IL-12</strong></td>
<td></td>
<td>Induces differentiation of T cells into Th1 cells. Activates NK cells.</td>
</tr>
<tr>
<td><strong>TNF-α</strong></td>
<td></td>
<td>Mediates septic shock. Activates endothelium. Causes WBC recruitment, vascular leak. Causes cachexia in malignancy.</td>
</tr>
<tr>
<td><strong>IL-2</strong></td>
<td>T Cells</td>
<td>Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.</td>
</tr>
<tr>
<td><strong>IL-3</strong></td>
<td>T Cells</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>T Cells</td>
<td>Secreted by NK cells and T cells in response to 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>IL-4</strong></td>
<td>Th2 Cells</td>
<td>Induces differentiation of T cells into Th2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG.</td>
</tr>
<tr>
<td><strong>IL-5</strong></td>
<td>Th2 Cells</td>
<td>Promotes growth and differentiation of B cells. Enhances class switching to IgA. Stimulates growth and differentiation of eosinophils.</td>
</tr>
<tr>
<td><strong>IL-10</strong></td>
<td>Th2 Cells</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. TGF-β and IL-10 both attenuate the immune response.</td>
</tr>
</tbody>
</table>
Respiratory burst (oxidative burst)

Involves the activation of the phagocyte NADPH oxidase complex (e.g., in neutrophils, monocytes), which utilizes O₂ 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 is a blue-green heme-containing pigment that gives sputum its color.

Phagocytes of patients with CGD can utilize H₂O₂ generated by invading organisms and convert it to ROS. Patients are at risk for infection by catalase species (e.g., S aureus, Aspergillus) capable of neutralizing their own H₂O₂, leaving phagocytes without ROS for fighting infections. Pyocyanin of P aeruginosa functions to generate ROS to kill competing microbes. 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 locally on uninfected cells, “priming them” for viral defense by helping to selectively degrade viral nucleic acid and protein.

Interfer with viruses.
<table>
<thead>
<tr>
<th><strong>Cell surface proteins</strong></th>
<th>MHC I present on all nucleated cells (ie, not mature RBCs).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T cells</strong></td>
<td>TCR (binds antigen-MHC complex)</td>
</tr>
<tr>
<td></td>
<td>CD3 (associated with TCR for signal transduction)</td>
</tr>
<tr>
<td></td>
<td>CD28 (binds B7 on APC)</td>
</tr>
<tr>
<td></td>
<td>CXCR4/CCR5 (co-receptors for HIV)</td>
</tr>
<tr>
<td><strong>Helper T cells</strong></td>
<td>CD4, CD40L</td>
</tr>
<tr>
<td><strong>Cytotoxic T cells</strong></td>
<td>CD8</td>
</tr>
<tr>
<td></td>
<td>CXCR4/CCR5</td>
</tr>
<tr>
<td><strong>Regulatory T cells</strong></td>
<td>CD4, CD25</td>
</tr>
<tr>
<td><strong>B cells</strong></td>
<td>Ig (binds antigen)</td>
</tr>
<tr>
<td></td>
<td>CD19, CD20, CD21 (receptor for EBV), CD40 MHC II, B7</td>
</tr>
<tr>
<td><strong>Macrophages</strong></td>
<td>CD14 (receptor for PAMPs, eg, LPS), CD40 CCR5 MHC II, B7</td>
</tr>
<tr>
<td></td>
<td>Fe and C3b receptors (enhanced phagocytosis)</td>
</tr>
<tr>
<td><strong>NK cells</strong></td>
<td>CD16 (binds Fe of IgG), CD56 (unique marker for NK)</td>
</tr>
<tr>
<td><strong>Hematopoietic stem cells</strong></td>
<td>CD34</td>
</tr>
</tbody>
</table>

**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.

**Effects of bacterial toxins**

Superantigens (S pyogenes and S aureus)—cross-link the β region of the T-cell receptor to the MHC class II on APCs. Can activate any CD4+ T cell → massive release of cytokines.

Endotoxins/lipopolysaccharide (gram ⊝ bacteria)—directly stimulate macrophages by binding to endotoxin receptor TLR4/CD14; Th cells are not involved.

**Antigenic variation**

Classic examples:
- Bacteria—Salmonella (2 flagellar variants), Borrelia recurrentis (relapsing fever), N gonorrhoeae (pilus protein)
- Viruses—influenza, HIV, HCV
- Parasites—trypanosomes

Some mechanisms for variation include DNA rearrangement and RNA segment reassortment (eg, influenza major shift).
### 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, or Rabies virus, unvaccinated patients are given preformed antibodies (passive)—“To Be Healed Very Rapidly.” Combined passive and active immunizations can be given for hepatitis B or rabies exposure.

### Vaccination

Induces an active immune response (humoral and/or cellular) to specific pathogens.

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Description</th>
<th>Pros/Cons</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live attenuated vaccine</strong></td>
<td>Microorganism loses its pathogenicity but retains capacity for transient growth within inoculated host. Induces cellular and humoral responses. MMR is the only live attenuated vaccine given to persons with HIV.</td>
<td>Pro: induces strong, often lifelong immunity. Con: may revert to virulent form. Often contraindicated in pregnancy and immunodeficiency.</td>
<td>BCG, influenza (intranasal), measles, mumps, polio (Sabin), rubella, varicella, yellow fever.</td>
</tr>
<tr>
<td><strong>Inactivated or killed vaccine</strong></td>
<td>Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a humoral response.</td>
<td>Pro: safer than live vaccines. Con: weaker immune response; booster shots usually required.</td>
<td>Rabies, Influenza (injection), Polio (Salk), hepatitis A (“R.I.P. Always”).</td>
</tr>
</tbody>
</table>
Hypersensitivity types

Four types: Anaphylactic and Atopic (type I), Cytotoxic (antibody mediated, type II), Immune complex (type III), Delayed (cell mediated, type IV) (ACID).

Type I

- Anaphylactic and atopic—free antigen cross-links IgE on presensitized mast cells and basophils, triggering immediate release of vasoactive amines that act at postcapillary venules (ie, histamine). Reaction develops rapidly after antigen exposure because of preformed antibody. Delayed response follows due to production of arachidonic acid metabolites (eg, leukotrienes).
- First (type) and Fast (anaphylaxis). Types I, II, and III are all antibody mediated.
- Test: skin test for specific IgE.
- Examples:
  - Allergic and atopic disorders (eg, rhinitis, hay fever, eczema, hives, asthma)
  - Anaphylaxis (eg, bee sting, some food/drug allergies)

Type II

- Cytotoxic (antibody mediated)—IgM, IgG bind to fixed antigen on “enemy” cell → cellular destruction. Antibody and complement lead to MAC.
- 3 mechanisms:
  - Opsonization and phagocytosis
  - Complement- and Fc receptor–mediated inflammation
  - Antibody-mediated cellular dysfunction
- Disease tends to be specific to tissue or site where antigen is found.
- Type II is cy-2-toxic.
- Direct and indirect Coombs’ tests:
  - Direct—detects antibodies that have adhered to patient’s RBCs (eg, test an Rh ⊕ infant of an Rh ⊖ mother).
  - Indirect—detects serum antibodies that can adhere to other RBCs (eg, test an Rh ⊖ woman for Rh ⊕ antibodies).
- Examples:
  - Acute hemolytic transfusion reactions
  - Autoimmune hemolytic anemia
  - Bullous pemphigoid
  - Erythroblastosis fetalis
  - Goodpasture syndrome
  - Graves disease
  - Guillain-Barré syndrome
  - Idiopathic thrombocytopenic purpura
  - Myasthenia gravis
  - Pemphigus vulgaris
  - Pericarditis
  - Rheumatic fever
Hypersensitivity types (continued)

Type III

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

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

Examples:
- Arthus reaction
- SLE
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis
- Serum sickness

Serum sickness—an immune complex disease in which antibodies to foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

Most serum sickness is now caused by drugs (not serum) acting as haptens. Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 5–10 days after antigen exposure.

Arthus reaction—a local subacute antibody-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.

Antigen-antibody complexes cause the Arthus reaction.
Test: immunofluorescent staining.

Type IV

Delayed (T-cell–mediated) type—sensitized T cells encounter antigen and then release cytokines (leads to macrophage activation).
Response does not involve antibodies (vs types I, II, and III).

4th and last—delayed. Cell mediated; therefore, it is not transferable by serum.
4 T’s = T cells, Transplant rejections, TB skin tests, Touching (contact dermatitis).
Test: patch test, PPD.
Examples:
- Contact dermatitis (eg, poison ivy, nickel allergy)
- Graft-versus-host disease
- Multiple sclerosis
<table>
<thead>
<tr>
<th>Blood transfusion reactions</th>
<th>Pathogenesis</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic reaction</strong></td>
<td>Type I hypersensitivity reaction against plasma proteins in transfused blood.</td>
<td>Urticaria, pruritus, wheezing, fever. Treat with antihistamines.</td>
</tr>
<tr>
<td><strong>Anaphylactic reaction</strong></td>
<td>Severe allergic reaction. IgA-deficient individuals must receive blood products without IgA.</td>
<td>Dyspnea, bronchospasm, hypotension, respiratory arrest, shock. Treat with epinephrine.</td>
</tr>
<tr>
<td><strong>Febrile nonhemolytic transfusion reaction</strong></td>
<td>Type II hypersensitivity reaction. Host antibodies against donor HLA antigens and WBCs.</td>
<td>Fever, headaches, chills, flushing.</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>
</tr>
</tbody>
</table>
## Autoantibodies

<table>
<thead>
<tr>
<th>AUTOANTIBODY</th>
<th>ASSOCIATED DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ACh receptor</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Anti-basement membrane</td>
<td>Goodpasture syndrome</td>
</tr>
<tr>
<td>Anticardiolipin, lupus anticoagulant</td>
<td>SLE, antiphospholipid syndrome</td>
</tr>
<tr>
<td>Anticentromere</td>
<td>Limited scleroderma (CREST syndrome)</td>
</tr>
<tr>
<td>Anti-desmoglein (anti-desmosome)</td>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td>Anti-dsDNA, anti-Smith</td>
<td>SLE</td>
</tr>
<tr>
<td>Anti-glutamic acid decarboxylase (GAD-65)</td>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>Anti-hemidesmosome</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>Anti-histone</td>
<td>Drug-induced lupus</td>
</tr>
<tr>
<td>Anti-Jo-1, anti-SRP, anti-Mi-2</td>
<td>Polymyositis, dermatomyositis</td>
</tr>
<tr>
<td>Antimicrosomal, antithyroglobulin</td>
<td>Hashimoto thyroiditis</td>
</tr>
<tr>
<td>Antimitochondrial</td>
<td>1° biliary cirrhosis</td>
</tr>
<tr>
<td>Antinuclear (ANA)</td>
<td>SLE, nonspecific</td>
</tr>
<tr>
<td>Antiparietal cell</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Antiphospholipase A₂ receptor</td>
<td>1° membranous nephropathy</td>
</tr>
<tr>
<td>Anti-Scl-70 (anti-DNA topoisomerase I)</td>
<td>Scleroderma (diffuse)</td>
</tr>
<tr>
<td>Anti-smooth muscle</td>
<td>Autoimmune hepatitis type 1</td>
</tr>
<tr>
<td>Anti-SSA, anti-SSB (anti-Ro, anti-La)</td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Anti-TSH receptor</td>
<td>Graves disease</td>
</tr>
<tr>
<td>Anti-U1 RNP (ribonucleoprotein)</td>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td>Voltage-gated calcium channel antibodies</td>
<td>Lambert-Eaton syndrome</td>
</tr>
<tr>
<td>IgA anti-endomysial, IgA anti-tissue transglutaminase</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>MPO-ANCA/p-ANCA</td>
<td>Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)</td>
</tr>
<tr>
<td>PR3-ANCA/c-ANCA</td>
<td>Granulomatosis with polyangiitis (Wegener)</td>
</tr>
<tr>
<td>Rheumatoid factor (IgM antibody that targets IgG Fc region), anti-CCP (more specific)</td>
<td>Rheumatoid arthritis</td>
</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.</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.</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Defect in B-cell differentiation. Many causes.</td>
<td>Can be acquired in 20s–30s; † 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⁺. Absent thymic shadow on CXR. 22q11 deletion detected by FISH.</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 (Job syndrome)</td>
<td>Deficiency of Th17 cells due to STAT3 mutation → impaired recruitment of neutrophils to sites of infection.</td>
<td>FATED: coarse Facies, cold (noninflamed) staphylococcal Abscesses, retained primary Tceth, † IgE, Dermatologic problems (eczema).</td>
<td>† IgE, † IFN-γ.</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), adenosine deaminase deficiency (autosomal recessive).</td>
<td>Failure to thrive, chronic diarrhea, thrush. Recurrent viral, bacterial, fungal, and protozoal infections. Treatment: bone marrow transplant (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 repair DNA double strand breaks → cell cycle arrest.</td>
<td>Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia), IgA deficiency.</td>
<td>↑ AFP. IgA, IgG, and IgE. Lymphopenia, cerebellar atrophy.</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 <em>Pneumocystis</em>, <em>Cryptosporidium</em>, CMV.</td>
<td>Normal or ↑ IgM. ↑ IgG, IgA, IgE.</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Mutation in WAS gene; T cells unable to reorganize actin cytoskeleton. X-linked recessive.</td>
<td>WATER: Wiskott-Aldrich: Thrombocytopenia, Eczema, Recurrent infections. ↑ risk of autoimmune disease and malignancy.</td>
<td>↑ to normal IgG, IgM. ↑ IgE, IgA. Fewer and smaller platelets.</td>
</tr>
<tr>
<td><strong>Phagocyte dysfunction</strong></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 bacterial skin and mucosal infections, absent pus formation, impaired wound healing, delayed separation of umbilical cord (&gt; 30 days).</td>
<td>↑ neutrophils. 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 recessive most common.</td>
<td>↑ susceptibility to <em>Catalase</em> ⊕ organisms (<em>Cats Need PLACESS to Belch their Hairballs</em>: <em>Nocardia</em>, <em>Pseudomonas</em>, <em>Listeria</em>, <em>Aspergillus</em>, <em>Candida</em>, <em>E. coli</em>, <em>Staphylococci</em>, <em>Serratia</em>, <em>B cepacia</em>, <em>H pylori</em>)</td>
<td>Abnormal dihydrorhodamine (flow cytometry) test (↑ green fluorescence). Nitroblue tetrazolium dye reduction test obsolete.</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: Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus Influenzae type B, Neisseria meningitidis, Escherichia coli, Salmonella, Klebsiella pneumoniae, group B Strep (Please SHINE my SKIS)</td>
<td>Staphylococcus, Burkholderia cepacia, Pseudomonas aeruginosa, Serratia, Nocardia</td>
<td>Encapsulated species with early component deficiencies Neisseria with late component (MAC) deficiencies</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>CMV, EBV, JCV, 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 GI giardiasis (no IgA)</td>
<td>Candida (systemic), Aspergillus</td>
<td>N/A</td>
<td></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

<p>| <strong>Autograft</strong> | From self. |
| <strong>Syngeneic graft (isograft)</strong> | From identical twin or clone. |
| <strong>Allograft</strong> | From nonidentical individual of same species. |
| <strong>Xenograft</strong> | From different species. |</p>
<table>
<thead>
<tr>
<th>Transplant 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 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. 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>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>Transplant rejection prophylaxis, 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>Transplant rejection prophylaxis.</td>
<td>Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism.</td>
<td></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.</td>
<td>“PanSirtopenia” (pancytopenia), insulin resistance, hyperlipidemia; not nephrotoxic.</td>
<td>Kidney “sir-ives.” Synergistic with cyclosporine. Also used in drug-eluting stents.</td>
</tr>
<tr>
<td>Daclizumab, basiliximab</td>
<td>Monoclonal antibodies; block IL-2R.</td>
<td>Kidney transplant rejection prophylaxis.</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>Transplant rejection prophylaxis, rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions.</td>
<td>Leukopenia, anemia, thrombocytopenia.</td>
<td>6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol. Pronounce “azathio-purine.”</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Inhibit NF-κB. Suppress both B- and T-cell function by ↓ transcription of many cytokines. Induce apoptosis of T lymphocytes.</td>
<td>Transplant rejection prophylaxis, many autoimmune and inflammatory disorders.</td>
<td>Hyperglycemia, osteoporosis, central obesity, muscle breakdown, psychosis, acne, hypertension, cataracts, avascular necrosis (femoral head).</td>
<td>Can cause iatrogenic Cushing syndrome.</td>
</tr>
</tbody>
</table>
Immunosuppression targets

DNA replication
Calcineurin
Proliferation genes
Inflammatory cytokine genes
NFκB
6–MP
Purine nucleotides
De novo purine synthesis
mTOR
NFAT–P
PRPP
amidotransferase
IMP dehydrogenase

Calcineurin + Tacrolimus
FKBP + SRL (rapamycin)
Mycophenolate
FKBP + Azathioprine
Basiliximab, daclizumab
Cyclophilin + Cyclosporine
Calcineurin
FKBP + Tacrolimus
IL-2R
Calcineurin
FFKBP + Tacrolimus

Corticosteroids

Recombinant cytokines and clinical uses

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLINICAL USES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldesleukin (IL-2)</td>
<td>Renal cell carcinoma, metastatic melanoma</td>
</tr>
<tr>
<td>Epoetin alfa (erythropoietin)</td>
<td>Anemias (especially in renal failure)</td>
</tr>
<tr>
<td>Filgrastim (G-CSF)</td>
<td>Recovery of bone marrow</td>
</tr>
<tr>
<td>Sargramostim (GM-CSF)</td>
<td>Recovery of bone marrow</td>
</tr>
<tr>
<td>IFN-α</td>
<td>Chronic hepatitis B and C, Kaposi sarcoma, malignant melanoma</td>
</tr>
<tr>
<td>IFN-β</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Romiplostim, eltrombopag (thrombopoietin receptor agonists)</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Oprelvekin (IL-11)</td>
<td>Thrombocytopenia</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</td>
<td></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</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2/neu</td>
<td>Breast 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, 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>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><strong>Other Applications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td>Platelet glycoproteins IIb/IIIa</td>
<td>Antiplatelet 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>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>
<tr>
<td>Ranibizumab, bevacizumab</td>
<td>VEGF</td>
<td>Neovascular age-related macular degeneration</td>
<td></td>
</tr>
</tbody>
</table>
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.
Apoptosis

ATP-dependent programmed cell death. Intrinsic or extrinsic pathway; both pathways → activation of cytosolic proteases called caspases that mediate cellular breakdown → 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 endonucleases cleaving at internucleosomal regions). DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

Cell membrane typically remains intact without significant inflammation (unlike necrosis).

**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 such as BAX and BAK (proapoptotic) and Bcl-2 (antiapoptotic).

Bcl-2 prevents cytochrome c release by binding to and inhibiting APAF-1. APAF-1 normally binds cytochrome c and induces activation of caspase 9, initiating caspase cascade. If Bcl-2 is overexpressed (eg, follicular lymphoma t[14;18]), then APAF-1 is overly inhibited, → caspase activation and tumorigenesis.

**Extrinsic (death receptor) pathway**

2 pathways:
- Ligand receptor interactions (FasL binding to Fas [CD95] or TNF-α binding to TNF)
- 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; proteins denature, then enzymatic degradation</td>
<td>Cell outlines preserved; ↑ cytoplasmic binding of acidophilic dyes</td>
</tr>
<tr>
<td>Liquefactive</td>
<td>Bacterial abscesses, brain infarcts (due to ↑ fat content)</td>
<td>Neutrophils release lysosomal enzymes that digest the tissue; enzymatic degradation first, then proteins denature</td>
<td>Early: cellular debris and macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caseous</td>
<td>TB, systemic fungi (eg, <em>Histoplasma capsulatum</em>, <em>Nocardia</em>)</td>
<td>Macrophages wall off the infecting microorganism</td>
<td>Fragmented cells and debris surrounded by lymphocytes and macrophages</td>
</tr>
<tr>
<td>Fat</td>
<td>Enzymatic: acute pancreatitis (saponification of peripancreatic fat)</td>
<td>Damaged cells release lipase, which breaks down triglycerides in fat cells</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, giant cell [temporal] arteritis)</td>
<td>Immune complexes combine with fibrin → vessel wall damage</td>
<td>Vessel walls are thick and pink</td>
</tr>
<tr>
<td>Gangrenous</td>
<td>Distal extremity, 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>

![Image of necrosis types](image-url)
### Cell injury

<table>
<thead>
<tr>
<th>REVERSIBLE WITH O₂</th>
<th>IRREVERSIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular/mitochondrial swelling (↓ ATP → ↓ activity of Na⁺/K⁺ pumps)</td>
<td>Mitochondrial permeability/vacuolization; phospholipid-containing amorphous densities within mitochondria (swelling alone is reversible)</td>
</tr>
<tr>
<td>Nuclear chromatin clumping</td>
<td>Nuclear pyknosis (condensation), karyorrhexis (fragmentation), karyolysis (fading)</td>
</tr>
<tr>
<td>Membrane blebbing</td>
<td>Plasma membrane damage (degradation of membrane phospholipid)</td>
</tr>
<tr>
<td>↓ glycogen</td>
<td>Lysosomal rupture</td>
</tr>
<tr>
<td>Fatty change</td>
<td></td>
</tr>
<tr>
<td>Ribosomal/polysomal detachment (↓ protein synthesis)</td>
<td></td>
</tr>
</tbody>
</table>

### Ischemia

Inadequate blood supply to meet demand.

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, 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.
### Infarcts: red vs pale

**Red**

Red (hemorrhagic) infarcts occur in venous occlusion and tissues with multiple blood supplies, such as liver, lung, intestine, testes; reperfusion (eg, after angioplasty). Reperfusion injury is due to damage by free radicals.

**Red** = reperfusion.

**Pale**

Pale (anemic) infarcts occur in solid organs with a single (end-arterial) blood supply, such as heart, kidney, and spleen.

---

### Inflammation

Characterized by *rubor* (redness), *dolor* (pain), *calor* (heat), *tumor* (swelling), and *functio laesa* (loss of function).

<table>
<thead>
<tr>
<th>Vascular component</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ vascular permeability, vasodilation, endothelial injury.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cellular component</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils extravasate from circulation to injured tissue to participate in inflammation through phagocytosis, degranulation, and inflammatory mediator release.</td>
<td></td>
</tr>
</tbody>
</table>

| Acute | Neutrophil, eosinophil, and antibody mediated. Acute inflammation is rapid onset (seconds to minutes) and of short duration (minutes to days). Outcomes include complete resolution, abscess formation, or progression to chronic inflammation. |

| Chronic | Mononuclear cell (monocytes/macrophages, lymphocytes, plasma cells) and fibroblast mediated. Characterized by persistent destruction and repair. Associated with blood vessel proliferation, fibrosis. Granuloma: nodular collections of epithelioid macrophages and giant cells. Outcomes include scarring and amyloidosis. |
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—degeneration of axon distal to site of injury. Macrophages remove debris and myelin.

Types of calcification

Dystrophic calcification

Ca\(^{2+}\) deposition in abnormal tissues 2° to injury or necrosis. Tends to be localized (eg, calcific aortic stenosis). A shows dystrophic calcification (yellow star), small bony tissue (yellow arrows), and thick fibrotic wall (red arrows).

Seen in TB (lungs and pericardium), liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, Mönckeberg arteriosclerosis, congenital CMV + toxoplasmosis, psammoma bodies.

Is not directly associated with serum Ca\(^{2+}\) levels (patients are usually normocalcemic).

Metastatic calcification

Widespread (ie, diffuse, metastatic) deposition of Ca\(^{2+}\) in normal tissue 2° to hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (eg, chronic renal failure with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, warfarin).

A shows metastatic calcifications of alveolar walls in acute pneumonitis (blue arrows).

Ca\(^{2+}\) deposits predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; \(\uparrow \) pH favors deposition).

Patients are usually not normocalcemic.
**Leukocyte extravasation**

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</td>
<td>Margination and rolling—defective in leukocyte adhesion deficiency type 2 (Sialyl-LewisX)</td>
<td>E-selectin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-selectin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GlyCAM-1, CD34</td>
</tr>
<tr>
<td>2</td>
<td>Tight-binding—defective in leukocyte adhesion deficiency type 1 (CD18 integrin subunit)</td>
<td>ICAM-1 (CD54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VCAM-1 (CD106)</td>
</tr>
<tr>
<td>3</td>
<td>Diapedesis—WBC travels between endothelial cells and exits blood vessel</td>
<td>PECAM-1 (CD31)</td>
</tr>
<tr>
<td>4</td>
<td>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>
</tr>
</tbody>
</table>

**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, 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
- Drug/chemical toxicity: carbon tetrachloride and acetaminophen overdose (hepatotoxicity)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)
Inhalational injury and sequelae

Pulmonary complication associated with smoke and fire. Caused by heat, particulates (< 1 µm diameter), or irritants (eg, NH₃) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, or arsenic poisoning. Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A, 18 hours after inhalation injury; B, resolution at 11 days after injury).

Scar formation

70–80% of tensile strength regained at 3 months; little additional tensile strength will be regained afterward.

<table>
<thead>
<tr>
<th>SCAR TYPE</th>
<th>Hypertrophic A</th>
<th>Keloid B</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLLAGEN SYNTHESIS</td>
<td>Parallel</td>
<td>Disorganized</td>
</tr>
<tr>
<td>COLLAGEN ORGANIZATION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTENT OF SCAR</td>
<td>Confined to borders of original wound</td>
<td>Extends beyond borders of original wound with “clawlike” projections</td>
</tr>
<tr>
<td>SCAR EVOLUTION OVER YEARS</td>
<td>Possible spontaneous regression</td>
<td>Possible progressive growth</td>
</tr>
<tr>
<td>RECURRENT</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>
PATHOLOGY

PATHOLOGY—INFLAMMATION

SECTION II

223

Wound healing

<table>
<thead>
<tr>
<th>Tissue mediators</th>
<th>MEDIATOR</th>
<th>ROLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PDGF</td>
<td>Secreted by activated platelets and macrophages. Induces vascular remodeling and smooth muscle cell migration. Stimulates fibroblast growth for collagen synthesis.</td>
</tr>
<tr>
<td></td>
<td>FGF</td>
<td>Stimulates angiogenesis.</td>
</tr>
<tr>
<td></td>
<td>EGF</td>
<td>Stimulates cell growth via tyrosine kinases (e.g., EGFR/ErbB1).</td>
</tr>
<tr>
<td></td>
<td>TGF-β</td>
<td>Angiogenesis, fibrosis, cell cycle arrest.</td>
</tr>
<tr>
<td></td>
<td>Metalloproteinases</td>
<td>Tissue remodeling.</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>Stimulates angiogenesis.</td>
</tr>
</tbody>
</table>

PHASE OF WOUND HEALING | EFFECTOR CELLS | CHARACTERISTICS
Inflammatory (up to 3 days after wound) | Platelets, neutrophils, macrophages | Clot formation, vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later.

Proliferative (day 3–weeks after wound) | Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages | Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts).

Remodeling (1 week–6+ months after wound) | Fibroblasts | Type III collagen replaced by type I collagen, tensile strength of tissue.

Granulomatous diseases

Bacterial:
* Mycobacteria (tuberculosis, leprosy)
* Bartonella henselae (cat scratch disease)
* Listeria monocytogenes (granulomatosis infantiseptica)
* Treponema pallidum (3rd syphilis)

Fungal: endemic mycoses (e.g., histoplasmosis)
Parasitic: schistosomiasis

Chronic granulomatous disease

Autoinflammatory:
* Sarcoidosis
* Crohn disease
* Primary biliary cirrhosis
* Subacute (de Quervain/granulomatous) thyroiditis
* Granulomatosis with polyangiitis (Wegener)
* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
* Giant cell (temporal) arteritis
* Takayasu arteritis

Foreign material: berylliosis, talcosis, hypersensitivity pneumonitis

Th1 cells secrete IFN-γ, activating macrophages. TNF-α from macrophages induces and maintains granuloma formation. Anti-TNF drugs can, as a side effect, cause sequestering granulomas to break down, leading to 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 more common with infectious causes (e.g., TB). Diagnosing sarcoidosis requires noncaseating granulomas on biopsy.
### Exudate vs Transudate

<table>
<thead>
<tr>
<th>Exudate (&quot;Thick...&quot;)</th>
<th>Transudate (&quot;and thin&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular (cloudy)</td>
<td>Hypocellular (clear)</td>
</tr>
<tr>
<td>↑ protein, ↑ LDH (vs serum)</td>
<td>↓ protein, ↓ LDH (vs serum)</td>
</tr>
<tr>
<td>Specific gravity &gt; 1.020</td>
<td>Specific gravity &lt; 1.012</td>
</tr>
<tr>
<td>Due to:</td>
<td>Due to:</td>
</tr>
<tr>
<td>• Lymphatic obstruction (chyrous)</td>
<td>• ↑ hydrostatic pressure (e.g., HF, Na⁺ retention)</td>
</tr>
<tr>
<td>• Inflammation/infection</td>
<td>• ↓ oncotic pressure (e.g., cirrhosis, nephrotic syndrome)</td>
</tr>
<tr>
<td>• Malignancy</td>
<td></td>
</tr>
</tbody>
</table>

### Erythrocyte sedimentation rate

Products of inflammation (e.g., fibrinogen) coat RBCs and cause aggregation. The denser RBC aggregates fall at a faster rate within a pipette tube. 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 (e.g., giant cell [temporal] arteritis, polymyalgia rheumatica)</td>
<td>HF</td>
</tr>
<tr>
<td>Cancer (e.g., metastases, multiple myeloma)</td>
<td>Microcytosis</td>
</tr>
<tr>
<td>Renal disease (end-stage or nephrotic syndrome)</td>
<td>Hypofibrinogenemia</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
</tbody>
</table>
Amyloidosis

Abnormal aggregation of proteins (or their fragments) into β-pleated linear sheets → damage and apoptosis. Amyloid deposits visualized by Congo red stain A, polarized light (apple green birefringence) B, and H&E stain C shows deposits in glomerular mesangial areas [white arrows], tubular basement membranes [black arrows].

<table>
<thead>
<tr>
<th>COMMON TYPES</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (primary)</td>
<td>Due to deposition of proteins from Ig Light chains. Can occur as a plasma cell disorder or associated with multiple myeloma. Often affects multiple organ systems, including renal (nephrotic syndrome), cardiac (restrictive cardiomyopathy, arrhythmia), hematologic (easy bruising, splenomegaly), GI (hepatomegaly), and neurologic (neuropathy).</td>
</tr>
<tr>
<td>AA (secondary)</td>
<td>Seen with chronic inflammatory conditions such as rheumatoid arthritis, IBD, spondyloarthropathy, familial Mediterranean fever, protracted infection. Fibrils composed of serum Amyloid A. Often multisystem like AL amyloidosis.</td>
</tr>
<tr>
<td>Dialysis-related</td>
<td>Fibrils composed of β₂-microglobulin in patients with ESRD and/or on long-term dialysis. May present as carpal tunnel syndrome.</td>
</tr>
<tr>
<td>Heritable</td>
<td>Heterogeneous group of disorders, including familial amyloid polyneuropathies due to transthyretin gene mutation.</td>
</tr>
<tr>
<td>Age-related (senile) systemic</td>
<td>Due to deposition of normal (wild-type) transthyretin (TTR) predominantly in cardiac ventricles. Slower progression of cardiac dysfunction relative to AL amyloidosis.</td>
</tr>
<tr>
<td>Organ-specific</td>
<td>Amyloid deposition localized to a single organ. Most important form is amyloidosis in Alzheimer disease due to deposition of β-amylloid protein cleaved from amyloid precursor protein (APP). Islet amyloid polypeptide (IAPP) is commonly seen in diabetes mellitus type 2 and is caused by deposition of amylin in pancreatic islets. Isolated atrial amyloidosis due to atrial natriuretic peptide is common in normal aging.</td>
</tr>
</tbody>
</table>

Lipofuscin

A yellow-brown “wear and tear” pigment associated with normal aging. Formed by oxidation and polymerization of autophagocytosed organellar membranes. Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.
## Reactive cellular changes

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrophy</strong></td>
<td>↓ in tissue mass due to ↓ in size and/or number of cells. Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.</td>
</tr>
<tr>
<td><strong>Hypertrophy</strong></td>
<td>↑ in size of cells.</td>
</tr>
<tr>
<td><strong>Hyperplasia</strong></td>
<td>↑ in number of cells. May be a risk factor for future malignancy (eg, endometrial hyperplasia) but not considered premalignant.</td>
</tr>
<tr>
<td><strong>Metaplasia</strong></td>
<td>Replacement of one cell type by another. Usually due to exposure to an irritant, such as gastric acid or cigarette smoke. Reversible if the irritant is removed but may undergo malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma).</td>
</tr>
</tbody>
</table>

## Proneoplastic and neoplastic cellular changes

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neoplasia</strong></td>
<td>Uncontrolled, clonal proliferation of cells. Can be benign or malignant.</td>
</tr>
<tr>
<td><strong>Dysplasia</strong></td>
<td>Disordered, non-neoplastic cell growth. Used only with epithelial cells. Mild dysplasia is usually reversible; severe dysplasia usually progresses to carcinoma in situ.</td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
<td>The degree to which a malignant tumor resembles its tissue of origin. Well-differentiated tumors closely resemble their tissue of origin; poorly differentiated look almost nothing like their tissue of origin.</td>
</tr>
<tr>
<td><strong>Anaplasia</strong></td>
<td>Complete lack of differentiation of cells in a malignant neoplasm.</td>
</tr>
</tbody>
</table>
### Neoplastic progression


### Normal cells

Normal cells with basal → apical differentiation. See cervical example A, which shows normal cells and spectrum of dysplasia, as discussed below.

### Dysplasia

Abnormal proliferation of cells with loss of size, shape, and orientation. Compare vs hyperplasia (cells ↑ in number).

### Carcinoma in situ/preinvasive

Neoplastic cells have not invaded the intact basement membrane.

1. nuclear/cytoplasmic (N/C) ratio and clumped chromatin.
2. Neoplastic cells encompass entire thickness.

### 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, eg, metastatic cells in liver parenchyma.

“Seed and soil” theory of metastasis:

1. Seed = tumor embolus.
2. Soil = target organ is often the first-encountered capillary bed (eg, liver, lungs, bone, brain, etc).
Tumor grade vs stage

**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**
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

Stage almost always has more prognostic value than grade.

Tumor nomenclature

**Carcinoma** implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms imply malignancy.

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).

**Benign** tumor is usually well differentiated, well demarcated, low mitotic activity, no metastasis, no necrosis.

**Malignant** tumor may show poor differentiation, erratic growth, local invasion, metastasis, and apoptosis. Upregulation of telomerase prevents chromosome shortening and cell death.

<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>Blood cells</td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td></td>
<td>Blood vessels</td>
<td>Hemangioma</td>
</tr>
<tr>
<td></td>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
</tr>
<tr>
<td></td>
<td>Striated muscle</td>
<td>Rhabdomyoma</td>
</tr>
<tr>
<td></td>
<td>Connective tissue</td>
<td>Fibroma</td>
</tr>
<tr>
<td></td>
<td>Bone</td>
<td>Osteoma</td>
</tr>
<tr>
<td></td>
<td>Fat</td>
<td>Lipoma</td>
</tr>
<tr>
<td></td>
<td>Melanocyte</td>
<td>Nevus/mole</td>
</tr>
</tbody>
</table>

Cancer epidemiology

Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included in list).

<table>
<thead>
<tr>
<th>INCIDENCE</th>
<th>MALE</th>
<th>FEMALE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate</td>
<td>1. Breast</td>
<td>Lung cancer incidence has dropped in men, but has not changed significantly in women.</td>
<td></td>
</tr>
<tr>
<td>2. Lung</td>
<td>2. Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Colon/rectum</td>
<td>3. Colon/rectum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MORTALITY</th>
<th>MALE</th>
<th>FEMALE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lung</td>
<td>1. Lung</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></td>
<td></td>
</tr>
<tr>
<td>3. Colon/rectum</td>
<td>3. Colon/rectum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Paraneoplastic syndromes

<table>
<thead>
<tr>
<th>MANIFESTATION</th>
<th>DESCRIPTION/MECHANISM</th>
<th>MOST COMMONLY ASSOCIATED CANCER(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
<td></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><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></td>
<td>† 1,25-(OH)₂ vitamin D₃ (calcitriol)</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>† ACTH</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Hyponatremia (SIADH)</td>
<td>† ADH</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>Renal cell carcinoma, hepatocellular carcinoma, hemangioblastoma, pheochromocytoma, 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>Thymoma</td>
</tr>
<tr>
<td>Trousseau syndrome</td>
<td>Migratory superficial thrombophlebitis</td>
<td>Adenocarcinomas, especially pancreatic</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 Hu, Yo, and Tr antigens in Purkinje cells</td>
<td>Small cell lung cancer, gynecologic and breast cancers, and Hodgkin lymphoma</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 AChR at NMJ</td>
<td>Thymoma</td>
</tr>
</tbody>
</table>
### Oncogenes

Gain of function $\rightarrow$ ↑ cancer risk. Need damage to only 1 allele.

<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</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</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>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>MYCN</td>
<td>Transcription factor</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>RET</td>
<td>Tyrosine kinase</td>
<td>MEN 2A and 2B, medullary thyroid cancer</td>
</tr>
</tbody>
</table>

### Tumor suppressor genes

Loss of function $\rightarrow$ ↑ cancer risk; both alleles must be lost for expression of disease.

<table>
<thead>
<tr>
<th>GENE</th>
<th>ASSOCIATED CONDITION</th>
<th>GENE PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Colorectal cancer (associated with FAP)</td>
<td>DNA repair protein</td>
</tr>
<tr>
<td>BRCA1/BRCA2</td>
<td>Breast and ovarian cancer</td>
<td>p16, blocks G1 $\rightarrow$ S phase</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Melanoma, pancreatic cancer</td>
<td>DCC—Deleted in Colon Cancer</td>
</tr>
<tr>
<td>DCC</td>
<td>Colon cancer</td>
<td>DPC—Deleted in Pancreatic Cancer</td>
</tr>
<tr>
<td>DPC4/SMAD4</td>
<td>Pancreatic cancer</td>
<td>Menin</td>
</tr>
<tr>
<td>NF1</td>
<td>Neurofibromatosis type 1</td>
<td>Ras GTPase activating protein (neurofibromin)</td>
</tr>
<tr>
<td>NF2</td>
<td>Neurofibromatosis type 2</td>
<td>Merlin (schwannomin) protein</td>
</tr>
<tr>
<td>PTEN</td>
<td>Breast cancer, prostate cancer, endometrial cancer</td>
<td>Inhibits E2F; blocks G1 $\rightarrow$ S phase</td>
</tr>
<tr>
<td>Rb</td>
<td>Retinoblastoma, osteosarcoma</td>
<td>$p53$, activates p21, blocks G1 $\rightarrow$ S phase</td>
</tr>
<tr>
<td>TSC1</td>
<td>Tuberous sclerosis</td>
<td>Hamartin protein</td>
</tr>
<tr>
<td>TSC2</td>
<td>Tuberous sclerosis</td>
<td>Tuberin protein</td>
</tr>
<tr>
<td>VHL</td>
<td>von Hippel-Lindau disease, renal cell carcinoma</td>
<td>Inhibits hypoxia inducible factor 1a</td>
</tr>
<tr>
<td>WT1/WT2</td>
<td>Wilms Tumor (nephroblastoma)</td>
<td></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, lymphoma</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>ORGAN</th>
<th>IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aflatoxins (Aspergillus)</strong></td>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Blood</td>
<td>Leukemia/lymphoma</td>
</tr>
<tr>
<td>Aromatic amines (eg, benzidine, 2-naphthylamine)</td>
<td>Bladder</td>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Liver</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Lung</td>
<td>Bronchogenic carcinoma &gt; mesothelioma</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Liver</td>
<td>Centrilobular necrosis, fatty change</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>Bladder</td>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Cervix</td>
<td>Cervical carcinoma</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td>Squamous cell carcinoma/adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Larynx</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Squamous cell and small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Pancreatic adenocarcinoma</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Esophagus</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>Thyroid</td>
<td>Papillary thyroid carcinoma</td>
</tr>
<tr>
<td>Nitrosamines (smoked foods)</td>
<td>Stomach</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Radon</td>
<td>Lung</td>
<td>Lung cancer (2nd leading cause after cigarette smoke)</td>
</tr>
<tr>
<td>Vinyl chloride</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 usually made via biopsy.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP).</td>
</tr>
<tr>
<td>α-fetoprotein</td>
<td>Hepatocellular carcinoma, hepatoblastoma, yolk sac (endodermal sinus) tumor, mixed germ cell tumor.</td>
</tr>
<tr>
<td>β-hCG</td>
<td>Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.</td>
</tr>
<tr>
<td>CA 15-3/CA 27-29</td>
<td>Breast cancer.</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreatic adenocarcinoma.</td>
</tr>
<tr>
<td>CA 125</td>
<td>Ovarian cancer.</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Medullary thyroid carcinoma.</td>
</tr>
<tr>
<td>CEA</td>
<td>CarcinoEmbryonic Antigen. Very nonspecific but produced by ~ 70% of colorectal and pancreatic cancers; also produced by gastric, breast, and medullary thyroid carcinomas.</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate-specific antigen. Prostate cancer. Can also be elevated in BPH and prostatitis. Questionable risk/benefit for screening.</td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td>Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenal cell 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).</td>
</tr>
<tr>
<td>Cachexia</td>
<td>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.</td>
</tr>
</tbody>
</table>
**Common metastases**

Most sarcomas spread hematogenously; most carcinomas spread via lymphatics (except hepatocellular carcinoma, renal cell carcinoma, follicular thyroid carcinoma, and choriocarcinoma).

<table>
<thead>
<tr>
<th>SITE OF METASTASIS</th>
<th>1º TUMOR</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Lung &gt; breast &gt; prostate &gt; melanoma &gt; GI.</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; lung, thyroid, kidney.</td>
<td>Bone metastasis &gt;&gt; 1º bone tumors (eg, multiple myeloma, lytic). Common mets to bone: breast (mixed), lung (mixed), thyroid (lytic), kidney (lytic), prostate (blastic). Predilection for axial skeleton.</td>
</tr>
</tbody>
</table>
Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., 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. Specific drug dosages or trade names are generally not testable. 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 on NSAIDs. Much of the material is clinically relevant. We occasionally mention drugs that are no longer available in the US, but help illustrate high-yield pharmacologic or disease mechanisms. They are highlighted as being of historical significance and should not appear on the USMLE. However, recently approved drugs are fair game for the exam.
**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](image)

**Lineweaver-Burk plot**

- y-intercept, ↓ $V_{max}$
- The further to the right the x-intercept (ie, closer to zero), the greater the $K_m$ and the lower the affinity.

Reversible competitive inhibitors cross each other competitively, whereas noncompetitive inhibitors do not.

**Effects of enzyme inhibition**

- Noncompetitive inhibitor
- Competitive inhibitor (reversible)
- Uninhibited

<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>

**Saturation**

$V_{max}$ = $\frac{1}{[S]}$ at $\frac{1}{V}$
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>$V_d$</th>
<th>COMPARTMENT</th>
<th>DRUG TYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Blood</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.

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \ (\text{elimination constant})$$

Half-life ($t_{1/2}$)
The time required to change the amount of drug in the body by $\frac{1}{2}$ 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.

$$t_{1/2} = \frac{0.693 \times V_d}{CL} \text{ in first-order elimination}$$

<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 ↓ 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>MDMA and LSD</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 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.

Capacity-limited elimination. PEA. (A pea is round, shaped like the “0” in zero-order.)

Flow-dependent elimination.

Urine pH and drug elimination  Ionized species are trapped in urine and cleared quickly. Neutral forms can be reabsorbed.

Weak acids  Examples: phenobarbital, methotrexate, aspirin. Trapped in basic environments. Treat overdose with bicarbonate.

$$RCOOH \Leftrightarrow RCOO^- + H^+$$

Weak bases  Example: amphetamines, TCAs. Trapped in acidic environments. Treat overdose with ammonium chloride.

$$RNH_3^+ \Leftrightarrow RNH_2 + H^+$$

Drug metabolism

Phase I  Reduction, oxidation, hydrolysis with cytochrome P-450 usually yield slightly polar, water-soluble metabolites (often still active).

Geriatric patients lose phase I first.

Phase II  Conjugation (Methylation, Glucuronidation, Acetylation, Sulfation) usually yields very polar, inactive metabolites (renally excreted).

Geriatric patients have More GAS (phase II). Patients who are slow acetylators have ↓ side effects from certain drugs because of ↓ rate of metabolism.
**Efficacy vs potency**

**Efficacy**  
Maximal effect a drug can produce. Represented by the y-value ($V_{max}$). $y$-value = $V_{max}$ = efficacy. Unrelated to potency (i.e., 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 = $EC_{50}$ = potency = drug needed. Unrelated to efficacy (i.e., potent drugs can have high or low efficacy).
Pharmacology

PHARMACOLOGY—PHARMACOKINETICS & PHARMACODYNAMICS

Receptor binding

<table>
<thead>
<tr>
<th>Receptor binding</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>

Therapeutic index

Measurement of drug safety.

TD$_{50}$ = median toxic dose

ED$_{50}$ = median effective dose

Therapeutic window—dosage range that can safely and effectively treat disease.

TTIE: Therapeutic Index = TD$_{50}$ / ED$_{50}$.

Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, digoxin, lithium, theophylline, warfarin). LD$_{50}$ (lethal median dose) often replaces TD$_{50}$ in animal studies.
Central and peripheral nervous system

Note that the adrenal medulla and sweat glands are part of the sympathetic nervous system but are innervated by cholinergic fibers.
Botulinum toxin prevents release of acetylcholine at cholinergic terminals.

**ACh receptors**

Nicotinic ACh receptors are ligand-gated Na⁺/K⁺ channels. Two subtypes: **N<sub>N</sub>** (found in autonomic ganglia, adrenal medulla) and **N<sub>M</sub>** (found in neuromuscular junction of skeletal muscle).
Muscarinic ACh receptors are G-protein–coupled receptors that usually act through 2nd messengers. 5 subtypes: **M<sub>1-5</sub>** found in heart, smooth muscle, brain, exocrine glands, and on sweat glands (cholinergic sympathetic).
### G-protein–linked 2nd messengers

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>G-PROTEIN CLASS</th>
<th>MAJOR FUNCTIONS</th>
</tr>
</thead>
<tbody>
<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, ↑ renin release, ↑ lipolysis</td>
</tr>
<tr>
<td>β₂</td>
<td>s</td>
<td>Vasodilation, bronchodilation, ↑ lipolysis, ↑ insulin release, ↑ uterine tone (tocolysis), ciliary muscle relaxation, ↑ aqueous humor production</td>
</tr>
<tr>
<td>β₃</td>
<td>s</td>
<td>↑ lipolysis, ↑ thermogenesis in skeletal muscle</td>
</tr>
</tbody>
</table>

**Parasympathetic**

<table>
<thead>
<tr>
<th>M₁</th>
<th>q</th>
<th>CNS, enteric nervous system</th>
</tr>
</thead>
<tbody>
<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)</td>
</tr>
</tbody>
</table>

**Dopamine**

<table>
<thead>
<tr>
<th>D₁</th>
<th>s</th>
<th>Relaxes renal vascular smooth muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₂</td>
<td>i</td>
<td>Modulates transmitter release, especially in brain</td>
</tr>
</tbody>
</table>

**Histamine**

<table>
<thead>
<tr>
<th>H₁</th>
<th>q</th>
<th>↑ nasal and bronchial mucus production, ↑ vascular permeability, contraction of bronchioles, pruritus, pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂</td>
<td>s</td>
<td>↑ gastric acid secretion</td>
</tr>
</tbody>
</table>

**Vasopressin**

<table>
<thead>
<tr>
<th>V₁</th>
<th>q</th>
<th>↑ vascular smooth muscle contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>V₂</td>
<td>s</td>
<td>↑ H₂O permeability and reabsorption in collecting tubules of kidney (V₂ is found in the 2 kidneys)</td>
</tr>
</tbody>
</table>

“After *qi*sses (kisses), you get a *qi*q (kick) out of *si*q (sick) *sq*qs (super qinky sex).”

**HAV e 1 M& M.**

\[ H A V e 1 \text{ M} & \text{M.} \]

**MAD 2’s.**

\[ H A V e 2 \text{ M} & \text{M.} \]
Autonomic drugs

CHOLINERGIC

**Axon**
- Choline
- Hemicholinium
- Vesamicol
- Ca^{2+}
- Botulinum
- Acetylcholine (ACh)
- Acetyl-CoA
- Choline + acetate
- Acetylcholinesterase (AChE)
- ACh receptor
- AChE inhibitors

**Postsynaptic Membrane**

NORADRENERGIC

**Axon**
- Tyrosine
- Metyrosine
- Dopamine
- Reserpine
- Bretylium, guanethidine
- Amphetamine, ephedrine
- Cocaine, TCAs, amphetamine
- Tyramine
- NE
- Adrenoreceptors α or β

**Postsynaptic Membrane**

---

*a* Release of norepinephrine from a sympathetic nerve ending is modulated by norepinephrine itself, acting on presynaptic α₂-autoreceptors.

*b* 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.

**Tyramine**

Normally degraded by monoamine oxidase (MAO). Levels ↑ in patients taking MAO inhibitors who ingest tyramine-rich foods (eg, cheese, wine). Excess tyramine enters presynaptic vesicles and displaces other neurotransmitters (eg, NE) → ↑ active presynaptic neurotransmitters → ↑ diffusion of neurotransmitters into synaptic cleft → ↑ sympathetic stimulation. Classically results in a hypertensive crisis.
## Cholinomimetic agents

<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; resistant to AChE. “Bethany, call (bethanechol) me to activate your bowels and bladder.”</td>
<td>Postoperative ileus, neurogenic ileus, urinary retention</td>
</tr>
<tr>
<td><strong>Carbachol</strong></td>
<td>Carbon copy of acetylcholine.</td>
<td>Constricts pupil and relieves intraocular pressure in open-angle glaucoma</td>
</tr>
<tr>
<td><strong>Methacholine</strong></td>
<td>Stimulates muscarinic receptors in airway when 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 glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE. “You cry, drool, and sweat on your ‘pilo.’”</td>
<td>Potent stimulator of sweat, tears, and saliva. Open-angle and closed-angle glaucoma, xerostomia (Sjögren syndrome)</td>
</tr>
<tr>
<td><strong>Indirect agonists (anticholinesterases)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Donepezil, galantamine, rivastigmine</strong></td>
<td>† ACh.</td>
<td>Alzheimer disease.</td>
</tr>
<tr>
<td><strong>Edrophonium</strong></td>
<td>† ACh.</td>
<td>Historically, diagnosis of myasthenia gravis (extremely short acting). Myasthenia now diagnosed by anti-AChR Ab (anti-acetylcholine receptor antibody) test.</td>
</tr>
<tr>
<td><strong>Neostigmine</strong></td>
<td>† ACh. Neo CNS = No CNS penetration (quaternary amine).</td>
<td>Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative).</td>
</tr>
<tr>
<td><strong>Physostigmine</strong></td>
<td>† ACh. Physostigmine “phyxes” atropine overdose.</td>
<td>Anticholinergic toxicity; crosses blood-brain barrier → CNS (ternary amine).</td>
</tr>
<tr>
<td><strong>Pyridostigmine</strong></td>
<td>† ACh; † muscle strength. Pyridostigmine gets rid of myasthenia gravis.</td>
<td>Myasthenia gravis (long acting); does not penetrate CNS (ternary amine).</td>
</tr>
</tbody>
</table>

Note: With all cholinomimetic agents, watch for exacerbation of COPD, asthma, and peptic ulcers when giving to susceptible patients.

## Cholinesterase inhibitor poisoning

Often due to organophosphates, such as parathion, that irreversibly inhibit AChE. Causes Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Excitation of skeletal muscle and CNS, Lacrimation, Sweating, and Salivation. May lead to respiratory failure if untreated.

**DUMBBELSS.** Organophosphates are often components of insecticides; poisoning usually seen in farmers. Antidote—atropine (competitive inhibitor) + pralidoxime (regenerates AChE if given early).
**Muscarnic 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>Benztrapine</td>
<td>CNS</td>
<td>Parkinson disease (“park my Benz”). 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 (“I pray I can breathe soon!”).</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**

Muscarnic 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 DUMBBELLSS in cholinesterase inhibitor poisoning. Does not block excitation of skeletal muscle and CNS (mediated by nicotinic receptors).</td>
</tr>
<tr>
<td>Airway</td>
<td>↓ 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
- Jimson weed (*Datura*) → gardener’s pupil (mydriasis due to plant alkaloids)
<table>
<thead>
<tr>
<th><strong>Direct sympathomimetics</strong></th>
<th><strong>APPLICATIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol, salmeterol</td>
<td>$\beta_2 &gt; \beta_1$</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>$\beta_1 &gt; \beta_2, \alpha$</td>
</tr>
<tr>
<td>Dopamine</td>
<td>$D_1 = D_2 &gt; \beta &gt; \alpha$</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>$\beta &gt; \alpha$</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>$\beta_1 = \beta_2$</td>
</tr>
<tr>
<td>Midodrine</td>
<td>$\alpha_1$</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>$\alpha_1 &gt; \alpha_2 &gt; \beta_1$</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>$\alpha_1 &gt; \alpha_2$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Indirect sympathomimetics</strong></th>
<th><strong>APPLICATIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Indirect general agonist, reuptake inhibitor, also releases stored catecholamines</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Indirect general agonist, reuptake inhibitor</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Indirect general agonist, releases stored catecholamines</td>
</tr>
</tbody>
</table>
**Norepinephrine vs isoproterenol**

Norepinephrine elevates systolic and diastolic pressures as a result of $\alpha_1$-mediated vasoconstriction → mean arterial pressure → reflex bradycardia. However, isoproterenol (no longer commonly 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</td>
<td>CNS depression, bradycardia, hypotension, respiratory depression, miosis</td>
</tr>
<tr>
<td>$\alpha$-methyldopa</td>
<td>Hypertension in pregnancy</td>
<td>Direct Coombs $\oplus$ hemolysis, SLE-like syndrome</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 (irreversible)</td>
<td>Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis</td>
<td>Orthostatic hypotension, reflex tachycardia</td>
</tr>
<tr>
<td>Phenotolamine (reversible)</td>
<td>Give to patients on MAO inhibitors who eat tyramine-containing foods</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>

**α-blockade of epinephrine vs phenylephrine**

Shown above are the effects of an α-blocker (eg, phentolamine) on blood pressure responses to epinephrine and phenylephrine. The epinephrine response exhibits reversal of the mean blood pressure change, from a net increase (the α response) to a net decrease (the β₂ response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a “pure” α-agonist without β action.
**β-blockers**

<table>
<thead>
<tr>
<th>APPLICATION</th>
<th>ACTIONS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>↓ heart rate and contractility, resulting in ↓ O₂ consumption</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>↓ mortality</td>
<td></td>
</tr>
<tr>
<td>SVT (metoprolol, esmolol)</td>
<td>↓ AV conduction velocity (class II antiarrhythmic)</td>
<td></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>HF</td>
<td>↓ mortality (bisoprolol, carvedilol, metoprolol)</td>
<td></td>
</tr>
<tr>
<td>Glaucoma (timolol)</td>
<td>↓ secretion of aqueous humor</td>
<td></td>
</tr>
<tr>
<td>Variceal bleeding (nadolol, propranolol)</td>
<td>↓ hepatic venous pressure gradient and portal hypertension</td>
<td></td>
</tr>
</tbody>
</table>

**ADVERSE EFFECTS**

- Erectile dysfunction, cardiovascular adverse effects (bradycardia, AV block, HF), CNS adverse effects (seizures, sedation, sleep alterations), dyslipidemia (metoprolol), and asthma/COPD exacerbations

**SELECTIVITY**

- Selective antagonists mostly go from A to M (β₁ with 1st half of alphabet)
- Nonselective antagonists mostly go from N to Z (β₂ with 2nd half of alphabet)
- Nonselective α- and β-antagonists have modified suffixes (instead of “-olol”)

- Nebivolol combines cardiac-selective β₁-adrenergic blockade with stimulation of β₁-receptors, which activate nitric oxide synthase in the vasculature
<table>
<thead>
<tr>
<th>Ingested seafood toxins</th>
<th>ACTION</th>
<th>SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetrodotoxin</strong></td>
<td>Pufferfish.</td>
<td>Highly potent toxin; binds fast voltage-gated Na⁺ channels in cardiac/nerve tissue, preventing depolarization.</td>
<td>Nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes.</td>
</tr>
<tr>
<td><strong>Ciguatoxin</strong></td>
<td>Reef fish such as barracuda, snapper, and moray eel.</td>
<td>Opens Na⁺ channels, causing depolarization.</td>
<td>Symptoms mimic cholinergic poisoning.</td>
</tr>
<tr>
<td><strong>Histamine (scombroid poisoning)</strong></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>
</tr>
</tbody>
</table>
### 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>Amphetamines (basic)</td>
<td>NH₄Cl (acidify urine)</td>
</tr>
<tr>
<td>Antimuscarinic, anticholinergic agents</td>
<td>Phystostigmine, 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>Saline, atropine, glucagon</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>100% O₂, hyperbaric O₂</td>
</tr>
<tr>
<td>Copper</td>
<td>Penicillamine, trientine</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Nitrate + thiosulfate, hydroxocobalamin</td>
</tr>
<tr>
<td>Digitalis (digoxin)</td>
<td>Anti-dig Fab fragments</td>
</tr>
<tr>
<td>Gold</td>
<td>Penicillamine, dimercaprol (BAL), succimer</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Iron</td>
<td>Deroxamine, 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</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</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K (delayed effect), fresh frozen plasma (immediate)</td>
</tr>
</tbody>
</table>

### Drug reactions—cardiovascular

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary vasospasm</td>
<td>Cocaine, sumatriptan, ergot alkaloids</td>
</tr>
<tr>
<td>Cutaneous flushing</td>
<td>Vancomycin, Adenosine, Niacin, Ca²⁺ channel blockers, Echinocandins (VANCE)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>Anthracyclines (eg, doxorubicin, daunorubicin); prevent with dexrazoxane</td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>AntiArrhythmics (class IA, III), antiBiotics (eg, macrolides), anti“C”ychotics (eg, haloperidol), antiDepressants (eg, TCAs), antiEmetics (eg, ondansetron) (ABCDE).</td>
</tr>
</tbody>
</table>
### 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 2º to glucocorticoid withdrawal</td>
<td></td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Tamoxifen, clomiphene</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Tacrolimus, Protease inhibitors, Niacin, HCTZ, Corticosteroids</td>
<td>Taking Pills Necessitates Having blood checked</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Lithium, amiodarone, sulfonamides</td>
<td></td>
</tr>
</tbody>
</table>

### Drug reactions—GI

<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>Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Acamprosate, acarbose, cholinesterase inhibitors, colchicine, erythromycin, ezetimibe, metformin, misoprostol, orlistat, pramlintide, quinidine, SSIs</td>
<td></td>
</tr>
<tr>
<td>Focal to massive hepatic necrosis</td>
<td>Halothane, <em>Amanita phalloides</em> (death cap mushroom), Valproic acid, Acetaminophen</td>
<td>Liver “HAVAc”</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Rifampin, izoniazid, 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>Tetracyclines, bisphosphonates, potassium chloride</td>
<td>Caustic effect minimized with upright posture and adequate water ingestion.</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Clindamycin, ampicillin, cephalosporins</td>
<td>Antibiotics predispose to superinfection by resistant <em>C. difficile</em></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>Methyldopa, penicillin</td>
<td></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, Nitrofurantoin</td>
<td>Hemolysis IS D PAIN</td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>Phenytion, Methotrexate, Sulfa drugs</td>
<td>Having a blast with PMS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Thrombotic complications</td>
<td>OCPs, hormone replacement therapy</td>
<td></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>Fat redistribution</td>
<td>Protease inhibitors, Glucocorticoids</td>
<td>Fat PiG</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>Phenytoin, Ca(^{2+}) channel blockers, cyclosporine</td>
<td></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>Fibrates, niacin, colchicine, hydroxychloroquine, interferon-α, penicillamine, statins, glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Corticosteroids, heparin</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>SLE-like syndrome</td>
<td>Sulfonamides, Hydralazine, Isoniazid, Procaïnamide, Phenytoin, Etanercept</td>
<td>Having lupus is “SHIPP-E”</td>
</tr>
<tr>
<td>Teeth discoloration</td>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Tendonitis, tendon rupture, 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></td>
</tr>
<tr>
<td>Parkinson-like syndrome</td>
<td>Antipsychotics, Reserpine, Metoclopramide</td>
<td>Cogwheel rigidity of ARM</td>
</tr>
<tr>
<td>Seizures</td>
<td>Isoniazid (vitamin B(_6) 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>
</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>Diabetes insipidus</td>
<td>Lithium, demeclocycline</td>
<td></td>
</tr>
<tr>
<td>Fanconi syndrome</td>
<td>Tenofovir, ifosfamide</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>Methicillin, NSAIDs, furosemide</td>
<td></td>
</tr>
<tr>
<td>SIADH</td>
<td>Carbamazepine, Cyclophosphamide, SSRIs</td>
<td>Can’t Concentrate Serum Sodium</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>
</tr>
</thead>
<tbody>
<tr>
<td>Antimuscarinic</td>
<td>Atropine, TCAs, H₁-blockers, antipsychotics</td>
</tr>
<tr>
<td>Disulfiram-like reaction</td>
<td>Metronidazole, certain cephalosporins, griseofulvin, procarbazine, 1st-generation sulfonylureas</td>
</tr>
<tr>
<td>Nephrotoxicity/ototoxicity</td>
<td>Aminoglycosides, vancomycin, loop diuretics, cisplatin. Cisplatin toxicity may respond to amifostine.</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>Chronic alcohol</td>
<td>Anti-epileptics</td>
<td>Acute Alcohol Abuse</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Theophylline</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Warfarin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>OCPs</td>
<td>Cimetidine/ciprofloxacin</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td></td>
<td>Isoniazid (INH)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Chronic alcoholics Steal</td>
<td>Always Think When Outdoors</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Phen-Phen and Never</td>
<td></td>
<td>Macrolides (except azithromycin)</td>
</tr>
<tr>
<td>Refuse Greasy Carbs</td>
<td></td>
<td>AAA RACKS IN GQ</td>
</tr>
</tbody>
</table>

### Sulfa drugs

- Sulfonamide antibiotics, Sulfasalazine, Probenecid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonylelas.

Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, and urticaria (hives). Symptoms range from mild to life threatening.
## 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>Peptidoglycan synthesis inhibitor</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>-etine</td>
<td>SSRI</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>-ipramine, -triptyline</td>
<td>TCA</td>
<td>Imipramine, amitriptyline</td>
</tr>
<tr>
<td>-triptan</td>
<td>5-HT&lt;sub&gt;1B/1D&lt;/sub&gt; agonists</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>β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>Albuterol</td>
</tr>
<tr>
<td>-zosin</td>
<td>α&lt;sub&gt;1&lt;/sub&gt;-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 Ca&lt;sup&gt;2+&lt;/sup&gt; 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>-statin</td>
<td>HMG-CoA reductase inhibitor</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>-xaban</td>
<td>Direct factor Xa inhibitors</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>-glitazone</td>
<td>PPAR-γ activator</td>
<td>Rosiglitazone</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>-tidine</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;-antagonist</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>-tropin</td>
<td>Pituitary hormone</td>
<td>Somatotropin</td>
</tr>
<tr>
<td>-ximab</td>
<td>Chimeric monoclonal Ab</td>
<td>Basiliximab</td>
</tr>
<tr>
<td>-zumab</td>
<td>Humanized monoclonal Ab</td>
<td>Daclizumab</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

“Learn that you are a machine, your heart an engine, your lungs a fanning machine and a sieve, your brain with its two lobes an electric battery.”
—Andrew T. Still
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
**Heart embryology**

<table>
<thead>
<tr>
<th>EMBRYONIC STRUCTURE</th>
<th>GIVES RISE TO</th>
</tr>
</thead>
<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 (primary 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 (VSD)—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 $\rightarrow$ patent 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; 1 resistance in pulmonary vasculature $\rightarrow$ 1 left atrial pressure vs right atrial pressure; foramen ovale closes (now called fossa ovale); 1 in $O_2$ (from respiration) and 4 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 $E_2$ help PDA open.

### Fetal-postnatal derivatives

<table>
<thead>
<tr>
<th>Allantois $\rightarrow$ urachus</th>
<th>Media $\rightarrow$ umbilical ligament</th>
<th>Urachus is part of allantoic duct between bladder and umbilicus.</th>
</tr>
</thead>
<tbody>
<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>Media $\rightarrow$ umbilical ligaments</td>
<td></td>
</tr>
<tr>
<td>Umbilical vein</td>
<td>Ligamentum teres hepatitis</td>
<td>Contained in falciform ligament.</td>
</tr>
</tbody>
</table>
Coronary artery anatomy

SA and AV nodes are usually supplied by RCA. 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).

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.
Cardiac output

\[ CO = \text{stroke volume (SV)} \times \text{heart rate (HR)} \]

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)

\[ \text{MAP} = \frac{1}{3} \text{diastolic pressure} + \frac{2}{3} \text{systolic pressure} \]

Pulse pressure = systolic pressure – diastolic pressure

Pulse pressure is proportional to SV, inversely proportional to arterial compliance.

\[ \text{SV} = \text{end-diastolic volume (EDV)} - \text{end-systolic volume (ESV)} \]

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), 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**.

<table>
<thead>
<tr>
<th>↑ SV with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Contractility (eg, anxiety, exercise)</td>
</tr>
<tr>
<td>↑ Preload (eg, early pregnancy)</td>
</tr>
<tr>
<td>↓ Afterload</td>
</tr>
</tbody>
</table>

**SV CAP.**

A failing heart has ↓ SV (systolic and/or diastolic dysfunction)

#### Contractility

**Contractility (and SV)** ↑ with:

- Catecholamines (inhibition of phospholamban → ↑ Ca\(^{2+}\) entry into sarcoplasmic reticulum → ↑ Ca\(^{2+}\)-induced Ca\(^{2+}\) release)
- ↑ intracellular Ca\(^{2+}\)
- ↓ extracellular Na\(^{+}\) (↓ activity of Na\(^{+}/Ca\(^{2+}\) exchanger)
- Digitalis (blocks Na\(^{+}/K\(^{+}\) pump → ↑ intracellular Na\(^{+}\) → ↓ Na\(^{+}/Ca\(^{2+}\) exchanger activity → ↑ intracellular Ca\(^{2+}\))

#### Myocardial oxygen demand

↑ MyoCARDial O\(_2\) demand is ↑ by:

- ↑ Contractility
- ↑ Afterload (proportional to arterial pressure)
- ↑ heart Rate
- ↑ Diameter of ventricle (↑ wall tension)

#### Preload

Preload approximated by ventricular EDV; depends on venous tone and circulating blood volume.

**VEndilators** (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.

**VAndilators** (eg, hydrAline) ↓ Afterload (Arterial).

ACE inhibitors and ARBs ↓ both preload and afterload.

Chronic hypertension (↑ MAP) → LV hypertrophy.

#### Ejection fraction

\[
EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}
\]

Left ventricular EF is an index of ventricular contractility; normal EF is ≥ 55%.

EF ↓ in systolic HF.

EF normal in diastolic HF.
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

\[ = \frac{\text{driving pressure (ΔP)}}{\text{flow (Q)}} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4} \]

Total resistance of vessels in series:

\[ R_T = R_1 + R_2 + R_3 + \ldots \]

Total resistance of vessels in parallel:

\[ \frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \ldots \]

Viscosity depends mostly on hematocrit

Viscosity † in hyperproteinemic states (eg, multiple myeloma), polycythemia

Viscosity ‡ in anemia

Capillaries have highest total cross-sectional area and lowest flow velocity.

Removal of organs in parallel arrangement (eg, nephrectomy) \( \rightarrow \) ‡ TPR and † CO.

Pressure gradient drives flow from high pressure to low pressure.

Arterioles account for most of TPR. Veins provide most of blood storage capacity.
Cardiac and vascular function curves

Intersection of curves = operating point of heart (ie, venous return and CO are equal).

<table>
<thead>
<tr>
<th>CURVE</th>
<th>EFFECT</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Inotropy</td>
<td>Changes in contractility → altered CO for a given RA pressure (preload).</td>
<td>1 Catecholamines, digoxin ⊕ 2 Uncompensated HF, narcotic overdose ⊗</td>
</tr>
<tr>
<td>B Venous return</td>
<td>Changes in circulating volume or venous tone → altered RA pressure for a given CO. Mean systemic pressure (x-intercept) changes with volume/venous tone.</td>
<td>3 Fluid infusion, sympathetic activity ⊕ 4 Acute hemorrhage, spinal anesthesia ⊗</td>
</tr>
<tr>
<td>C Total peripheral resistance</td>
<td>At a given mean systemic pressure (x-intercept) and RA pressure, changes in TPR → altered CO.</td>
<td>5 Vasopressors ⊕ 6 Exercise, AV shunt ⊗</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 → 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 and young adults).

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—atrial relaxation and downward displacement of closed tricuspid valve during ventricular contraction. Absent in tricuspid regurgitation. Prominent in tricuspid insufficiency and right HF.
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 (e.g., 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 (e.g., 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
  - Flow murmur

**Tricuspid area:**
- Holosystolic murmur
  - Tricuspid regurgitation
  - Ventricular septal defect
  - Diastolic murmur
  - Tricuspid stenosis
  - Atrial septal defect (↑ flow across tricuspid valve)

**Mitral area:**
- Holosystolic murmur
  - Mitral regurgitation
  - Diastolic murmur
  - Mitral stenosis

**Left sternal border:**
- Diastolic murmur
  - Aortic regurgitation
  - Pulmonic regurgitation
  - Systolic murmur
  - Hypertrophic cardiomyopathy

**Bedside Maneuver** | **Effect**
--- | ---
Inspiration (↑ venous return to right atrium) | ↑ intensity of right heart sounds
Hand grip (↑ afterload) | ↑ intensity of MR, AR, VSD murmurs
 | ↓ intensity of hypertrophic cardiomyopathy murmurs
 | MVP: later onset of click/murmur
Valsalva (phase II), standing up (↓ preload) | ↓ intensity of most murmurs (including AS)
 | ↑ intensity of hypertrophic cardiomyopathy murmur
 | MVP: earlier onset of click/murmur
Rapid squatting (↑ venous return, ↑ preload, ↑ afterload) | ↓ intensity of hypertrophic cardiomyopathy murmur
 | ↑ intensity of AS murmur
 | MVP: later onset of click/murmur

Systolic heart sounds include aortic/pulmonic stenosis, mitral/tricuspid regurgitation, VSD, MVP.
Diastolic heart sounds include aortic/pulmonic regurgitation, mitral/tricuspid stenosis.
### Heart murmurs

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Aortic stenosis</strong></td>
<td>Crescendo-decrescendo systolic ejection murmur (ejection click may be present). LV &gt;&gt; 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 (&gt; 60 years old) or in younger patients with early-onset calcification of bicuspid aortic valve.</td>
</tr>
</tbody>
</table>

| **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 and radiates to right sternal border. 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 dilation, 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 late diastolic murmur (4 interval between S2 and OS correlates with † severity). LA >> LV pressure during diastole. Often occurs † to rheumatic fever. Chronic MS can result in LA dilatation. |

| **Continuous** | Continuous machine-like murmur. Loudest at S2. Often due to congenital rubella or prematurity. Best heard at left infraclavicular area. |
**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 Ca²⁺ 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** = inactivation of the Ca²⁺ 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 \( I_{Na} \) 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 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, 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 preexcitation 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)
- AntiCytotoxics (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>Atrial fibrillation</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></td>
</tr>
<tr>
<td>Atrial flutter</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></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.</td>
<td></td>
</tr>
</tbody>
</table>

AV block

| 1st degree | The PR interval is prolonged (> 200 msec). Benign and asymptomatic. No treatment required.                                                                 |                                |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|                                |

| 2nd degree |                                                                                                                                                                                                          |                                |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|                                |
| Mobitz type I (Wenckebach) | 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).                  |                                |
| Mobitz type II | 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.                                             |                                |
| 3rd degree (complete) | The atria and ventricles beat independently of each other. P waves and QRS complexes not rhythmically associated. Atrial rate > ventricular rate. Usually treated with pacemaker. Can be caused by Lyme disease. |                                |
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.

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 → vasoconstriction, ↓ 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.
- Contributes to Cushing reaction (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).

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>FACTORS DETERMINING AUTOREGULATION</th>
<th>Note: the pulmonary vasculature is unique in that 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: lactate, adenosine, K⁺, H⁺, CO₂</td>
<td>CO₂, H⁺, Adenosine, Lactate, K⁺ (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: 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

\[ J_v = K_f \left( P_c - P_i \right) - \zeta \left( \pi_c - \pi_i \right) \]

- \( J_v \) = net fluid flow
- \( K_f \) = permeability of capillary to fluid
- \( \zeta \) = permeability of capillary to protein

Edema—excess fluid outflow into interstitium commonly caused by:

* ↑ capillary pressure (↑ \( P_c \); e.g., HF)
* ↓ plasma proteins (↓ \( \pi_c \); e.g., nephrotic syndrome, liver failure, protein malnutrition)
* ↑ capillary permeability (↑ \( K_f \); e.g., toxins, infections, burns)
* ↑ interstitial fluid colloid osmotic pressure (↑ \( \pi_i \); e.g., lymphatic blockage)
### Congenital heart diseases

**RIGHT-TO-LEFT SHUNTS**

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
</table>
| 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.
  - Pulmonary infundibular stenosis (most important determinant for prognosis)
  - Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR
  - Overriding aorta
  - 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 and right HF. Can be caused by lithium exposure in utero.

![Diagram of congenital heart diseases](image-url)
### Congenital heart diseases (continued)

<table>
<thead>
<tr>
<th>LEFT-TO-RIGHT SHUNTS</th>
<th>Right-to-Left shunts: caRly cyanosis.</th>
<th>Left-to-Right shunts: “LateR” cyanosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late cyanosis (2° to Eisenmenger syndrome)—“blue kids.”</td>
<td>Frequency: VSD &gt; ASD &gt; PDA.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ventricular septal defect</th>
<th>O₂ saturation † in RV and pulmonary artery.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atrial septal defect</th>
<th>O₂ saturation † in RA, RV, and pulmonary artery.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect in interatrial septum [D]; loud S₁; wide, fixed split S₂. Ostium secundum defects most common and usually occur as isolated findings; ostium primum defects rarer yet 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.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patent ductus arteriosus</th>
<th>&quot;Endomethacin&quot; (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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 [E] can eventually result in late cyanosis in the lower extremities (differential cyanosis).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eisenmenger syndrome</th>
<th>“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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 [D], and polycythemia. Age of onset varies.</td>
<td></td>
</tr>
</tbody>
</table>

### 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</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 ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg

### Risk factors
- Age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, 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 disease (eg, fibromuscular dysplasia [“string of beads” appearance A], usually found in younger women) and 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 (eg, encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF; aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

### Predisposes to
- CAD, LVH, HF, AF; aortic dissection, aortic aneurysm; stroke; chronic kidney disease (hypertensive nephropathy) B; retinopathy.
<table>
<thead>
<tr>
<th>Hyperlipidemia signs</th>
<th></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 in hypercholesterolemia.</td>
</tr>
</tbody>
</table>

| Arteriosclerosis              | Hardening of arteries, with arterial wall thickening and loss of elasticity. |
| Arteriolosclerosis            | 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). |
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.

**RISK FACTORS**
Modifiable: smoking, hypertension, hyperlipidemia (↑ LDL), diabetes.
Nonmodifiable: 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.

**Thoracic aortic aneurysm**
Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also historically associated with 3° syphilis (obliterative endarteritis of the vasa vasorum).

**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 chest pain, of sudden onset, 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 descending aorta and/or aortic arch. No ascending aorta involvement. 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; exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin.
- Variant (Prinzmetal) — occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Known triggers include tobacco, cocaine, and triptans, but trigger is often unknown. 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); frequency or intensity of 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 and shunts blood toward well-perfused areas → ↓ flow and ischemia in poststenotic region. Principle behind pharmacologic stress tests.

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 implantable cardioverter-defibrillator (ICD).

Chronic ischemic heart disease

Progressive onset of HF over many years due to chronic ischemic myocardial damage.

Myocardial infarction

Most often acute thrombosis due to rupture of coronary artery atherosclerotic plaque. ↑ 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></td>
<td>Occluded artery</td>
<td>Dark mottling; pale with tetrazolium stain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infarct</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dark mottling; pale with tetrazolium stain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></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></td>
<td></td>
<td></td>
<td></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 → tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation. LV pseudoaneurysm (risk of rupture).</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></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>
<tr>
<td></td>
<td></td>
<td></td>
<td></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.

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>Cardiac arrhythmia</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>Postinfarction fibrinous pericarditis</td>
<td>Occurs 1–3 days after MI. Friction rub.</td>
</tr>
<tr>
<td>Papillary muscle rupture</td>
<td>Occurs 2–7 days after MI. Posteromedial papillary muscle rupture ↑ risk due to single blood supply from posterior descending artery. Can result in severe mitral regurgitation.</td>
</tr>
<tr>
<td>Interventricular septal rupture</td>
<td>Occurs 3–5 days after MI. Macrophage-mediated degradation → VSD.</td>
</tr>
<tr>
<td>Ventricular pseudoaneurysm formation</td>
<td>Occurs 3–14 days after MI. Contained free wall rupture ↓ CO, risk of arrhythmia, embolus from mural thrombus.</td>
</tr>
<tr>
<td>Ventricular free wall rupture</td>
<td>Occurs 5–14 days after MI. Free wall rupture → cardiac tamponade.</td>
</tr>
<tr>
<td>True ventricular aneurysm</td>
<td>Occurs 2 weeks to several months after MI. Outward bulge with contraction (“dyskinesia”), associated with fibrosis.</td>
</tr>
<tr>
<td>Dressler syndrome</td>
<td>Occurs several weeks after MI. Autoimmune phenomenon resulting in fibrinous pericarditis.</td>
</tr>
<tr>
<td>LV failure and pulmonary edema</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>Cardiomyopathy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dilated cardiomyopathy</strong></td>
<td>Most common cardiomyopathy (90% of cases). Often idiopathic or familial. Other etiologies include chronic alcohol abuse, wet beriberi, Coxsackie B viral myocarditis, chronic cocaine use, Chagas disease, doxorubicin toxicity, hemochromatosis, sarcoidosis, peripartum cardiomyopathy. Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR. Treatment: Na+ restriction, ACE inhibitors, β-blockers, diuretics, digoxin, ICD, heart transplant.</td>
</tr>
<tr>
<td><strong>Hypertrophic cardiomyopathy</strong></td>
<td>60–70% of cases are familial, autosomal dominant (commonly a β-myosin heavy-chain mutation). Can be associated with Friedreich ataxia. Causes syncope during exercise and may lead to sudden death 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>
</tr>
<tr>
<td><strong>Restrictive/infiltrative cardiomyopathy</strong></td>
<td>Major causes include sarcoidosis, amyloidosis, postradiation fibrosis, endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Löffler syndrome (endomyocardial fibrosis with a prominent eosinophilic infiltrate), and hemochromatosis (although dilated cardiomyopathy is more common).</td>
</tr>
</tbody>
</table>
Heart failure

Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include 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 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>CAUSE</th>
<th>SKIN</th>
<th>PCWP (PRELOAD)</th>
<th>CO</th>
<th>SVR (AFTERLOAD)</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic Hemorrhage, dehydratio,n burns</td>
<td>Cold, clammy</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>IV fluids</td>
</tr>
<tr>
<td>Cardiogenic Acute MI, HF, valvular dysfunction, arrhythmia</td>
<td>Cold, clammy</td>
<td>↑</td>
<td>↓↓</td>
<td>↑</td>
<td>Inotropes, diuresis</td>
</tr>
<tr>
<td>Obstructive Cardiac tamponade, pulmonary embolism</td>
<td>Cold, clammy</td>
<td>↑</td>
<td>↓↓</td>
<td>↑</td>
<td>Relieve obstruction</td>
</tr>
<tr>
<td>Distributive Sepsis, anaphylaxis, CNS injury</td>
<td>Warm, Dry</td>
<td>↓</td>
<td>↑</td>
<td>↓↓</td>
<td>IV fluids, pressors</td>
</tr>
</tbody>
</table>
Bacterial endocarditis

Fever (most common symptom), new murmur, Roth spots (round white spots on retina surrounded by hemorrhage), Osler nodes (tender raised lesions on finger or toe pads), Janeway lesions (small, painless, erythematous lesions on palm or sole), glomerulonephritis, septic arterial or pulmonary emboli, splinter hemorrhages on nail bed. Multiple blood cultures necessary for diagnosis.

* Acute—S aureus (high virulence).
  Large vegetations on previously normal valves. Rapid onset.

S bovis (gallolyticus) is present in colon cancer, S epidermidis on prosthetic valves. Endocarditis may also be nonbacterial (marantic/thrombotic) to malignancy, hypercoagulable state, or lupus.

Mitrval 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.

Culture —most likely Coxiella burnetii, Bartonella spp., HACEK (Haemophilus, Aggregatibacter (formerly Actinobacillus), Cardiobacterium, Eikenella, Kingella)

♥ Bacteria FROM JANE ♥:
Fever
Roth spots
Osler nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhage
Emboli

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.

Culture —most likely Coxiella burnetii, Bartonella spp., HACEK (Haemophilus, Aggregatibacter (formerly Actinobacillus), Cardiobacterium, Eikenella, Kingella)

♥ Bacteria FROM JANE ♥:
Fever
Roth spots
Osler nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhage
Emboli
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.

**Acute pericarditis**

Inflammation of the pericardium [A, arrows]. Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [white arrow 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), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

**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 and ascending aortic arch. Leads to “tree bark” appearance of aorta. Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.
Cardiac tumors: Most common heart tumor is a metastasis.

Myxomas: Most common 1st cardiac tumor in adults. 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 hear early diastolic “tumor plop” sound.

Rhabdomyomas: Most frequent 1st cardiac tumor in children (associated with tuberous sclerosis).

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 venae cavae → JVD. May be seen with constrictive pericarditis, restrictive cardiomyopathies, right atrial or ventricular tumors.
## Vasculitides

<table>
<thead>
<tr>
<th>Large-vessel vasculitis</th>
<th>Pathology/Labs</th>
</tr>
</thead>
<tbody>
<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. 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. “Pulseless disease” (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances. Granulomatous thickening and narrowing of aortic arch and proximal great vessels. ↑ ESR. Treat with corticosteroids.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medium-vessel vasculitis</th>
<th></th>
</tr>
</thead>
<tbody>
<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. CRASH and burn. 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. Segmental thrombosing vasculitis. Treat with smoking cessation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Small-vessel vasculitis</th>
<th></th>
</tr>
</thead>
<tbody>
<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. No granulomas. MPO-ANCA/p-ANCA (anti-myeloperoxidase). Treat with cyclophosphamide, corticosteroids.</td>
</tr>
</tbody>
</table>
### Vasculitides (continued)

<table>
<thead>
<tr>
<th>Small-vessel vasculitis (continued)</th>
<th>Epidemiology/Presentation</th>
<th>Pathology/Labs</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td><strong>Henoch-Schönlein purpura</strong></td>
<td>Most common childhood systemic vasculitis. Often follows URI. Classic triad: * Skin: palpable purpura on buttocks/legs * Arthralgias * GI: abdominal pain</td>
<td>Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease).</td>
</tr>
</tbody>
</table>

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![Images related to vasculitides](image-url)
### Hypertension Treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (essential) hypertension</td>
<td>Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca&lt;sup&gt;2+&lt;/sup&gt; channel blockers.</td>
</tr>
</tbody>
</table>
| Hypertension with heart failure  | Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists.  
|                                  | β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock. |
| Hypertension with diabetes mellitus | ACE inhibitors/ARBs, Ca<sup>2+</sup> channel blockers, thiazide diuretics, β-blockers.  
|                                  | ACE inhibitors/ARBs are protective against diabetic nephropathy. |
| Hypertension in pregnancy        | Hydralazine, labetalol, methyldopa, nifedipine. |

### Calcium Channel Blockers

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Clinical Use</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| 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). | Dihydropyridines (except nimodipine): hypertension, angina (including Prinzmetal), Raynaud phenomenon.  
Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).  
Clevidipine: hypertensive urgency or emergency.  
Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter. | Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia, constipation.  
Dihydropyridine: peripheral edema, flushing, dizziness, gingival hyperplasia. |

### Hydralazine

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Clinical Use</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>

### Hypertensive Emergency

Drugs include clevidipine, fenoldopam, labetalol, nicardipine, nitroprusside.

**Nitroprusside**

Short acting; ↑ cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide).

**Fenoldopam**

Dopamine D<sub>1</sub> receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. ↓ BP, ↑ natriuresis. Also used postoperatively as an antihypertensive. Can cause hypotension and tachycardia.
**Nitrogen**
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.

**Antianginal Therapy**
Goal is reduction of myocardial O₂ consumption (MVO₂) by ↓ 1 or more of the determinants of MVO₂: 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>MVO₂</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Verapamil is similar to β-blockers in effect. Pindolol and acebutolol—partial β-agonists contraindicated in angina.

**Ranolazine**
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.
### 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>HMG-CoA reductase inhibitors</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>(eg, lovastatin, pravastatin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid resins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine, colestipol, colesvelam</td>
<td></td>
<td></td>
<td></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>Ezetimibe</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>Fibrates</td>
<td></td>
<td></td>
<td></td>
<td>Upregulate LPL — ↑ TG clearance</td>
<td>Myopathy (↑ risk with statins), cholesterol gallstones</td>
</tr>
<tr>
<td>Gemfibrozil, bezafibrate, fenofibrate</td>
<td></td>
<td></td>
<td></td>
<td>Activates PPAR-α to induce HDL synthesis</td>
<td></td>
</tr>
<tr>
<td>Niacin (vitamin B₃)</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>
</tbody>
</table>

---

**Liver**
- Acetyl CoA → HMG-CoA
- HMG-CoA reductase
- Mevalonate
- Triacylglyceride
- Cholesterol
- LDL receptor
- HDL receptor
- Apo E receptor

**Blood**
- CHY
- LPL
- FFA
- HDL pool
- VLDL pool
- LDL
- HDL
- Apo E
- Lysosomes
- Lipolysis
- Adipose tissue
- HDL receptor
- LDL receptor
- LDL rem

**Enterocyte**
- CHY
- LPL
- FFA
- Lipolysis
- Fibrates (gemfibrozil, bezafibrate, fenofibrate)

**Intestinal lumen**
- Bile acid resins (cholestyramine, colestipol, colesvelam)
- Cholesterol
- FFA
- Bile acids

**ADIPOSE LIPOLYSIS**
- Niacin

---

**MEVALONATE SYNTHESIS**
- Statins (lovastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin)

---

**CHOLESTEROL ABSORPTION**
- Ezetimibe

---

**BILE ACID REABSORPTION**
### Cardiac glycosides

**Digoxin.**

**MECHANISM**

- Direct inhibition of Na⁺/K⁺ ATPase
- Indirect inhibition of Na⁺/Ca²⁺ exchanger.
- ↑ [Ca²⁺]ᵢ → positive inotropy. Stimulates vagus nerve → ↓ HR.

**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, Mg²⁺.
**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]).

<table>
<thead>
<tr>
<th><strong>Class IA</strong></th>
<th>Quinidine, Procainamide, Disopyramide. “The Queen Proclaims Diso’s pyramid.”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), heart failure (disopyramide), thrombocytopenia, torsades de pointes due to ↑ QT interval.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Class IB</strong></th>
<th>Lidocaine, Mexiletine. “I’d Buy Liddy’s Mexican Tacos.”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>↑ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue. Phenytoin can also fall into the IB category.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias. IB is Best post-MI.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>CNS stimulation/depression, cardiovascular depression.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Class IC</strong></th>
<th>Flecainide, Propafenone. “Can I have Fries, Please.”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>SVTs, including atrial fibrillation. Only as a last resort in refractory VT.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Proarrhythmic, especially post-MI (contraindicated). IC is Contraindicated in structural and ischemic heart disease.</td>
</tr>
</tbody>
</table>
**Antiarrhythmics—β-blockers (class II)**

**Mechanism**
Decrease SA and AV nodal activity by ↑ cAMP, ↑ Ca²⁺ 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.

---

**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/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.

**MECHANISM**

- ↓ conduction velocity,
- ↑ ERP,
- ↑ PR interval.

**CLINICAL USE**

Prevention of nodal arrhythmias (eg, SVT), rate control in atrial fibrillation.

**ADVERSE EFFECTS**

Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).

---

**Other antiarrhythmics**

**Adenosine**

- ↑ K⁺ out of cells → hyperpolarizing the cell and ↓ I\(_{\text{Ca}}\). 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.

**Mg\(^{2+}\)**

Effective in torsades de pointes and digoxin toxicity.
Endocrine

“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*
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 tissue is derived from endoderm. Parafollicular cells (aka, C cells) of the thyroid are derived from neural crest.

Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

<table>
<thead>
<tr>
<th>ANATOMY</th>
<th>PRIMARY REGULATORY CONTROL</th>
<th>SECRETORY PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zona Glomerulosa</td>
<td>Renin-angiotensin</td>
<td>Aldosterone</td>
</tr>
<tr>
<td>Zona Fasciculata</td>
<td>ACTH, CRH</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Zona Reticularis</td>
<td>ACTH, CRH</td>
<td>Sex hormones (eg, androgens)</td>
</tr>
<tr>
<td>MEDULLA</td>
<td>Preganglionic sympathetic fibers</td>
<td>Catecholamines (epinephrine, norepinephrine)</td>
</tr>
</tbody>
</table>

GFR corresponds with Salt (Na⁺), 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. 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 and MSH are derivatives of proopiomelanocortin (POMC).

**FLAT Fg:** 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.

**SOURCE**
Released from pancreatic β cells.

**FUNCTION**
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.

**Insulin-dependent glucose transporters:**
- GLUT-4: adipose tissue, striated muscle (exercise can also increase GLUT-4 expression)
- GLUT-1: RBCs, brain, cornea, placenta
- GLUT-2 (bidirectional): β islet cells, liver, kidney, small intestine
- GLUT-3: brain, placenta
- GLUT-5 (fructose): spermatocytes, GI tract

Brain utilizes glucose for metabolism normally and ketone bodies during starvation. RBCs always utilize glucose because they lack mitochondria for aerobic metabolism.

**BRICK L** (insulin-independent glucose uptake): Brain, RBCs, Intestine, Cornea, Kidney, Liver.

**REGULATION**
Glucose is the major regulator of insulin release. ↑ insulin response with oral vs IV glucose because of incretins such as glucagon-like peptide 1 (GLP-1), which are released after meals and ↑ β cell sensitivity to glucose.

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 7 → Ca2+ influx and stimulation of insulin exocytosis 8.
Glucagon

**SOURCE**
Made by α cells of pancreas.

**FUNCTION**
Catabolic effects of glucagon:
- Glycogenolysis, gluconeogenesis
- Lipolysis and ketone production

**REGULATION**
Secrected 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>CRH</td>
<td>↑ ACTH, MSH, β-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>GnRH</td>
<td>↑ FSH, LH</td>
<td>Suppressed by hyperprolactinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonic GnRH suppresses HPG axis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulsatile GnRH leads to puberty, fertility</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></td>
</tr>
</tbody>
</table>

...
**Prolactin**

**SOURCE**
- Secreted mainly by anterior pituitary.
- Structurally homologous to growth hormone.

**FUNCTION**
- Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release.
- Excessive amounts of prolactin associated with ↓ libido.

**REGULATION**
- Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (eg, in 1° or 2° hypothyroidism).
- Dopamine agonists (eg, bromocriptine) inhibit prolactin secretion and can be used in treatment of prolactinoma.
- Dopamine antagonists (eg, most antipsychotics) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion.

---

*Image of a diagram showing the regulation of prolactin levels with various factors influencing its secretion and action.*
### Growth hormone (somatotropin)

<table>
<thead>
<tr>
<th>Source</th>
<th>Secreted by anterior pituitary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).</td>
</tr>
<tr>
<td>Regulation</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treat with somatostatin analogs (eg, octreotide) or surgery.</td>
</tr>
</tbody>
</table>

### 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 hungre.**

**Leptin**

- Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → congenital obesity. Sleep deprivation or starvation → ↓ leptin production.
- **Leptin keeps you thin.**

**Endocannabinoids**

- Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.
- **The munchies.**

### Antidiuretic hormone

<table>
<thead>
<tr>
<th>Source</th>
<th>Synthesized in hypothalamus (supraoptic nuclei), stored and secreted by posterior pituitary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Regulates serum osmolarity (V₂-receptors) and blood pressure (V₁-receptors). Primary function is serum osmolarity regulation (ADH ↑ serum osmolarity, ↑ urine osmolarity) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.</td>
</tr>
<tr>
<td></td>
<td>ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI.</td>
</tr>
<tr>
<td></td>
<td>Nephrogenic DI can be caused by mutation in V₂-receptor.</td>
</tr>
<tr>
<td></td>
<td>Desmopressin acetate (ADH analog) is a treatment for central DI and nocturnal enuresis.</td>
</tr>
<tr>
<td>Regulation</td>
<td>Osmoreceptors in hypothalamus; hypovolemia.</td>
</tr>
</tbody>
</table>
Adrenal steroids and congenital adrenal hyperplasias

**A** 17α-hydroxylase

- **Enzyme Deficiency:** 17α-hydroxylase
- **Mineralocorticoids:** ±
- **Cortisol:** ↓
- **Sex Hormones:** ↓
- **BP:** ↑
- **[K+]:** ↓
- **Labs:** androstenedione
- **Presentation:** XY: ambiguous genitalia, undescended testes. XX: lacks 2° sexual development.

**B** 21-hydroxylase

- **Enzyme Deficiency:** 21-hydroxylase
- **Mineralocorticoids:** ↓
- **Cortisol:** ↓
- **Sex Hormones:** ↑
- **BP:** ↑
- **[K+]:** ↑
- **Labs:** renin activity, 17-hydroxyprogesterone
- **Presentation:** Most common. Presents in infancy (salt wasting) or childhood (precocious puberty). XX: virilization.

**C** 11β-hydroxylase

- **Enzyme Deficiency:** 11β-hydroxylase
- **Mineralocorticoids:** ↓
- **Cortisol:** ↓
- **Sex Hormones:** ↑
- **BP:** ↑
- **[K+]:** ↓
- **Labs:** renin activity
- **Presentation:** XX: virilization.

*All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands due to ↑ ACTH stimulation (in response to ↓ cortisol).*
### Cortisol

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th><strong>FUNCTION</strong></th>
<th><strong>REGULATION</strong></th>
</tr>
</thead>
</table>
| Adrenal zona fasciculata. | † Blood pressure:  
   - Upregulates α₁-receptors on arterioles  
     → † sensitivity to norepinephrine and epinephrine  
   - At high concentrations, can bind to mineralocorticoid (aldosterone) receptors | CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol → CRH, ACTH, and cortisol secretion. |
| Bound to corticosteroid-binding globulin. | † Insulin resistance (diabetogenic)  
   † Gluconeogenesis, lipolysis, and proteolysis  
   † Fibroblast activity (causes striae)  
   † Inflammatory and Immune responses:  
     - Inhibits production of leukotrienes and prostaglandins  
     - Inhibits WBC adhesion → neutrophilia  
     - Blocks histamine release from mast cells  
     - Reduces eosinophils  
     - Blocks IL-2 production  
   † Bone formation († osteoblast activity) | Chronic stress induces prolonged secretion. |
| **Calcium homeostasis** | Plasma Ca\(^{2+}\) exists in three forms:  
   - Ionized (~ 45%)  
   - Bound to albumin (~ 40%)  
   - Bound to anions (~ 15%) | † in pH → † affinity of albumin († negative charge) to bind Ca\(^{2+}\) → hypocalcemia (cramps, pain, paresthesias, carpopedal spasm). |

### Vitamin D (cholecalciferol)

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th><strong>FUNCTION</strong></th>
<th><strong>REGULATION</strong></th>
</tr>
</thead>
</table>
| D\(_3\) from exposure of skin to sun, ingestion of fish and plants. D\(_2\) from ingestion of plants, fungi, yeasts. Both converted to 25-OH in liver and to 1,25-(OH)\(_2\) (active form) in kidney. | † absorption of dietary Ca\(^{2+}\) and PO\(_4\)\(^{3-}\). Enhances bone mineralization. | Deficiency → rickets in kids, osteomalacia in adults. Caused by malabsorption, † sunlight, poor diet, chronic kidney failure.  
24,25-(OH)\(_2\)D\(_3\) is an inactive form of vitamin D. PTH leads to † Ca\(^{2+}\) reabsorption and † PO\(_4\)\(^{3-}\) reabsorption in the kidney, whereas 1,25-(OH)\(_2\)D\(_3\) leads to † absorption of both Ca\(^{2+}\) and PO\(_4\)\(^{3-}\) in the gut. |
| **SOURCE** | **FUNCTION** | **REGULATION** |
| D\(_3\) from exposure of skin to sun, ingestion of fish and plants. D\(_2\) from ingestion of plants, fungi, yeasts. Both converted to 25-OH in liver and to 1,25-(OH)\(_2\) (active form) in kidney. | † absorption of dietary Ca\(^{2+}\) and PO\(_4\)\(^{3-}\). Enhances bone mineralization. | Deficiency → rickets in kids, osteomalacia in adults. Caused by malabsorption, † sunlight, poor diet, chronic kidney failure.  
24,25-(OH)\(_2\)D\(_3\) is an inactive form of vitamin D. PTH leads to † Ca\(^{2+}\) reabsorption and † PO\(_4\)\(^{3-}\) reabsorption in the kidney, whereas 1,25-(OH)\(_2\)D\(_3\) leads to † absorption of both Ca\(^{2+}\) and PO\(_4\)\(^{3-}\) in the gut. |

1,25-(OH)\(_2\) feedback inhibits its own 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.

**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.

PTH = Phosphate Trashig Hormone.

PTH-related peptide (PTHrP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma).
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 Ca^{2+} levels.

Thyroid hormones

(T\_3/T\_4)

Iodine-containing hormones that control the body's metabolic rate.

**SOURCE**
Follicles of thyroid. Most T\_3 formed in target tissues.

**FUNCTION**
Bone growth (synergism with GH)
CNS maturation
↑ β\_1 receptors in heart = ↑ CO, HR, SV, contractility
↑ basal metabolic rate via ↑ Na^+/K^-ATPase activity → ↑ O_2 consumption, RR, body temperature
↑ glycogenolysis, gluconeogenesis, lipolysis

**REGULATION**
TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. May also be stimulated by thyroid-stimulating immunoglobulin (TSI) in Graves disease. Negative feedback by free T\_3, T\_4 to anterior pituitary ↓ sensitivity to TRH. Wolff-Chaikoff effect—excess iodine temporarily inhibits thyroid peroxidase → ↓ iodine organification → ↓ T\_3/T\_4 production.

T\_3 functions—4 B's:
- Brain maturation
- Bone growth
- β-adrenergic effects
- Basal metabolic rate ↑

Thyroxine-binding globulin (TBG) binds most T\_3/T\_4 in blood; only free hormone is active. ↓ TBG in hepatic failure, steroids; ↑ TBG in pregnancy or OCP use (estrogen ↑ TBG).

T\_4 is major thyroid product; converted to T\_3 in peripheral tissue by 5'-deiodinase.

T\_3 binds nuclear receptor with greater affinity than T\_4.

Thyroid peroxidase is the enzyme responsible for oxidation and organification of iodide as well as coupling of monoiodotyrosine (MIT) and di-iodotyrosine (DIT). DIT + DIT = T\_4; DIT + MIT = T\_3.

Propylthiouracil inhibits both thyroid peroxidase and 5'-deiodinase. Methimazole inhibits thyroid peroxidase only.
### Signaling pathways of endocrine hormones

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Hormones</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>cAMP</td>
<td>FSH, LH, ACTH, TSH, CRH, hCG, ADH, MSH, PTH, calcitonin, GHRH, glucagon</td>
<td>FLAT ChAMP</td>
</tr>
<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</td>
<td>Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T₃/T₄, Vitamin D</td>
<td>PET CAT on TV</td>
</tr>
<tr>
<td>Receptor tyrosine</td>
<td>Insulin, IGF-1, FGF, PDGF, EGF</td>
<td>MAP kinase pathway</td>
</tr>
<tr>
<td>kinase</td>
<td></td>
<td>Think growth factors</td>
</tr>
<tr>
<td>Nonreceptor</td>
<td>Prolactin, Immuneomodulators (eg, cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin</td>
<td>JAK/STAT pathway</td>
</tr>
<tr>
<td>tyrosine kinase</td>
<td></td>
<td>Think acidophils and cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIGGLET</td>
</tr>
</tbody>
</table>

### Signaling pathway 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**

† cortisol 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. Can also present with pseudohyperaldosteronism.
* 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 (thinning, striae), osteoporosis, hyperglycemia (insulin resistance), amenorrhea, immunosuppression.

**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 with a high-dose (8 mg) dexamethasone suppression test and CRH stimulation test. Ectopic secretion will not decrease with dexamethasone because the source is resistant to negative feedback; ectopic secretion will not increase with CRH because pituitary ACTH is suppressed.

---

**Diagram**

1. Measure ACTH
   - Suppressed
     - ACTH-independent Cushing syndrome
     - Exogenous glucocorticoids or adrenal tumor (consider MRI to confirm)
     - High-dose dexamethasone suppression test
     - Adequate suppression = Cushing disease
   - Elevated
     - ACTH-dependent Cushing syndrome
     - CRH stimulation test
     - ↑ ACTH, cortisol = ectopic ACTH secretion
     - No suppression = ectopic ACTH secretion
### 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 (hypovolemic volume contraction), hyperkalemia, metabolic acidosis, skin and mucosal hyperpigmentation (due to ↑ MSH, a byproduct of ACTH production from pro-opiomelanocortin [POMC]).

- **Acute**—sudden onset (e.g., due to massive hemorrhage). May present with shock in acute adrenal crisis.
- **Chronic**—aka 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).

### 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, ↓ or normal K⁺, metabolic alkalosis. No edema due to aldosterone escape mechanism.

### Primary hyperaldosteronism

Seen with adrenal adenoma (Conn syndrome) or idiopathic adrenal hyperplasia. ↑ aldosterone, ↓ renin.

### Secondary hyperaldosteronism

Seen in patients with renovascular hypertension, juxtaglomerular cell tumor (due to independent activation of renin-angiotensin-aldosterone system). ↑ aldosterone, ↑ renin.

### Primary pigments the skin/mucosa. Associated with autoimmune polyglandular syndromes.

### Waterhouse-Friderichsen syndrome

—acute 1° adrenal insufficiency due to adrenal hemorrhage associated with septicemia (usually Neisseria meningitidis), DIC, endotoxic shock.

### Secondary Spares the skin/mucosa.
Neuroendocrine tumors

Group of neoplasms originating from Kulchitsky and enterochromaffin-like cells. Occur in various organs (eg, thyroid: medullary carcinoma; lungs: small cell carcinoma; pancreas: islet cell tumor; adrenals: pheochromocytoma). Cells contain amine precursor uptake decarboxylase (APUD) and secrete different hormones (eg, 5-HIAA, neuron-specific enolase [NSE], chromogranin A).

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. 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).

Up to 25% of cases associated with germline mutations (eg, NF-1, VHL, RET [MEN 2A, 2B]).

**Rule of 10’s:**
- 10% malignant
- 10% bilateral
- 10% extra-adrenal
- 10% calcify
- 10% kids

#### Symptoms
Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension.

Symptoms occur in “spells”—relapse and remit.

**Episodic hyperadrenergic symptoms (5 P’s):**
- Pressure († BP)
- Pain (headache)
- Perspiration
- Palpitations (tachycardia)
- Pallor

#### Findings
† catecholamines and 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.

**Phenoxybenzamine** (16 letters) is given for pheochromocytoma (also 16 letters).
### Hypothyroidism vs hyperthyroidism

<table>
<thead>
<tr>
<th>Sign/Symptoms</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cold intolerance</strong> (heat production)</td>
<td>Heat intolerance (heat production)</td>
<td>Weight loss, appetite</td>
</tr>
<tr>
<td><strong>Weight gain, appetite</strong></td>
<td>Weight loss, appetite</td>
<td>Hyperactivity, anxiety, insomnia, hand tremor</td>
</tr>
<tr>
<td><strong>Hypothyroid myopathy</strong> (proximal muscle weakness, CK)</td>
<td>Thyrotoxic myopathy (proximal muscle weakness, normal CK)</td>
<td></td>
</tr>
<tr>
<td><strong>Myxedema</strong> (facial/periorbital)</td>
<td>Pretibial myxedema (Graves disease), periorbital edema</td>
<td></td>
</tr>
<tr>
<td><strong>Dry, cool skin; coarse, brittle hair</strong></td>
<td>Warm, moist skin; fine hair</td>
<td></td>
</tr>
<tr>
<td><strong>Bradycardia, dyspnea on exertion</strong></td>
<td>Chest pain, palpitations, arrhythmias, number and sensitivity of β-adrenergic receptors</td>
<td></td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong> (due to LDL receptor expression)</td>
<td>Hypocholesterolemia (due to LDL receptor expression)</td>
<td></td>
</tr>
</tbody>
</table>

### 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 adenoma</td>
<td>Thyroid cyst</td>
</tr>
</tbody>
</table>
### Hypothyroidism

**Hashimoto thyroiditis**  
Most common cause of hypothyroidism in iodine-sufficient regions; an autoimmune disorder with antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies. Associated with HLA-DR5. ↑ risk of non-Hodgkin lymphoma (typically of B-cell origin).  
May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture.  
Histologic findings: Hürthle cells, lymphoid aggregates with germinal centers.  
Findings: moderately enlarged, **nontender** thyroid.

**Congenital hypothyroidism (cretinism)**  
Severe fetal hypothyroidism due to maternal hypothyroidism, thyroid agenesis, thyroid dysgenesis (most common cause in US), iodine deficiency, dyshormonogenetic goiter.  

**Subacute granulomatous thyroiditis (de Quervain)**  
Self-limited disease often following a flu-like illness (eg, viral infection).  
May be hyperthyroid early in course, followed by hypothyroidism.  
Histology: granulomatous inflammation.  
Findings: ↑ ESR, jaw pain, very tender thyroid. (de Quervain is associated with pain.)

**Riedel thyroiditis**  
Thyroid replaced by fibrous tissue with inflammatory infiltrate.  
Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma.  
⅓ are hypothyroid.  
Considered a manifestation of IgG4-related systemic disease (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis).  
Findings: fixed, hard (rock-like), **painless** goiter.

**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 A. Often presents during stress (eg, pregnancy). Tall, crowded follicular epithelial cells; scalloped colloid B.

#### Toxic multinodular goiter
Focal patches of hyperfunctioning follicular cells C 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. Opposite of Wolff-Chaikoff effect.
**Thyroid adenoma**  
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).

**Thyroid cancer**  
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, respectively).

**Papillary carcinoma**  
Most common, excellent prognosis. Empty-appearing nuclei with central clearing (“Orphan Annie” eyes), psammoma bodies, nuclear grooves. Risk with RET and BRAF mutations, childhood irradiation.

**Follicular carcinoma**  
Good prognosis, invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with RAS mutation.

**Medullary carcinoma**  
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).

**Undifferentiated/anaplastic carcinoma**  
Older patients; invades local structures, very poor prognosis.

**Lymphoma**  
Associated with Hashimoto thyroiditis.
Hypoparathyroidism
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.

**Pseudohypoparathyroidism type 1A** (Albright hereditary osteodystrophy)—unresponsiveness of kidney to PTH → hypocalcemia despite ↑ PTH levels. Characterized by shortened 4th/5th digits, short stature. Autosomal dominant. Due to defective Gs protein α-subunit causing end-organ resistance to PTH. Defect must be inherited from mother due to imprinting.

**Pseudopseudohypoparathyroidism**—physical exam features of Albright hereditary osteodystrophy but without end-organ PTH resistance. Occurs when defective Gs protein α-subunit is inherited from father.

**Familial hypocalciuric hypercalcemia**
Defective Ca²⁺-sensing receptor (CaSR) in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca²⁺ levels required to suppress PTH. Excessive renal Ca²⁺ reuptake → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.
### Hyperparathyroidism

**Primary hyperparathyroidism**

Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal stones), hypophosphatemia, ↑PTH, ↑ALP, ↑cAMP in urine. Most often asymptomatic. May present with weakness and constipation ("groans"), abdominal/flank pain (kidney stones, acute pancreatitis), depression ("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). "Stones, bones, groans, and psychiatric overtones."

**Secondary hyperparathyroidism**

2° hyperplasia due to ↓Ca²⁺ absorption and/or ↑PO₄³⁻, most often in chronic renal disease (causes hypovitaminosis D → ↓Ca²⁺ absorption). **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, ↑Ca²⁺.

### Pituitary adenoma

Benign tumor, most commonly prolactinoma (arises from lactotrophs). Adenoma A may be functional (hormone producing) or nonfunctional (silent). Nonfunctional tumors present with mass effect (bitemporal hemianopia, hypopituitarism, headache). Functional tumor presentation is based on the hormone produced. Treatment for prolactinoma: dopamine agonists (eg, ergot alkaloids such as bromocriptine, cabergoline), transsphenoidal resection.

### 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**

<table>
<thead>
<tr>
<th>FINDINGS</th>
<th>Excess GH in adults. Typically caused by pituitary adenoma.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FINDINGS</td>
<td>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). ↑ risk of colorectal polyps and cancer.</td>
</tr>
</tbody>
</table>

| 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). |

**Laron syndrome (dwarfism)**

| FINDINGS          | Defective growth hormone receptors → ↓ linear growth. ↑ GH, ↓ IGF-1. Clinical features include 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></th>
<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>
<td>Hereditary (ADH receptor mutation), 2° to hypercalcemia, hypokalemia, lithium, demeclocycline (ADH antagonist)</td>
</tr>
<tr>
<td><strong>FINDINGS</strong></td>
<td>↑ ADH</td>
<td>Normal or ↑ ADH levels</td>
</tr>
<tr>
<td></td>
<td>Urine specific gravity &lt; 1.006</td>
<td>Urine specific gravity &lt; 1.006</td>
</tr>
<tr>
<td></td>
<td>Serum osmolality &gt; 290 mOsm/kg</td>
<td>Serum osmolality &gt; 290 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>Hyperosmotic volume contraction</td>
<td>Hyperosmotic volume contraction</td>
</tr>
<tr>
<td><strong>WATER DEPRIVATION TEST</strong></td>
<td>&gt; 50% ↑ in urine osmolality only after administration of ADH analog</td>
<td>Minimal change in urine osmolality, even after administration of ADH analog</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Desmopressin acetate</td>
<td>HCTZ, indomethacin, amiloride</td>
</tr>
<tr>
<td></td>
<td>Hydration</td>
<td>Hydration, avoidance of offending agent</td>
</tr>
</tbody>
</table>

*aNo water intake for 2–3 hr followed by hourly measurements of urine volume and osmolarity and plasma Na⁺ concentration and osmolarity. ADH analog (desmopressin acetate) is administered if serum osmolality > 295–300 mOsm/kg, plasma Na⁺ ≥ 145, 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↓ aldosterone and ↑ ANP and BNP
→ ↑ urinary Na⁺ secretion → normalization of extracellular fluid volume → 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).

Causes include:
- Ectopic ADH (eg, small cell lung cancer)
- CNS disorders/head trauma
- Pulmonary disease
- Drugs (eg, cyclophosphamide)

Treatment: fluid restriction, salt tablets, IV hypertonic saline, diuretics, conivaptan, tolvaptan, demeclocycline.
**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
- **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 coma (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 ↓ absent sorbitol dehydrogenase):
- Neuropathy (motor, sensory [glove and stocking distribution], and autonomic degeneration)
- Cataracts

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>TEST</th>
<th>DIAGNOSTIC CUTOFF</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>≥ 126 mg/dL</td>
<td>Fasting for &gt; 8 hours</td>
<td></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>
<td></td>
</tr>
</tbody>
</table>

**Insulin deficiency**

- ↓ tissue glucose uptake → Hyperglycemia, glycosuria
- ↑ glycolysis → ↑ glycogenolysis → ↑ gluconeogenesis
- ↓ proteolysis → ↑ proteolysis
- ↑ lipolysis

- ↑ plasma osmolality
- ↑ thirst
- Osmotic diuresis
- Loss of water, Na⁺, and K⁺
- Hypovolemia
- Circulation failure, ↓ tissue perfusion
- Coma/death

- ↓ protein, weight loss
- ↑ plasma free fatty acids

- ↑ ketogenesis, ketonemia, ketonuria
- Hyperventilation
- Anion gap metabolic acidosis
- ↑ serum lactate
### Type 1 vs Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Variable</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>Insulin Necessary in Treatment</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Age (Exceptions Commonly Occur)</td>
<td>&lt; 30 yr</td>
<td>&gt; 40 yr</td>
</tr>
<tr>
<td>Association with Obesity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Genetic Predisposition</td>
<td>Relatively weak (50% concordance in identical twins), polygenic</td>
<td>Relatively strong (90% concordance in identical twins), polygenic</td>
</tr>
<tr>
<td>Association with HLA System</td>
<td>Yes (HLA-DR3 and -DR4)</td>
<td>No</td>
</tr>
<tr>
<td>Glucose Intolerance</td>
<td>Severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Insulin Sensitivity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ketoadosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>β-Cell Numbers in the Islets</td>
<td>▼</td>
<td>Variable (with amyloid deposits)</td>
</tr>
<tr>
<td>Serum Insulin Level</td>
<td>▼</td>
<td>Variable</td>
</tr>
<tr>
<td>Classic Symptoms of Polyuria, Polydipsia, Polyphagia, Weight Loss</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 (therefore total body K⁺ is depleted).

**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 hyperglycemia nonketotic syndrome

State of profound hyperglycemia-induced dehydration and ↑ serum osmolarity, classically seen in elderly type 2 diabetics with limited ability to drink. Hyperglycemia → excessive osmotic diuresis → dehydration → eventual onset of HHNS. 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 osmolarity (> 320 mOsm/kg), no acidosis (pH > 7.3, 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. May present with diabetes/glucose intolerance, steatorrhea, gallstones. Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Carcinoid syndrome

Rare syndrome caused by carcinoid tumors (neuroendocrine cells, 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), ↑ 5-hydroxyindoleacetic acid (5-HIAA) in urine, niacin deficiency (pellagra). 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>
</table>
| **MEN 1** | Pituitary tumors (prolactin or GH)  
Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare)  
Parathyroid adenomas  
Associated with mutation of MEN1 (menin, a tumor suppressor, chromosome 11) |  |
| **MEN 2A** | Parathyroid hyperplasia  
Medullary thyroid carcinoma—neoplasm of parafollicular or C cells; secretes calcitonin; prophylactic thyroidectomy required  
Pheochromocytoma (secretes catecholamines)  
Associated with mutation in RET (codes for receptor tyrosine kinase) in cells of neural crest origin |  |
| **MEN 2B** | Medullary thyroid carcinoma  
Pheochromocytoma  
Mucosal neuromas (oral/intestinal ganglioneuromatosis)  
Associated with marfanoid habitus; mutation in RET gene |  |

MEN 1 = 3 P’s: Pituitary, Parathyroid, and Pancreas  
MEN 2A = 2 P’s: Parathyroids and Pheochromocytoma  
MEN 2B = 1 P: Pheochromocytoma
## ENDOCRINE—PHARMACOLOGY

### Diabetes mellitus drugs
Treatment strategies:
- **Type 1 DM**—low-carbohydrate diet, insulin replacement
- **Type 2 DM**—dietary modification and exercise for weight loss; oral agents, non-insulin injectables, insulin replacement
- **Gestational DM (GDM)**—dietary modifications, exercise, insulin replacement if lifestyle modification fails

<table>
<thead>
<tr>
<th>DRUG CLASSES</th>
<th>ACTION</th>
<th>CLINICAL USE</th>
<th>RISKS/CONCERNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin preparations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, rapid acting</strong></td>
<td>Binds insulin receptor (tyrosine kinase activity) rapidly, no LAG. Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen, protein synthesis; ↑ K⁺ uptake. Fat: ↑ TG storage.</td>
<td>Type 1 DM, type 2 DM, GDM (postprandial glucose control).</td>
<td>Hypoglycemia, lipodystrophy, rare hypersensitivity reactions.</td>
</tr>
<tr>
<td>Lispro, Aspart, Glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, short acting</strong></td>
<td></td>
<td>Type 1 DM, type 2 DM, GDM, DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, intermediate acting</strong></td>
<td></td>
<td>Type 1 DM, type 2 DM, GDM.</td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, long acting</strong></td>
<td></td>
<td>Type 1 DM, type 2 DM, GDM (basal glucose control).</td>
<td></td>
</tr>
<tr>
<td>Detemir, glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hypoglycemic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biguanides</strong></td>
<td>Exact mechanism unknown. ↓ gluconeogenesis, ↑ glycolysis, ↑ peripheral glucose uptake (↑ insulin sensitivity).</td>
<td>Oral. First-line therapy in type 2 DM, causes modest weight loss. Can be used in patients without islet function.</td>
<td>GI upset; most serious adverse effect is lactic acidosis (thus contraindicated in renal insufficiency).</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td>Close K⁺ channel in β-cell membrane → cell depolarizes → insulin release via ↑ Ca²⁺ influx.</td>
<td>Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.</td>
<td>Risk of hypoglycemia ↑ in renal failure, weight gain. First generation: disulfiram-like effects. Second generation: hypoglycemia.</td>
</tr>
<tr>
<td>First generation: chlorpropamide, tolbutamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second generation: glibenpiride, glipizide, glyburide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glitazones/thiazolidinediones</strong></td>
<td>↑ insulin sensitivity in peripheral tissue. Binds to PPAR-γ nuclear transcription regulator.</td>
<td>Used as monotherapy in type 2 DM or combined with above agents. Safe to use in renal impairment.</td>
<td>Weight gain, edema. Hepatotoxicity, HF, ↑ risk of fractures.</td>
</tr>
<tr>
<td>Pioglitazone, rosiglitazone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Diabetes mellitus drugs (continued)

#### Oral hypoglycemic drugs (continued)

<table>
<thead>
<tr>
<th><strong>Meglitinides</strong></th>
<th>Stimulate postprandial insulin release by binding to K+ channels on β-cell membranes (site differs from sulfonylureas).</th>
<th>Used as monotherapy in type 2 DM or combined with metformin.</th>
<th>Hypoglycemia ( ↑ risk with renal failure), weight gain.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nateglinide, repaglinide</strong></td>
<td>† glucose-dependent insulin release, ↓ glucagon release, ↓ gastric emptying, ↑ satiety.</td>
<td>Type 2 DM.</td>
<td>Nausea, vomiting, pancreatitis; modest weight loss.</td>
</tr>
<tr>
<td><strong>GLP-1 analogs</strong></td>
<td>Inhibits DPP-4 enzyme that deactivates GLP-1, thereby ↑ glucose-dependent insulin release, ↑ glucagon release, ↓ gastric emptying, ↑ satiety.</td>
<td>Type 2 DM.</td>
<td>Mild urinary or respiratory infections; weight neutral.</td>
</tr>
<tr>
<td><strong>Exenatide, liraglutide (sc injection)</strong></td>
<td>Block reabsorption of glucose in PCT.</td>
<td>Type 2 DM.</td>
<td>Glucosuria, UTIs, vaginal yeast infections, hyperkalemia, dehydration (orthostatic hypotension).</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td>Inhibit intestinal brush-border α-glucosidases. Delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.</td>
<td>Type 2 DM.</td>
<td>GI disturbances.</td>
</tr>
<tr>
<td><strong>Linagliptin, saxagliptin, sitagliptin</strong></td>
<td>Propylthiouracil (PTU), methimazole.</td>
<td>Block thyroid peroxidase, inhibiting the oxidation of iodide and the organification (coupling) of iodine → inhibition of thyroid hormone synthesis. Propylthiouracil also blocks 5′-deiodinase → ↓ peripheral conversion of T4 to T3.</td>
<td>Hyperthyroidism. PTU blocks Peripheral conversion and is used in Pregnancy.</td>
</tr>
<tr>
<td><strong>Thionamides</strong></td>
<td>Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity. Methimazole is a possible teratogen (can cause aplasia cutis).</td>
<td>Thyroid hormone replacement.</td>
<td>Hypothyroidism, myxedema. Used off-label as weight loss supplements.</td>
</tr>
<tr>
<td><strong>Levothyroxine (T4), triiodothyronine (T3)</strong></td>
<td>Tachycardia, heat intolerance, tremors, arrhythmias.</td>
<td>Thyroid hormone replacement.</td>
<td>Hypothyroidism, myxedema. Used off-label as weight loss supplements.</td>
</tr>
</tbody>
</table>
### 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 acetate</td>
<td>Central (not nephrogenic) DI.</td>
</tr>
<tr>
<td>GH</td>
<td>GH deficiency, Turner syndrome.</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Stimulates labor, uterine contractions, milk let-down; 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>

### Glucocorticoids

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Beclomethasone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, triamcinolone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Use</td>
<td>Metabolic, catabolic, anti-inflammatory, and immunosuppressive effects mediated by interactions with glucocorticoid response elements, inhibition of phospholipase A₂, and inhibition of transcription factors such as NF-κB.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Iatrogenic Cushing syndrome (hypertension, weight gain, moon facies, truncal obesity, buffalo hump, thinning of skin, striae, acne, osteoporosis, hyperglycemia, amenorrhea, immunosuppression), adrenocortical atrophy, peptic ulcers, steroid diabetes, steroid psychosis, cataracts. Adrenal insufficiency when drug stopped abruptly after chronic use.</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>1° or 2° hyperparathyroidism.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Hypocalcemia.</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
Gastrointestinal—Embryology

**Normal gastrointestinal embryology**
- Foregut—pharynx to duodenum.
- Midgut—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—sternal defects
  - Lateral fold closure—omphalocele, gastroschisis
  - Caudal fold closure—bladder extrophy

**Gastrochisis**—extrusion of abdominal contents through abdominal folds (typically right of umbilicus); not covered by peritoneum.

**Omphalocele**—persistence of herniation of abdominal contents into umbilical cord, sealed by peritoneum A.

**Tracheoesophageal anomalies**
Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%). Polyhydramnios in utero. Neonates drool, choke, and vomit with first feeding. TEF allows 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 the CXR shows gasless abdomen.

**Intestinal atresia**
- Presents with bilious vomiting and abdominal distension within first 1–2 days of life.
- *Duodenal atresia*—failure to recanalize → dilation of stomach and proximal duodenum (“double bubble” on x-ray A). Associated with Down syndrome.
- *Jejunal and ileal atresia*—disruption of mesenteric vessels → ischemic necrosis → segmental resorption (bowel discontinuity or “apple peel”).

---

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**Hypertrophic pyloric stenosis**

Most common cause of gastric outlet obstruction in infants (1:600). Palpable “olive” mass in epigastric region 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). 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**—ventral pancreatic bud abnormally encircles 2nd part of duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing and nonbilious 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**

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>Falciform</td>
<td>Liver to anterior abdominal wall</td>
<td>Ligamentum teres hepatis (derivative of fetal umbilical vein)</td>
<td>Derivative of ventral mesentery</td>
</tr>
<tr>
<td>Hepatoduodenal</td>
<td>Liver to duodenum</td>
<td>Portal triad: proper hepatic artery, portal vein, common bile duct</td>
<td>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.</td>
</tr>
<tr>
<td>Gastrohepatic</td>
<td>Liver to lesser curvature of stomach</td>
<td>Gastric arteries</td>
<td>Separates greater and lesser sacs on the right. May be cut during surgery to access lesser sac.</td>
</tr>
<tr>
<td>Gastrocolic (not shown)</td>
<td>Greater curvature and transverse colon</td>
<td>Gastroepiploic arteries</td>
<td>Part of greater omentum</td>
</tr>
<tr>
<td>Gastroplenic</td>
<td>Greater curvature and spleen</td>
<td>Short gastrics, left gastroepiploic vessels</td>
<td>Separates greater and lesser sacs on the left. Part of greater omentum</td>
</tr>
<tr>
<td>Splenorenal</td>
<td>Spleen to posterior abdominal wall</td>
<td>Splenic artery and vein, tail of pancreas</td>
<td></td>
</tr>
</tbody>
</table>
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><strong>Esophagus</strong></td>
<td>Nonkeratinized stratified squamous epithelium.</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>Gastric glands.</td>
</tr>
<tr>
<td><strong>Duodenum</strong></td>
<td>Villi and microvilli † absorptive surface. Brunner glands (HCO₃⁻-secreting cells of submucosa) and crypts of Lieberkühn.</td>
</tr>
<tr>
<td><strong>Jejunum</strong></td>
<td>Plicae circulares and crypts of Lieberkühn.</td>
</tr>
<tr>
<td><strong>Ileum</strong></td>
<td>Peyer 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><strong>Colon</strong></td>
<td>Crypts of Lieberkühn but no villi; abundant goblet cells.</td>
</tr>
</tbody>
</table>
Abdominal aorta and branches

Arteries supplying GI structures branch **anteriorly.** Arteries supplying non-GI structures branch **laterally** and **posteriorly.**

**Superior mesenteric artery syndrome**

Characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when transverse (third) portion of duodenum is compressed between SMA and aorta. Typically occurs in conditions associated with diminished mesenteric fat (e.g., low body weight/malnutrition).

**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><strong>Foregut</strong></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><strong>Midgut</strong></td>
<td>SMA</td>
<td>Vagus</td>
<td>L1</td>
<td>Distal duodenum to proximal 2/3 of transverse colon</td>
</tr>
<tr>
<td><strong>Hindgut</strong></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>
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
### Portosystemic anastomoses

**Diagram**

- Pathologic blood flow in portal HTN
- Flow through TIPS, re-establishing normal flow direction
- Normal venous drainage

<table>
<thead>
<tr>
<th>SITE OF ANASTOMOSIS</th>
<th>CLINICAL SIGN</th>
<th>PORTAL ↔ SYSTEMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Esophagus</td>
<td>Esophageal varices</td>
<td>Left gastric ↔ azygos</td>
</tr>
<tr>
<td>2 Umbilicus</td>
<td>Caput medusae</td>
<td>Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.</td>
</tr>
<tr>
<td>3 Rectum</td>
<td>Anorectal varices</td>
<td>Superior rectal ↔ middle and inferior rectal</td>
</tr>
</tbody>
</table>

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.
Pectinate (dentate) line

Formed where endoderm (hindgut) meets ectoderm.

**Above pectinate line**—internal hemorrhoids, adenocarcinoma.
Arterial supply from superior rectal artery (branch of IMA).
Venous drainage: superior rectal vein → inferior mesenteric vein → portal system.

Internal hemorrhoids receive visceral innervation and are therefore **not painful**.
Lymphatic drainage to internal iliocanal nodes.

**Below pectinate line**—external hemorrhoids, anal fissures, squamous cell carcinoma.
Arterial supply from inferior rectal artery (branch of internal pudendal artery).
Venous drainage: inferior rectal vein → internal pudendal vein → common iliac vein → common iliac vein → IVC.

External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed.
Lymphatic drainage to superficial inguinal nodes.

**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.
Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids. Kupffer cells, which are specialized macrophages, form the lining of these sinusoids (black arrows in A; yellow arrow shows hepatic venule). Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated).

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
- Contains cytochrome P-450 system
- Most sensitive to metabolic toxins
- Site of alcoholic hepatitis
Gallstones (filling defects, red arrows in A) 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 ➔ painless jaundice.

**Femoral region**

<table>
<thead>
<tr>
<th>Organ</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. | |

**Gastrointestinal**

**Gastrointestinal—Anatomy**

**SECTION III** 347
Inguinal canal

- Parietal peritoneum
- Extrapitoneal 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
- Inferior epigastric vessels
- Abdominal wall site of protrusion of direct hernia
- Medial umbilical ligament
- Median 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)
- External spermatic fascia (external oblique)
### Hernias

A 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 pleuropitoneal membrane or as a result of 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** is most common. Gastroesophageal junction is displaced upward; “hourglass stomach.”

**Paraesophageal hernia**—gastroesophageal junction is usually normal. 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. Occurs in infants owing to failure of processus vaginalis to close (can form hydrocele). Much more common in males.

An indirect inguinal hernia follows the path of descent of the testes. Covered by all 3 layers of spermatic fascia.

#### Direct inguinal hernia

Protrudes through the inguinal (Hesselbach) triangle. Bulges directly through abdominal wall medial to inferior epigastric vessels. Goes through the external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually in older men.

MDs don’t LIE:

- Medial to inferior epigastric vessels = **Direct hernia**.
- Lateral to inferior epigastric vessels = **Indirect hernia**.

#### Femoral hernia

Protrudes below inguinal ligament through femoral canal below and lateral to pubic tuber. More common in **females**.

More likely to present with incarceration or strangulation than inguinal hernias.

**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>Gastrin</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 Zollinger-Ellison syndrome (gastrinoma).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ growth of gastric mucosa</td>
<td>by pH &lt; 1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ gastric motility</td>
<td>by chronic PPI use. ↓ in Zollinger-Ellison syndrome (gastrinoma).</td>
<td></td>
</tr>
<tr>
<td>Somatostatin</td>
<td>D cells (pancreatic islets, GI mucosa)</td>
<td>↓ gastric acid and pepsinogen secretion</td>
<td>by acid</td>
<td>Inhibits secretion of various hormones (encourages somato-stasis). Octreotide is an analog used to treat acromegaly, carcinoid syndrome, and variceal bleeding.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ pancreatic and small intestine fluid secretion</td>
<td>↓ by vagal stimulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ gallbladder contraction</td>
<td>↓ by pH &lt; 1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ insulin and glucagon release</td>
<td>↓ by chronic PPI use. ↓ in Zollinger-Ellison syndrome (gastrinoma).</td>
<td></td>
</tr>
<tr>
<td>Cholecystokinin</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></td>
<td></td>
<td>↑ gallbladder contraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ gastric emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ sphincter of Oddi relaxation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretin</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>Glucose-dependent insulinotropic peptide</td>
<td>K cells (duodenum, jejunum)</td>
<td>Exocrine: ↓ gastric H⁺ secretion</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></td>
<td></td>
<td>Endocrine: ↑ insulin release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motilin</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>Vasoactive intestinal polypeptide</td>
<td>Parasympathetic ganglia in sphincters, gallbladder, small intestine</td>
<td>↑ intestinal water and electrolyte secretion</td>
<td>by distention and vagal stimulation</td>
<td>VIPoma — non-α, non-β islet cell pancreatic tumor that secretes VIP. Watery Diarrhea, Hypokalemia, and Achlorhydria (WDHA syndrome).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ relaxation of intestinal smooth muscle and sphincters</td>
<td>↓ by adrenergic input</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
<td>↑ smooth muscle relaxation, including lower esophageal sphincter (LES)</td>
<td></td>
<td>Loss of NO secretion is implicated in ↑ LES tone of achalasia.</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Stomach</td>
<td>↑ appetite</td>
<td>in fasting state</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>Intrinsic factor</td>
<td>Parietal cells (stomach)</td>
<td>Vitamin B₁₂–binding protein (required for B₁₂ uptake in terminal ileum)</td>
<td>Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.</td>
<td></td>
</tr>
<tr>
<td>Gastric acid</td>
<td>Parietal cells (stomach)</td>
<td>↓ stomach pH</td>
<td>↑ by histamine, ACh, gastrin, ↓ by somatostatin, GIP, prostaglandin, secretin</td>
<td></td>
</tr>
<tr>
<td>Pepsin</td>
<td>Chief cells (stomach)</td>
<td>Protein digestion</td>
<td>↑ by vagal stimulation, local acid</td>
<td>Pepsinogen (inactive) is converted to pepsin (active) in the presence of H⁺.</td>
</tr>
<tr>
<td>Bicarbonate</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>

Locations of gastrointestinal secretory cells

Gastrin ↑ 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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secreted as proenzymes also known as zymogens</td>
</tr>
<tr>
<td>Trypsinogen</td>
<td>Converted to active enzyme trypsin</td>
<td>Activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop)</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 by facilitated diffusion by GLUT-5. All are transported to blood by GLUT-2.

D-xylene absorption test: distinguishes GI mucosal damage from other causes of malabsorption.

Vitamin/mineral absorption

- **Iron**
  - Absorbed as Fe²⁺ in duodenum.
  - Iron Fist, Bro
  - Clinically relevant in patients with small bowel disease or after resection.

- **Folate**
  - Absorbed in small bowel.

- **B₁₂**
  - Absorbed in terminal ileum along with bile salts, requires intrinsic factor.

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 only means of eliminating cholesterol)
- Antimicrobial activity (via membrane disruption)
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 glucurionate, and excreted in bile.

Direct bilirubin—conjugated with glucuronic acid; water soluble.
Indirect bilirubin—unconjugated; water insoluble.

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.
- Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous components.
- Warthin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers.
**Achalasia**

Failure of relaxation of LES due to loss of myenteric (Auerbach) plexus. High LES resting pressure and uncoordinated or absent peristalsis → progressive dysphagia to solids and liquids (vs obstruction—solids only). Barium swallow shows dilated esophagus with an area of distal stenosis. Associated with ↑ risk of esophageal cancer, especially squamous cell carcinoma.

*A-chalasia* = absence of relaxation.

“Bird’s beak” on barium swallow A. 2° achalasia 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>Boerhaave syndrome</td>
<td>Transmural, usually distal esophageal rupture with pneumomediastinum (arrows in A) due to violent retching; surgical emergency.</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</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. Unresponsive to GERD therapy.</td>
</tr>
<tr>
<td>Esophageal strictures</td>
<td>Associated with caustic ingestion and acid reflux.</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>Dilated submucosal veins B C in lower 1/3 of esophagus 2° to portal hypertension. Common in cirrhotics, may be source of life-threatening hematemesis.</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Associated with reflux, infection in immunocompromised (<em>Candida</em>: white pseudomembrane; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or medications.</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</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>Mallory-Weiss syndrome</td>
<td>Mucosal lacerations at the gastroesophageal junction due to severe vomiting. Leads to hematemesis that can be painful. Usually found in alcoholics and bulimics.</td>
</tr>
<tr>
<td>Plummer-Vinson syndrome</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>Scleroderma esophageal dysmotility</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>
Specialized intestinal metaplasia A—replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [stained blue in B]) in distal esophagus. Due to chronic reflux esophagitis (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).

**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.
  Affects antrum first and spreads to body of stomach.

- **Autoimmune**
  Autoantibodies to parietal cells and intrinsic factor. ↑ risk of pernicious anemia.
  Affects body/fundus of stomach.

**Ménétrier disease**
Gastric hyperplasia of mucosa → hypertrophied rugae (looking like brain gyri), excess mucus production with resultant protein loss and parietal cell atrophy with ↓ acid production. Precancerous.

**Gastric cancer**
Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign.
- **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 (linitis plastica).

Virchow node — involvement of left supraclavicular 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 be Greater 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 A with referred pain to the shoulder via phrenic nerve.
### Malabsorption syndromes

Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies. Screen for fecal fat (eg, Sudan stain).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Diagnosis and Treatment</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) → malabsorption and steatorrhea. Associated with HLA-DQ2, HLA-DQ8, northern European descent, dermatitis herpetiformis, ↓ bone density. Findings: IgA anti-tissue transglutaminase, anti-endomysial, anti-deamidated gliadin peptide antibodies; villous atrophy (arrow in A shows blunting), crypt hyperplasia (double arrows in A), and intraepithelial lymphocytosis. Moderately ↑ risk of malignancy (eg, T-cell lymphoma).</td>
<td>D-mucosal absorption primarily affects distal duodenum and/or proximal jejunum. D-xylene test: passively absorbed in proximal small intestine; blood and urine levels ↓ with mucosa defects or bacterial overgrowth, normal in pancreatic insufficiency. Treatment: gluten-free diet.</td>
</tr>
<tr>
<td><strong>Malabsorption</strong></td>
<td>Lactose intolerance Lactase deficiency. Normal-appearing villi, except when 2° to injury at tips of villi (eg, viral enteritis). Osmotic diarrhea with ↓ stool pH (colonic bacteria ferment lactose). Lactose hydrogen breath test: ⊖ for lactose malabsorption if postlactose breath hydrogen value rises &gt; 20 ppm compared with baseline.</td>
<td>D-duodenal pH (bicarbonate) and fecal elastase.</td>
</tr>
<tr>
<td><strong>Pancreatic insufficiency</strong></td>
<td>Due to chronic pancreatitis, cystic fibrosis, obstructing cancer. Causes malabsorption of fat and fat-soluble vitamins (A, D, E, K) as well as vitamin B₁₂.</td>
<td></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.</td>
<td>↑ 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 E mesenteric nodes. Cardiac symptoms, Arthralgias, and Neurologic symptoms are common. Most often occurs in older men.</td>
<td>Foamy Whipped cream in a CAN.</td>
</tr>
</tbody>
</table>
## Inflammatory bowel diseases

<table>
<thead>
<tr>
<th></th>
<th><strong>Crohn disease</strong></th>
<th><strong>Ulcerative colitis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOCATION</strong></td>
<td>Any portion of the GI tract, usually the terminal ileum and colon. Skip lesions, rectal sparing.</td>
<td>Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement.</td>
</tr>
<tr>
<td><strong>GROSS MORPHOLOGY</strong></td>
<td>Transmural inflammation → fistulas. Cobblestone mucosa, creeping fat, bowel wall thickening (“string sign” on barium swallow x-ray), linear ulcers, fissures.</td>
<td>Mucosal and submucosal inflammation only. Friable mucosal pseudopolyps (compare normal with diseased) with freely hanging mesentery. Loss of haustra → “lead pipe” appearance on imaging.</td>
</tr>
<tr>
<td><strong>MICROSCOPIC MORPHOLOGY</strong></td>
<td>Noncaseating granulomas and lymphoid aggregates.</td>
<td>Crypt abscesses and ulcers, bleeding, no granulomas.</td>
</tr>
<tr>
<td><strong>COMPLICATIONS</strong></td>
<td>Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis). Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.</td>
<td>Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis). Fulminant colitis, toxic megacolon, perforation.</td>
</tr>
<tr>
<td><strong>INTESTINAL MANIFESTATION</strong></td>
<td>Diarrhea that may or may not be bloody.</td>
<td>Bloody diarrhea.</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).</td>
<td>Kidney stones (usually calcium oxalate), gallstones. 1° sclerosing cholangitis. Associated with p-ANCA.</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), infliximab, adalimumab.</td>
<td>5-aminosalicylic preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.</td>
</tr>
</tbody>
</table>

For Crohn, think of a fat granny and an old crone skipping down a cobblestone road away from the wreck (rectal sparing). 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:
- Pain improves with defecation
- Change in stool frequency
- Change in appearance of stool
No structural abnormalities. Most common in middle-aged women. Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted.

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).
Treatment: appendectomy.

Diverticula of the GI tract

Diverticulum

Blind pouch A protruding from the alimentary tract that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed “false” in that they lack or have an attenuated muscularis externa. Most often in sigmoid colon.

“True” diverticulum—all 3 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 low-fiber diets.
Often asymptomatic or associated with vague discomfort.
Complications include diverticular bleeding (painless hematochezia), diverticulitis.

Diverticulitis

Diverticulosis with inflamed microperforations B classically causing LLQ pain, fever, leukocytosis. Treat with antibiotics.
Complications: abscess, fistula (colovesical fistula → pneumaturia), obstruction (inflammatory stenosis), perforation (→ peritonitis). Treat with percutaneous drainage or surgery.
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 duct. May contain ectopic acid–secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause melena, RLQ pain, intussusception, volvulus, or obstruction near terminal ileum. Contrast with omphalomesenteric cyst = cystic dilation of vitelline duct. Diagnosis: pertechnetate study for uptake by ectopic gastric mucosa.

The six 2’s:
- 2 times as likely in males.
- 2 inches long.
- 2 feet from the ileocecal valve.
- 2% of population.
- Commonly presents in first 2 years of life.
- May have 2 types of epithelia (gastric/pancreatic).

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."

Think of Hirschsprung as a giant spring that has sprung in the colon. Risk ↑ with Down syndrome.

Diagnosed by rectal suction biopsy.

Treatment: resection.

Malrotation

Anomaly of midgut rotation during fetal development → improper positioning of bowel, formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

Liver
Ladd bands
Small intestine
Large intestine
**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 more common in elderly.

**Intussusception**

Telescoping of proximal bowel segment into distal segment, commonly at ileocecal junction. Compromised blood supply → intermittent abdominal pain often with "currant jelly" stools. Unusual in adults (associated with intraluminal mass or tumor that acts as lead point that is pulled into the lumen). Majority of cases occur in children (usually idiopathic; may be associated with recent viral infection, such as adenovirus → Peyer patch hypertrophy → lead point; most common pathologic lead point is Meckel diverticulum). Abdominal emergency in early childhood, with bull’s-eye appearance on ultrasound.

**Other intestinal disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</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>Colonic ischemia</td>
<td>Reduction in intestinal blood flow causes ischemia. Crampy abdominal pain followed by hematochezia. Commonly occurs at watershed areas (splenic flexure, distal colon). Typically affects elderly.</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>Tortuous dilation of vessels → hematochezia. Most often found in cecum, terminal ileum, ascending colon. More common in older patients. Confirmed by angiography.</td>
</tr>
<tr>
<td>Adhesion</td>
<td>Fibrous band of scar tissue; commonly forms after surgery; most common cause of small bowel obstruction. Can have well-demarcated necrotic zones.</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 pneumatosi intestinalis, free air in abdomen, portal venous gas.</td>
</tr>
</tbody>
</table>
### Colonic polyps

Growth 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.

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic</td>
<td>Non-neoplastic. Generally smaller and majority located in rectosigmoid area.</td>
</tr>
<tr>
<td>Hamartomatous</td>
<td>Generally non-neoplastic; solitary lesions do not have a significant risk of malignant transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.</td>
</tr>
<tr>
<td>Adenomatous</td>
<td>Neoplastic, via chromosomal instability pathway with mutations in APC and KRAS. Tubular histology has less malignant potential than villous. Tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding.</td>
</tr>
<tr>
<td>Serrated</td>
<td>Premalignant, via CpG hypermethylation phenotype pathway with microsatellite instability and mutations in BRAF. “Saw-tooth” pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.</td>
</tr>
</tbody>
</table>

### Polyposis syndromes

<table>
<thead>
<tr>
<th>Polyposis 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 5q. 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 + malignant CNS tumor. 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 ↑ 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 ↑ risk of CRC.</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>Previously known as hereditary nonpolyposis colorectal cancer (HNPPC). 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.</td>
</tr>
</tbody>
</table>
**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**
Rectosigmoid > ascending > descending. Ascending—exophytic mass, iron deficiency anemia, weight loss. Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia. Rarely, presents with *Streptococcus bovis* bacteremia. Right side bleeds; left side obstructs.

**Diagnosis**
Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screen patients > 50 years old with colonoscopy, flexible sigmoidoscopy, fecal occult blood test, or fecal DNA test. “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 polyp pathway).

---

Chromosomal instability pathway:

<table>
<thead>
<tr>
<th>Normal colon</th>
<th>Loss of APC gene</th>
<th>Colon at risk</th>
<th>#RAS mutation</th>
<th>Loss of tumor suppressor gene(s)/p53, DCC</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Normal Colon" /></td>
<td><img src="image2" alt="Loss of APC" /></td>
<td><img src="image3" alt="Colon at Risk" /></td>
<td><img src="image4" alt="RAS Mutation" /></td>
<td><img src="image5" alt="Loss of Tumor Suppressor" /></td>
<td><img src="image6" alt="Carcinoma" /></td>
</tr>
<tr>
<td>↓ intercellular adhesion</td>
<td>↑ proliferation</td>
<td>Unregulated intracellular signaling</td>
<td>↑ tumorigenesis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cirrhosis and portal hypertension

Cirrhosis—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (red arrows in A; blue arrow shows splenomegaly) disrupt normal architecture of liver; ↑ risk for hepatocellular carcinoma (HCC). Etiologies include alcohol (60–70% of cases in the US), 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.
### Serum markers of liver pathology

#### Enzymes released in liver damage

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>In most liver disease: ALT &gt; AST</th>
<th>In alcoholic liver disease: AST &gt; ALT</th>
<th>AST &gt; ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase and alanine aminotransferase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>† in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease</td>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Functional liver markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>In various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis</th>
<th>In advanced liver disease</th>
<th>In advanced liver disease (production of clotting factors) and portal hypertension (splenomegaly/splenic sequestration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>Prothrombin</td>
<td></td>
<td>† in advanced liver disease</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td>† in advanced liver disease</td>
<td></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 B) 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.
**Alcoholic liver disease**

<table>
<thead>
<tr>
<th>Hepatic steatosis</th>
<th>Macrovesicular fatty change that may be reversible with alcohol cessation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcoholic hepatitis</strong></td>
<td>Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies (intracytoplasmic eosinophilic inclusions of damaged keratin filaments). Make a AST with alcohol: AST &gt; ALT (ratio usually &gt; 2:1).</td>
</tr>
<tr>
<td><strong>Alcoholic cirrhosis</strong></td>
<td>Final and irreversible form. Micronodular, irregularly shrunken liver with “hobnail” appearance. Sclerosis (arrows in C) around central vein (zone III). Manifestations of chronic liver disease (eg, jaundice, hypoalbuminemia).</td>
</tr>
</tbody>
</table>

**Non-alcoholic 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.

**Hepatic encephalopathy**

Cirrhosis → portosystemic shunts → ↑ NH₃ metabolism → neuropsychiatric dysfunction. Spectrum from disorientation/asterixis (mild) to difficult arousal or coma (severe). Triggers:
- ↑ NH₃ production and absorption (due to dietary protein, GI bleed, constipation, infection).
- ↓ NH₃ removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).
Treatment: lactulose (↑ NH₄⁺ generation) and rifaximin or neomycin (↓ NH₄⁺ 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 non-alcoholic 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: α-fetoprotein; ultrasound or contrast CT/MRI, biopsy.

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**Other liver tumors**

**Cavernous hemangioma**

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.

**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 (mottled appearance).
α₁-antitrypsin deficiency

Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS + globules in liver. Codominant trait.

In lungs, α₁-antitrypsin → uninhibited elastase in alveoli → ↓ elastic tissue → panacinar emphysema.

Jaundice

Abnormal yellowing of the skin and/or sclera due to bilirubin deposition. Hyperbilirubinemia 2° to ↓ production or ↓ disposition (impaired hepatic uptake, conjugation, excretion).

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:
* ↓ sclerosing cholangitis
* ↓ biliary cirrhosis

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 (bilirubin deposition in 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>Notes</th>
</tr>
</thead>
<tbody>
<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.</td>
<td>Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.</td>
</tr>
<tr>
<td><strong>3 Dubin-Johnson syndrome</strong></td>
<td>Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black liver. Benign.</td>
<td></td>
</tr>
<tr>
<td><strong>4 Rotor syndrome</strong></td>
<td>Is similar, but milder in presentation without black liver. Due to impaired hepatic uptake and excretion.</td>
<td></td>
</tr>
</tbody>
</table>

**Diagram:**

- **HEPATIC SINUSOID**
  - Circulating bilirubin (albumin bound, unconjugated, water insoluble)
  - Hemoglobin
  - Kupffer cell (macrophage)

- **Endothelial cell**
- **Space of Disse**
- **Hepatocyte**
- **BILIRUBIN UPTAKE**
- **CONJUGATION**
- **Conjugated bilirubin** (bilirubin diglucuronide, water soluble)
- **INTRACELLULAR TRANSPORT**
- **Bile canaliculus lumen**
- **Bile flow**
- **Obstructive jaundice (downstream)**
- **Stasis**

**Notes:**
- Conjugated bilirubin is water soluble and excreted in bile.
- Unconjugated bilirubin is water insoluble and deposited in tissues.
- Hepatocytes synthesize and transport conjugated bilirubin.

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All autosomal recessive.
Wilson disease (hepatolenticular degeneration)

Recessive mutations in hepatocyte copper-transporting ATPase (ATP7B gene; chromosome 13) → inadequate copper excretion into bile and blood (↓ serum ceruloplasmin, ↑ urine copper). Copper accumulates, especially in liver, brain, cornea, kidneys, joints. 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) A, hemolytic anemia, renal disease (eg, Fanconi syndrome). Treatment: chelation with penicillamine or trientine, oral zinc.

Hemochromatosis

Recessive mutations in HFE gene (C282Y > H63D, chromosome 6) → abnormal iron sensing and ↑ intestinal absorption (↑ ferritin, ↓ iron, ↑ TIBC → ↑ transferrin saturation). Iron overload can also be 2° 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 A. 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 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.

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>Primary sclerosing cholangitis</th>
<th>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).</th>
<th>Classically in middle-aged men with IBD.</th>
<th>Associated with ulcerative colitis. p-ANCA ⊕. ↑ IgM. Can lead to 2° biliary cirrhosis. ↑ risk of cholangiocarcinoma and gallbladder cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Autoimmune reaction → lymphocytic infiltrate + granulomas → destruction of intralobular bile ducts.</td>
<td>Classically in middle-aged women.</td>
<td>Anti-mitochondrial antibody ⊕, ↑ IgM. Associated with other autoimmune conditions (eg, Sjögren syndrome, Hashimoto thyroiditis, CREST, rheumatoid arthritis, celiac disease).</td>
</tr>
<tr>
<td>Secondary biliary cirrhosis</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>
<td>May be complicated by ascending cholangitis.</td>
</tr>
</tbody>
</table>
Gallstones (cholelithiasis)

1. cholesterol and/or bilirubin, 4 bile salts, and gallbladder stasis all cause stones.
2. types of stones:
   - Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, Native American origin.
   - Pigment stones (black = radiopaque, Ca\(^{2+}\) bilirubinate, hemolysis; brown = radiolucent, infection)—seen in patients with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN). Uncomplicated disease manifests as biliary colic—neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing a stone into the cystic duct. May present without pain (eg, in diabetics).
   - Diagnose with ultrasound. Treat with cholecystectomy if symptomatic.

Gastrointestinal—Pathology

Cholecystitis

Acute or chronic inflammation of gallbladder usually from choledolithiasis (stone at neck of gallbladder [red arrow in A] with gallbladder wall thickening [yellow arrows]). Gallstones most commonly blocking the cystic duct → 2nd infection; rarely acalculous due to ischemia and stasis, or 1st infection (CMV). Murphy sign ⊕: inspiratory arrest on RUQ palpation due to pain. ↑ ALP if bile duct becomes involved (eg, ascending cholangitis). Diagnose with ultrasound or cholescintigraphy (HIDA, or hepatobiliary iminodiacetic acid scan).

Porcelain gallbladder

Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging. Treatment: prophylactic cholecystectomy due to high rates of gallbladder cancer (mostly adenocarcinoma).
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), necrosis, hemorrhage, infection, organ failure (ARDS, shock, renal failure), hypocalcemia (precipitation of Ca²⁺ soaps).

Chronic pancreatitis

Chronic inflammation, atrophy, calcification of the pancreas. Major causes are alcohol abuse and idiopathic. Mutations in CFTR (cystic fibrosis) can cause chronic pancreatic insufficiency. Can lead to pancreatic insufficiency → 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); 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

**H₂ blockers**

Cimetidine, ranitidine, famotidine, nizatidine. **Take H₂ blockers before you dine.** Think “table for 2” to remember H₂.

**MECHANISM**
Reversible block of histamine H₂-receptors → ↓ H⁺ 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 H₂ blockers are relatively free of these effects.

**Proton pump inhibitors**

Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.

**MECHANISM**
Irreversibly inhibit H⁺/K⁺ ATPase in stomach parietal cells.

**CLINICAL USE**
Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome.

**ADVERSE EFFECTS**
↑ risk of C difficile infection, pneumonia. ↓ serum Mg²⁺ with long-term use.
### Antacid use
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 type</th>
<th>Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide</td>
<td>Constipation and hypophosphatemia; proximal muscle weakness, osteodystrophy, seizures</td>
<td>Aluminimum amount of feces.</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Hypercalcemia (milk-alkali syndrome), rebound acid ↑</td>
<td>Can chelate and ↓ effectiveness of other drugs (eg, tetracycline).</td>
</tr>
<tr>
<td>Magnesium hydroxide</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 mucous layer.
**CLINICAL USE** ↑ ulcer healing, travelers’ diarrhea.

### Misoprostol
**MECHANISM** A PGE₁ analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.
**CLINICAL USE** Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE₁ production); maintenance of a PDA. 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.

### Osmotic laxatives
Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose.
**MECHANISM** Provide osmotic load to draw water into the GI lumen.
**CLINICAL USE** Constipation. Lactulose also treats hepatic encephalopathy since gut flora degrade it into metabolites (lactic acid and acetic acid) that promote nitrogen excretion as NH₄⁺.
**ADVERSE EFFECTS** Diarrhea, dehydration; may be abused by bulimics.

### 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.
<table>
<thead>
<tr>
<th><strong>Loperamide</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Agonist at μ-opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential).</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Diarrhea.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Constipation, nausea.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ondansetron</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>5-HT₃ antagonist; vagal stimulation. Powerful central-acting antiemetic. At a party but feeling queasy? Keep on dancing with ondansetron!</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Control vomiting postoperatively and in patients undergoing cancer chemotherapy.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Headache, constipation, QT interval prolongation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Metoclopramide</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>D₂ receptor antagonist. ↑ resting tone, contractility, LES tone, motility. Does not influence colon transport time.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Diabetic and postsurgery gastroparesis, antiemetic.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>↑ 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).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Orlistat</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Weight loss.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Steatorrhea, ↓ absorption of fat-soluble vitamins.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ursodiol (ursodeoxycholic acid)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Nontoxic bile acid. ↑ bile secretion, ↓ cholesterol secretion and reabsorption.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Primary biliary cirrhosis, gallstone prevention or dissolution.</td>
</tr>
</tbody>
</table>
Hematology
and Oncology

“Of all that is written, I love only what a person has written with his own
blood.”
—Friedrich Nietzsche

“I used to get stressed out, but my cancer has put everything into
perspective.”
—Delta Goodrem

“The best blood will at some time get into a fool or a mosquito.”
—Austin O’Malley

“Carcinoma works cunningly from the inside out. Detection and
treatment often work more slowly and gropingly, from the outside in.”
—Christopher Hitchens

Study tip: When reviewing oncologic drugs, focus on mechanisms and
side effects rather than details of clinical uses, which may be lower yield.
Erythrocyte
Carries O₂ to tissues and CO₂ to lungs. Anucleate and lacks 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). Membrane contains Cl⁻/HCO₃⁻ antiporter, which allows RBCs to export HCO₃⁻ and transport CO₂ from the periphery to the lungs for elimination.

Eryth = red; cyte = cell.
Erythrocytosis = polycythemia = ↑ hematocrit.
Anisocytosis = varying sizes.
Poikilocytosis = varying shapes.
Reticulocyte = immature RBC; reflects erythroid proliferation.
Bluish color on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

Thrombocyte (platelet)
Involved in 1° hemostasis. Small cytoplasmic fragment derived from megakaryocytes. Life span of 8–10 days. When activated by endothelial injury, aggregates with other platelets and interacts with fibrinogen to form platelet plug. Contains 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.

Leukocyte
Divided into granulocytes (neutrophil, eosinophil, basophil) and mononuclear cells (monocytes, lymphocytes).

WBC differential from highest to lowest (normal ranges per USMLE):
- Neutrophils (54–62%)
- Lymphocytes (25–33%)
- Monocytes (3–7%)
- Eosinophils (1–3%)
- Basophils (0–0.75%)

Leuk = white; cyte = cell.

Neutrophils Like Making Everything Better.

Neutrophil

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, LTβ₄, kallikrein, platelet-activating factor.
### Monocyte

![Monocyte Image]

Differentiates into macrophage in tissues. Large, kidney-shaped nucleus. Extensive “frosted glass” cytoplasm. 

*Mono* = one (nucleus); *cyte* = cell. Monocyte: in the blood.

### Macrophage

![Macrophage Image]

Phagocytoses bacteria, cellular debris, and senescent RBCs. Long life in tissues. Macrophages differentiate from circulating blood monocytes. Activated by γ-interferon. Can function as antigen-presenting cell via MHC II. 

*Macro* = large; *phage* = eater. Macrophage: in the tissue. Important component of granuloma formation (eg, TB, sarcoidosis). Lipid A from bacterial LPS binds CD14 on macrophages to initiate septic shock.

### Eosinophil

![Eosinophil Image]


*Eosin* = pink dye; *philic* = loving. Causes of eosinophilia = NAACP. 

- Neoplasia
- Asthma
- Allergic processes
- Chronic adrenal insufficiency
- Parasites (invasive)

### Basophil

![Basophil Image]

Mediates allergic reaction. Densely basophilic granules contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand. 

*Basophilic*—staining readily with basic stains. Basophilia is uncommon, but can be a sign of myeloproliferative disease, particularly CML.

### Mast cell

![Mast cell Image]

Mediates allergic reaction in local tissues. Mast cells 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. IgE cross-links upon antigen binding → 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 cell**

Highly phagocytic APC. Functions as link between innate and adaptive immune systems. Expresses MHC class II and Fc receptors on surface. Called Langerhans cell in the skin.

---

**Lymphocyte**

Refers 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 cell**

Part of humoral immune response. Originates from stem cells in bone marrow and matures in marrow. Migrates 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 via MHC II.

---

**T cell**

Mediates cellular immune response. Originates from stem cells in the bone marrow, but matures in the thymus. T cells 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. The majority of circulating lymphocytes are T cells (80%).

---

**B** = Bone marrow.

**T** is for Thymus.

CD4+ helper T cells are the primary target of HIV.

**MHC × CD = 8** (eg, MHC 2 × CD4 = 8, and MHC 1 × CD8 = 8).
Plasma cell

Produces large amounts of antibody specific to a particular antigen. “Clock-face” chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (yellow arrows in A). Found in bone marrow and normally do not circulate in peripheral blood.

Multiple myeloma is a plasma cell cancer.

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 (HbA₁) = 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.

From fetal to adult hemoglobin:
- Alpha Always
- Gamma Goes
- Becomes Beta

Site of erythropoiesis

% of total globin synthesis

Weeks: 6 12 18 24 30 36

FETUS (weeks)

POSTNATAL (months)

ADULT >>

BIRTH
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>Rh⁻</td>
</tr>
<tr>
<td>O</td>
<td>Rh⁻</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
  - None

- **Clinical relevance**
  - Receive B or AB → hemolytic reaction
  - Receive A or AB → hemolytic reaction
  - Universal recipient of RBCs; universal donor of plasma
  - Receive any non-O → hemolytic reaction
  - Universal donor of RBCs; universal recipient of plasma
  - Universal recipient of RBCs
  - Treat mother with anti-D Ig (RhoGAM) during and after each pregnancy to prevent anti-D IgG formation

**Rh hemolytic disease of the newborn**

IgM does not cross placenta; IgG does cross placenta. Rh⁻ mothers exposed to fetal Rh⁺ blood (often during delivery) may make anti-D IgG. In subsequent pregnancies, anti-D IgG crosses the placenta → hemolytic disease of the newborn (erythroblastosis fetalis) in the next fetus that is Rh⁺. Administration of anti-D IgG (RhoGAM) to Rh⁻ pregnant women during third trimester prevents maternal anti-D IgG production. Rh⁻ mothers have anti-D IgG only if previously exposed to Rh⁺ blood.

**ABO hemolytic disease of the newborn**

Most common form. Usually occurs in a type O mother with a type A, B, or AB fetus. Can occur in a first pregnancy as maternal anti-A and/or anti-B IgG antibodies are formed early in life. Does not worsen with future pregnancies. Presents as mild jaundice in the neonate within 24 hours of birth; treatment is phototherapy or exchange transfusion.
### Hemoglobin electrophoresis

<table>
<thead>
<tr>
<th>Origin</th>
<th>AA → Normal adult</th>
<th>AF → Normal newborn</th>
<th>AS → Sickle cell trait</th>
<th>SS → Sickle cell disease</th>
<th>AC → Hb C trait</th>
<th>CC → Hb C disease</th>
<th>SC → Hb SC disease</th>
</tr>
</thead>
</table>

**A:** normal hemoglobin \( \beta \) chain (HbA, adult)  
**F:** normal hemoglobin \( \gamma \) chain (HbF, fetal)  
**S:** sickle cell hemoglobin \( \beta \) chain (HbS)  
**C:** hemoglobin C \( \beta \) chain (HbC)

On a gel, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbS, followed by HbC. This is because the missense mutations in HbS and HbC replace glutamic acid \( \ominus \) with valine (neutral) and lysine \( \oplus \), respectively, impacting the net protein charge.

### Coagulation and kinin pathways

**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)

**Kinin cascade**  
- Bradykinin  
- Vasodilation  
- Permeability  
- Pain

**Hemophilia A:** deficiency of factor VIII (XR)  
**Hemophilia B:** deficiency of factor IX (IXR)  
**Hemophilia C:** deficiency of factor XI (AR)

Note: Kallikrein activates bradykinin; ACE inactivates bradykinin  
* = require Ca\(^{2+}\), phospholipid  
= inhibited by vitamin K antagonist warfarin  
= cofactor  
= activates but not part of coagulation cascade

**Fibrinolytic system**  
- Alteplase, reteplase, streptokinase, tenecteplase

**Fibrin degradation products**  
- Aminocaproic acid  
- TPA (tissue plasminogen activator)
Coagulation cascade components

**Procoagulation**

- Oxidized vitamin K → Epoxide reductase → reduced vitamin K (acts as cofactor) → mature (active) II, VII, IX, X, C, S
- γ-glutamyl transferase → inactive precursors of II, VII, IX, X, C, S

**Anticoagulation**

- Thrombin - thrombomodulin complex (endothelial cells) → Protein C → activated protein C → cleaves and inactivates Va, VIIIa
- Protein S

---

Warfarin inhibits the enzyme vitamin K epoxide reductase.

Neonates lack enteric bacteria, which produce vitamin K.

**Vitamin K deficiency:** ↓ synthesis of factors II, VII, IX, X, protein C, protein S.

vWF carries/protects VIII.

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. vWF from the injured cell's intracellular spaces binds to the surface of damaged platelets. Platelets release ADP and Ca²⁺ (necessary for coagulation cascade), TXA₂.

4. **Activation**: ADP binding to receptor induces GpIIb/IIIa expression at platelet surface. ADP helps platelets adhere to endothelium.

5. **Aggregation**: Fibrinogen binds GpIIb/IIIa receptors and links platelets. Platelet plug stops bleeding; unstable, easily dislodged.

Thrombogenesis

Formation of insoluble fibrin mesh.
Aspirin irreversibly inhibits cyclooxygenase (TXA₂ synthesis).
Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa.
Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.
Ristocetin activates vWF to bind GpIb. Failure of agglutination 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><strong>Acanthocyte</strong> (&quot;spur cell&quot;)</td>
<td><img src="image1.png" alt="Image A" /></td>
<td>Liver disease, abetalipoproteinemia (states of cholesterol dysregulation).</td>
<td><em>Acantho</em> = spiny.</td>
</tr>
<tr>
<td><strong>Basophilic stippling</strong></td>
<td><img src="image2.png" alt="Image B" /></td>
<td>Lead poisoning, sideroblastic anemias, myelodysplastic syndromes.</td>
<td></td>
</tr>
<tr>
<td><strong>Dacrocyte</strong> (&quot;teardrop cell&quot;)</td>
<td><img src="image3.png" alt="Image C" /></td>
<td>Bone marrow infiltration (e.g., myelofibrosis).</td>
<td>RBC “sheds a tear” because it’s mechanically squeezed out of its home in the bone marrow.</td>
</tr>
<tr>
<td><strong>Degmacyte</strong> (&quot;bite cell&quot;)</td>
<td><img src="image4.png" alt="Image D" /></td>
<td>G6PD deficiency.</td>
<td></td>
</tr>
<tr>
<td><strong>Echinocyte</strong> (&quot;burr cell&quot;)</td>
<td><img src="image5.png" alt="Image E" /></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><strong>Elliptocyte</strong></td>
<td><img src="image6.png" alt="Image F" /></td>
<td>Hereditary elliptocytosis, usually asymptomatic; caused by mutation in genes encoding RBC membrane proteins (e.g., spectrin).</td>
<td></td>
</tr>
<tr>
<td><strong>Macro-ovalocyte</strong></td>
<td><img src="image7.png" alt="Image G" /></td>
<td>Megaloblastic anemia (also hypersegmented PMNs), marrow failure.</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>Ringed sideroblast</td>
<td><img src="image1" alt="Image" /></td>
<td>Sideroblastic anemia. Excess iron in mitochondria.</td>
<td></td>
</tr>
<tr>
<td>Schistocyte</td>
<td><img src="image2" alt="Image" /></td>
<td>DIC, TTP/HUS, HELLP syndrome, mechanical hemolysis (eg, heart valve prosthesis).</td>
<td>Examples include helmet cell.</td>
</tr>
<tr>
<td>Sickle cell</td>
<td><img src="image3" alt="Image" /></td>
<td>Sickle cell anemia.</td>
<td>Sickling occurs with dehydration, deoxygenation, and at high altitude.</td>
</tr>
<tr>
<td>Spherocyte</td>
<td><img src="image4" alt="Image" /></td>
<td>Hereditary spherocytosist, drug- and infection-induced hemolytic anemia.</td>
<td></td>
</tr>
<tr>
<td>Target cell</td>
<td><img src="image5" 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>Heinz bodies</td>
<td><img src="image6" 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>Howell-Jolly bodies</td>
<td><img src="image7" alt="Image" /></td>
<td>Seen in patients with functional hyposplenemia 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**

**MCV < 80 fL (Microcytic)**
- Iron deficiency (late)
- ACD (late)
- Thalassemias
- Lead poisoning
- Sideroblastic anemia*

**MCV 80–100 fL (Normocytic)**
- Nonhemolytic (Reticulocyte count normal or ↑)
- Hemolytic (Reticulocyte count ↑)

**MCV > 100 fL (Macrocytic)**
- Megaloblastic
- Non-megaloblastic

**INTRINSIC**
- Iron deficiency (early)
- ACD (early)
- Aplastic anemia
- Chronic kidney disease
- Paroxysmal nocturnal hemoglobinuria
- Sickle cell anemia

**EXTRINSIC**
- Autosomal
- ACD (late)
- Microangiopathy
- Macroangiopathy
- Infections

**HEMOLYTIC** (Reticulocyte count ↑)
- RBC membrane defect: hereditary spherocytosis
- RBC enzyme deficiency: G6PD, pyruvate kinase
- HbC disease
- Paroxysmal nocturnal hemoglobinuria

**NONHEMOLYTIC** (Reticulocyte count normal or ↓)
- Iron deficiency (early)
- ACD (early)
- Thalassemias
- Lead poisoning
- Sideroblastic anemia*

**MEGALOBLASTIC**
- Folate deficiency
- Liver disease

**NON-MEGALOBLASTIC**
- Liver disease
- Alcoholism
- Diamond-Blackfan anemia

On a peripheral blood smear, a lymphocyte nucleus is approximately the same size as a normocytic RBC. If RBC is larger than lymphocyte nucleus, consider macrocytosis; if RBC is smaller, consider microcytosis.*

*Copper deficiency can cause a microcytic sideroblastic anemia.

---

**Microcytic (MCV < 80 fL), hypochromic anemia**

**Iron deficiency**
- Iron due to chronic bleeding (e.g., GI loss, menorrhagia), malnutrition, absorption disorders, or ↑ demand (e.g., pregnancy) → ↓ final step in heme synthesis.
- Labs: ↓ iron, ↑ TIBC, ↓ ferritin. Microcytosis and hypochromasia (central pallor) [A].
- Symptoms: fatigue, conjunctival pallor [B], pica (consumption of nonfood substances), spoon nails (koilonychia).
- May manifest as Plummer-Vinson syndrome (triad of iron deficiency anemia, esophageal webs, and dysphagia).

**α-thalassemia**
- Defect: α-globin gene deletions → ↓ α-globin synthesis. cis deletion (both deletions occur on same chromosome) prevalent in Asian populations; trans deletion (deletions occur on separate chromosomes) prevalent in African populations.
- 4 allele deletion: No α-globin. Excess γ-globin forms γ₄ (Hb Barts). Incompatible with life (causes hydrops fetalis).
- 3 allele deletion: inheritance of chromosome with cis deletion + a chromosome with 1 allele deleted → HbH disease. Very little α-globin. Excess β-globin forms β₄ (HbH).
- 2 allele deletion: less clinically severe anemia.
- 1 allele deletion: no anemia (clinically silent).
Microcytic (MCV < 80 fL), 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 hematopoeisis → hepatosplenomegaly. ↑ risk of parvovirus B19–induced aplastic crisis. ↑ HbF (α₂γ₂). 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:
- **Lead** lines on gingivae (Burton lines) and on metaphyses of long bones on x-ray.
- Encephalopathy and Erythrocyte basophilic stippling.
- Abdominal colic and sideroblastic Anemia.
- Ddrops—wrist and foot drop. Dimercaprol and EDTA are 1st line of treatment.

**Succ**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**
Defect in heme synthesis due to X-linked defect in δ-ALA synthase gene.
Causes: genetic, acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead, vitamin B6 deficiency, copper deficiency, isoniazid).

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 δ-ALA synthase).
### Macrocytic (MCV > 100 fl) anemia

<table>
<thead>
<tr>
<th>Macrocytic (MCV &gt; 100 fl) anemia</th>
<th><strong>DESCRIPTION</strong></th>
<th><strong>FINDINGS</strong></th>
</tr>
</thead>
<tbody>
<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: insufficient intake (eg, veganism), malabsorption (eg, Crohn disease), pernicious anemia, <em>Diphyllobothrium latum</em> (fish tapeworm), gastrectomy.</td>
<td>↑ homocysteine, ↑ methylmalonic acid. Neurologic symptoms: subacute combined degeneration (due to involvement of B₁₂ in fatty acid pathways and myelin synthesis): spinocerebellar 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.</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 to bypass mutated enzyme.</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>
<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>
</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).

Intravascular hemolysis

Findings: ↓ haptoglobin, ↑ LDH, schistocytes and ↑ reticulocytes 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, ↑ LDH, no hemoglobinuria/hemosiderinuria, ↑ unconjugated bilirubin, which can cause jaundice. 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.</td>
</tr>
</tbody>
</table>

Aplastic anemia

Caused by failure or destruction of myeloid stem cells due to:
- Radiation and drugs (benzene, chloramphenicol, alkylating agents, antimetabolites)
- Viral agents (parvovirus B19, EBV, HIV, hepatitis viruses)
- Fanconi anemia (DNA repair defect causing bone marrow failure); also short stature, ↑ incidence of tumors/leukemia, café-au-lait spots, thumb/radial defects
- Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis

↓ reticulocyte count, ↑ EPO. Pancytopenia characterized by severe 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><strong>Pyruvate kinase deficiency</strong></td>
<td>Autosomal recessive. Defect in pyruvate kinase → ↓ ATP → rigid RBCs → extravascular hemolysis.</td>
</tr>
<tr>
<td><strong>HbC disease</strong></td>
<td>Glutamic acid–to-lysine mutation in β-globin. Causes extravascular hemolysis.</td>
</tr>
<tr>
<td><strong>Sickle cell anemia</strong></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 (deoxygènated HbS polymerizes) → anemia and 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>
</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>Warm (IgG)—chronic anemia seen in SLE and CLL and with certain drugs (eg, α-methylldopa) (“warm weather is Great”). <strong>Cold</strong> (IgM and complement)—acute anemia triggered by cold; seen in CLL, <em>Mycoplasma pneumonia</em> 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 in etiology.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Patient component</strong></th>
<th><strong>Reagent(s)</strong></th>
<th><strong>Result (agglutination)</strong></th>
<th><strong>Result (no agglutination)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Coombs</td>
<td>RBCs +/- anti-RBC Ab</td>
<td>Anti-human globulin (Coombs reagent)</td>
<td>Anti-RBC Ab present</td>
</tr>
<tr>
<td>Indirect Coombs</td>
<td>Patient serum +/- anti-donor RBC Ab</td>
<td>Anti-human globulin (Coombs reagent)</td>
<td>Anti-donor RBC Ab present</td>
</tr>
</tbody>
</table>

**Microangiopathic anemia**

Pathogenesis: RBCs are damaged when passing through obstructed or narrowed vessel lumina. Seen in DIC, TTP/HUS, SLE, and malignant hypertension.

**Macroangiopathic anemia**

Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.

**Infections**

† destruction of RBCs (eg, malaria, *Babesia*).
Lab values in anemia

<table>
<thead>
<tr>
<th></th>
<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>↓ (1°)</td>
<td>↓</td>
<td>↑ (1°)</td>
<td>—</td>
</tr>
<tr>
<td>Transferrin or TIBC</td>
<td>↑</td>
<td>↓</td>
<td>↓ (1°)</td>
<td>↑ (1°)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↓</td>
<td>↑ (1°)</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>% transferrin saturation</td>
<td>↓</td>
<td>—</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

*Transferrin—transports iron in blood.*
*TIBC—indirectly measures transferrin. Ferritin—1° iron storage protein of body.*

*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/mm³. Severe infections typical when &lt; 500 cells/mm³.</td>
<td>Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Absolute lymphocyte count &lt; 1500 cells/mm³ (&lt; 3000 cells/mm³ in children)</td>
<td>HIV, DiGeorge syndrome, SCID, SLE, corticosteroids, radiation, sepsis, postoperative</td>
</tr>
<tr>
<td>Eosinopenia</td>
<td>Absolute eosinophil count &lt; 30 cells/mm³</td>
<td>Cushing syndrome, corticosteroids</td>
</tr>
</tbody>
</table>

*Corticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids 4 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

*A left shift is a shift to a more immature cell in the maturation process.*

1 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).
**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, δ-ALA (blood)</td>
<td>Microcytic anemia (basophilic stippling A), 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</td>
<td>Porphobilinogen, δ-ALA, coporphobilinogen (urine)</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: glucose and heme, which inhibit ALA synthase.</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Uroporphyrinogen decarboxylase</td>
<td>Uroporphyrin (tea-colored urine)</td>
<td>Blistering cutaneous photosensitivity B. Most common porphyria.</td>
</tr>
</tbody>
</table>

**Location**

- **Mitochondria**
  - Glucose, heme
  - Glycine + succinyl-CoA → δ-aminolevulinic acid
  - δ-aminolevulinic acid synthase: rate-limiting step
  - δ-aminolevulinic acid dehydratase
  - Porphobilinogen
  - Hydroxymethylbilane
  - Uroporphyrinogen III
  - Coproporphyrinogen III
  - Ferrochelatase

- **Cytoplasm**
  - Protoporphyrin
  - Fe²⁺

- **Diseases**
  - Sideroblastic anemia (X linked)
  - Lead poisoning
  - Acute intermittent porphyria
  - Porphyria cutanea tarda

↓ heme → ↑ ALA synthase activity
↑ heme → ↓ ALA synthase activity
**Iron poisoning**

**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.

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.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PT</th>
<th>PTT</th>
<th>MECHANISM AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A, B, or C</td>
<td></td>
<td>↑</td>
<td>Intrinsic pathway coagulation defect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• A: deficiency of factor VIII → ↑ PTT; X-linked recessive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• B: deficiency of factor IX → ↑ PTT; X-linked recessive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• C: deficiency of factor XI → ↑ PTT; autosomal recessive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Macromorrhage in hemophilia—hemarthroses (bleeding into joints, such as knee 📷), easy bruising, bleeding after trauma or surgery (eg, dental procedures).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C).</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>↑</td>
<td>↑</td>
<td>General coagulation defect. Bleeding time normal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ activity of factors II, VII, IX, X, protein C, protein S.</td>
</tr>
</tbody>
</table>
### 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. ↓ GpIb → defect in platelet-to-vWF adhesion.</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>↓</td>
<td>↑</td>
<td>Characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure. Typical HUS is seen in children, accompanied by diarrhea and commonly caused by Shiga toxin-producing ( E coli ) (STEC) (eg, O157:H7). HUS in adults does not present with diarrhea; STEC infection not required. Same spectrum as TTP, with a similar clinical presentation and same initial treatment of plasmapheresis.</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>
<tbody>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>↓</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>Widespread activation of clotting → deficiency in clotting factors → bleeding state. Causes: Sepsis (gram ⊳), Trauma, Obstetric complications, acute Pancreatitis, Malignancy, Nephrotic syndrome, Transfusion (STOP Making New Thrombi). Labs: schistocytes, ↑ fibrin degradation products (d-dimers), ↓ fibrinogen, ↓ factors V and VIII.</td>
</tr>
</tbody>
</table>

*PTT may also be normal in von Willebrand disease.*

## 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 C ancel, and protein S S t, 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</td>
<td>↑ coagulation factor levels</td>
<td>DIC, cirrhosis, immediate warfarin 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

<table>
<thead>
<tr>
<th>Hodgkin</th>
<th>Non-Hodgkin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized, single group of nodes; contiguous spread (stage is strongest predictor of prognosis). Many patients have a relatively good prognosis.</td>
<td>Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread.</td>
</tr>
<tr>
<td>Characterized by Reed-Sternberg cells.</td>
<td>Majority involve B cells; a few are of T-cell lineage.</td>
</tr>
<tr>
<td>Bimodal distribution—young adulthood and &gt; 55 years; more common in men except for nodular sclerosing type.</td>
<td>Can occur in children and adults.</td>
</tr>
<tr>
<td>Associated with EBV.</td>
<td>May be associated with HIV and autoimmune diseases.</td>
</tr>
<tr>
<td>Constitutional (“B”) signs/symptoms: low-grade fever, night sweats, weight loss.</td>
<td>May present with constitutional signs/symptoms.</td>
</tr>
</tbody>
</table>

Reed-Sternberg cells

Distinctive tumor giant cell seen in Hodgkin lymphoma; 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. Necessary but not sufficient for a diagnosis of Hodgkin lymphoma.
### Non-Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Occurs in</th>
<th>Genetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burkitt lymphoma</strong></td>
<td>Adolescents or young adults</td>
<td><strong>t(8;14)—translocation of c-myc (8) and heavy-chain Ig (14)</strong></td>
<td>“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</td>
<td></td>
<td>Most common type of non-Hodgkin lymphoma in adults.</td>
</tr>
<tr>
<td><strong>Follicular lymphoma</strong></td>
<td>Adults</td>
<td><strong>t(14;18)—translocation of heavy-chain Ig (14) and BCL-2 (18)</strong></td>
<td>Indolent course; Bcl-2 inhibits apoptosis. Presents with painless “waxing and waning” lymphadenopathy. Follicular architecture: small cleaved cells (grade 1), large cells (grade 3), or mixture (grade 2).</td>
</tr>
<tr>
<td><strong>Mantle cell lymphoma</strong></td>
<td>Adult males</td>
<td><strong>t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14)</strong></td>
<td>Very aggressive, patients typically present with late-stage disease.</td>
</tr>
<tr>
<td><strong>Primary central nervous system lymphoma</strong></td>
<td>Adults</td>
<td>Most commonly associated with HIV/AIDS</td>
<td>Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. Mass lesion(s) on MRI, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.</td>
</tr>
</tbody>
</table>

### Neoplasms of mature T cells

<table>
<thead>
<tr>
<th>Type</th>
<th>Occurs in</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult T-cell lymphoma</strong></td>
<td>Adults</td>
<td>Caused by HTLV (associated with IV drug abuse)</td>
</tr>
<tr>
<td><strong>Mycosis fungoides/ Sézary syndrome</strong></td>
<td>Adults</td>
<td>Mycosis fungoides presents with skin patches plaques (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with “cerebriform” nuclei. May progress to Sézary syndrome (T-cell leukemia).</td>
</tr>
</tbody>
</table>
Monoclonal plasma cell ("fried egg" appearance) cancer that arises in the marrow and produces large amounts of IgG (55%) or IgA (25%). 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, 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 all 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 nuclei. Typically seen after chemotherapy.
Hematology and Oncology

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.

**TYPE** | **NOTES**
--- | ---
**Lymphoid neoplasms** |  |
**Acute lymphoblastic leukemia/lymphoma** | 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.

**Chronic lymphocytic leukemia/small lymphocytic lymphoma** | Age: > 60 years. Most common adult leukemia. CD20+, 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—SLL/CLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).

**Hairy cell leukemia** | Age: Adult males. Mature B-cell tumor. Cells have filamentous, hair-like projections (fuzzy appearing on LM C). Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly.
Stains TRAP (tartrate-resistant acid phosphatase) ⊕. TRAP stain largely replaced with flow cytometry.
Treatment: cladribine, pentostatin.

**Myeloid neoplasms** |  |
**Acute myelogenous leukemia** | Median onset 65 years. Auer rods D; myeloperoxidase ⊕ 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. t(15;17) → APL subtype responds to all-trans retinoic acid (vitamin A), inducing differentiation of promyelocytes; DIC is a common presentation.

**Chronic myelogenous leukemia** | 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).
**Chromosomal translocations**

<table>
<thead>
<tr>
<th>TRANSLOCATION</th>
<th>ASSOCIATED DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>Burkitt lymphoma (c-myc activation)</td>
</tr>
<tr>
<td>t(9;22) (Philadelphia chromosome)</td>
<td>CML (BCR-ABL hybrid), rarely ALL.</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.

<table>
<thead>
<tr>
<th>TRANSLOCATION</th>
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</tr>
</thead>
<tbody>
<tr>
<td>t(11;14)</td>
<td>Mantle cell lymphoma (cyclin D1 activation)</td>
</tr>
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<td>Follicular lymphoma (BCL-2 activation)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>APL (M3 type of AML)</td>
</tr>
</tbody>
</table>

**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.

![Image A](image1.png)

![Image B](image2.png)
Chronic myeloproliferative disorders

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

A form of 1° polycythemia. Disorder of ↑ hematocrit. 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. Responds to aspirin. ↑ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).

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. Erythromelalgia may occur.

Myelofibrosis

Obliteration of bone marrow with fibrosis due to ↑ fibroblast activity. Often associated with massive splenomegaly and "teardrop" RBCs. "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>
### Hematology and Oncology—Pharmacology

#### Heparin

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Lowers the activity of thrombin and factor Xa. Short half-life.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta). Follow PTT.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Bleeding, thrombocytopenia (HIT), osteoporosis, drug-drug interactions. For rapid reversal (antidote), use protamine sulfate (positively charged molecule that binds negatively charged heparin).</td>
</tr>
<tr>
<td>NOTES</td>
<td>Low-molecular-weight heparins (eg, enoxaparin, dalteparin) and fondaparinux act more on factor Xa, have better bioavailability, and 2–4 times longer half-life; can be administered subcutaneously and without laboratory monitoring. Not easily reversible.</td>
</tr>
</tbody>
</table>


#### Direct thrombin inhibitors

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Bivalirudin (related to hirudin, the anticoagulant used by leeches).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Venous thromboembolism, atrial fibrillation. Can be used in HIT. Does not require lab monitoring.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Bleeding; no specific reversal agent. Can attempt to use activated prothrombin complex concentrates (PCC) and/or fibrinolytics (eg, tranexamic acid).</td>
</tr>
</tbody>
</table>
Warfarin

**MECHANISM**

Interferes with γ-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 ↑ 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. Proteins C and S have shorter half-lives than clotting factors II, VII, IX, and X, resulting in early transient hypercoagulability with warfarin use. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthromboses.

For reversal of warfarin, give vitamin K. For rapid reversal, give fresh frozen plasma. 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.

---

**Heparin vs warfarin**

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRUCTURE</strong></td>
<td>Large, anionic, acidic polymer</td>
<td>Small, amphipathic molecule</td>
</tr>
<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 ↓ the action of IIa (thrombin) and factor Xa</td>
<td>Impairs synthesis of vitamin K–dependent clotting factors II, VII, IX, and X, and anti-coagulating proteins C and S</td>
</tr>
<tr>
<td><strong>DURATION OF ACTION</strong></td>
<td>Acute (hours)</td>
<td>Chronic (days)</td>
</tr>
<tr>
<td><strong>INHIBITS COAGULATION IN VITRO</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>AGENTS FOR REVERSAL</strong></td>
<td>Protamine sulfate</td>
<td>Vitamin K, fresh frozen plasma</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**

**ApiXaban, rivaroxaban.**

**MECHANISM**
Bind to and directly inhibit factor Xa.

**CLINICAL USE**
Treatment and prophylaxis for DVT and PE (rivaroxaban); stroke prophylaxis in patients with atrial fibrillation.
Oral agents do not usually require coagulation monitoring.

**ADVERSE EFFECTS**
Bleeding (no reversal agent available).

**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. Treat toxicity with aminocaproic acid, an inhibitor of fibrinolysis. Fresh frozen plasma and cryoprecipitate can also be used to correct factor deficiencies.

**ADP receptor inhibitors**

**Clopidogrel, prasugrel, ticagrelor (reversible), ticlopidine.**

**MECHANISM**
Inhibit platelet aggregation by irreversibly blocking ADP receptors. 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 III inhibitor; ↑ cAMP in platelets, resulting in inhibition of platelet aggregation; vasodilators.

**CLINICAL USE**
Intermittent claudication, coronary vasodilation, prevention of stroke or TIAs (combined with aspirin), angina prophylaxis.

**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 transluminal coronary angioplasty.

**ADVERSE EFFECTS**
Bleeding, thrombocytopenia.
Cancer drugs—cell cycle

**Microtubule inhibitors**
- Paclitaxel
- Vinblastine
- Vincristine

**Topoisomerase inhibitors**
- Etoposide
- Teniposide
- Irinotecan
- Topotecan

**Antimetabolites**
- Azathioprine
- Cladribine
- Cytarabine
- 5-fluorouracil
- Hydroxyurea
- Methotrexate
- 6-mercaptopurine

**Platinum agents (eg, cisplatin)**

**Alkylating agents:**
- Busulfan
- Cyclophosphamide
- Ifosfamide
- Nitrosoureas (eg, carmustine)

**Cell cycle—dependent drugs**
- Bleomycin
- DNA synthesis
- DNA repair
- Cytokinesis
- Mitosis
- S phase
- G2/M phase
- G1 phase
- G0 phase
- Resting

**Cancer drugs—targets**

- **Nucleotide synthesis**
  - MTX, 5-FU: ↓ thymidine synthesis
  - 6-MP: ↓ de novo purine synthesis
  - Hydroxyurea: inhibits ribonucleotide reductase

- **DNA synthesis**
  - Alkylation agents, cisplatin: cross-link DNA
  - Bleomycin: DNA strand breakage
  - Dactinomycin, doxorubicin: DNA intercalators
  - Etoposide: inhibits topoisomerase II
  - Irinotecan: inhibits topoisomerase I

- **RNA synthesis**
  - Vinca alkaloids: inhibit microtubule formation
  - Paclitaxel: inhibits microtubule disassembly

- **Protein synthesis**

- **Cellular division**
### Antimetabolites

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azathioprine, 6-mercaptopurine</strong></td>
<td>Purine (thiol) analogs → 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. 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 → inhibition of 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 folic acid. This complex inhibits thymidylate synthase → dTMP → DNA synthesis.</td>
<td>Colon cancer, pancreatic cancer, basal cell carcinoma (topical). Effects enhanced with the addition of leucovorin.</td>
<td>Myelosuppression—worsened with the addition of leucovorin (folinic acid).</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Folic acid analog that competitively inhibits dihydrofolate reductase → dTMP → 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.</td>
</tr>
</tbody>
</table>

*aAll 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.</td>
<td>Solid tumors, leukemias, lymphomas.</td>
<td>Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia. Dexrazoxane (iron chelating agent), used to prevent cardiotoxicity.</td>
</tr>
</tbody>
</table>

### Alkylation 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>CML. Also 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 N-7. Require bioactivation by liver.</td>
<td>Solid tumors, leukemia, lymphomas.</td>
<td>Myelosuppression; hemorrhagic cystitis, prevented with mesna (thiol group of mesna binds toxic metabolites) or N-acetylcysteine.</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 taxols</td>
<td>Hyperstabilize polymerized microtubules in M phase so that mitotic spindle cannot break down (anaphase cannot occur).</td>
<td>Ovarian and breast carcinomas.</td>
<td>Myelosuppression, neuropathy, hypersensitivity.</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).</td>
</tr>
</tbody>
</table>

### Cisplatin, carboplatin

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Cross-link DNA.</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Testicular, bladder, ovary, and lung carcinomas.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Etoposide, teniposide

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Etoposide inhibits topoisomerase II → ↓ DNA degradation.</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solid tumors (particularly testicular and small cell lung cancer), leukemias, lymphomas.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Irinotecan, topotecan

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Inhibit topoisomerase I and prevent DNA unwinding and replication.</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colon cancer (irinotecan); ovarian and small cell lung cancers (topotecan).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Hydroxyurea

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Inhibits ribonucleotide reductase → ↓ DNA Synthesis (S-phase specific).</th>
<th>CLINICAL USE</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Melanoma, CML, sickle cell disease (↑ HbF).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                                  | Severe myelosuppression.                                            |                                      |                                        |
**Prednisone, prednisolone**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Various; bind intracytoplasmic steroid receptor; alter gene transcription.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Most commonly used glucocorticoids in cancer chemotherapy. Used in CLL, non-Hodgkin lymphoma (part of combination chemotherapy regimen). Also used as immunosuppressants (eg, in autoimmune diseases).</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Cushing-like symptoms; weight gain, central obesity, muscle breakdown, cataracts, acne, osteoporosis, hypertension, peptic ulcers, hyperglycemia, psychosis.</td>
</tr>
</tbody>
</table>

**Bevacizumab**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Monoclonal antibody against VEGF. Inhibits angiogenesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Solid tumors (colorectal cancer, renal cell carcinoma).</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Hemorrhage, blood clots, and impaired wound healing.</td>
</tr>
</tbody>
</table>

**Erlotinib**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>EGFR tyrosine kinase inhibitor.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Non-small cell lung carcinoma.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Rash.</td>
</tr>
</tbody>
</table>

**Cetuximab**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Monoclonal antibody against EGFR.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Stage IV colorectal cancer (wild-type KRAS), head and neck cancer.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Rash, elevated LFTs, diarrhea.</td>
</tr>
</tbody>
</table>

**Imatinib**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Tyrosine kinase inhibitor of BCR-ABL (Philadelphia chromosome fusion gene in CML) and c-kit (common in GI stromal tumors).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>CML, GI stromal tumors.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Fluid retention.</td>
</tr>
</tbody>
</table>

**Rituximab**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Monoclonal antibody against CD20, which is found on most B-cell neoplasms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Non-Hodgkin lymphoma, CLL, ITP, rheumatoid arthritis.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>↑ risk of progressive multifocal leukoencephalopathy.</td>
</tr>
</tbody>
</table>
### 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 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 HER2-initiated cellular signaling and antibody-dependent cytotoxicity.

**CLINICAL USE**  
HER-2$^+$ breast cancer and gastric cancer (tras2zumab).

**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.

### Common chemotoxicities

- Cisplatin/Carboplatin → ototoxicity (and nephrotoxicity)
- Vincristine → peripheral neuropathy
- Bleomycin, BUSulfan → pulmonary fibrosis
- Doxorubicin → cardiotoxicity
- Trastuzumab → cardiotoxicity
- Cisplatin/Carboplatin → nephrotoxic (and acoustic nerve damage)
- CYclophosphamide → hemorrhagic cystitis
- 5-FU → myelosuppression
- 6-MP → myelosuppression
- Methotrexate → myelosuppression
“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

Musculoskeletal, Skin, and Connective Tissue

\- Anatomy and Physiology 416
\- Pathology 426
\- Dermatology 437
\- Pharmacology 446
### Knee exam
ACL: extends from lateral femoral condyle to anterior tibia.
PCL: extends from medial femoral condyle to posterior tibia.
Perform knee exam with patient supine.

<table>
<thead>
<tr>
<th>TEST</th>
<th>PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior drawer sign</td>
<td>Bending knee at 90° angle, ↑ anterior gliding of tibia due to ACL injury.</td>
</tr>
<tr>
<td>Posterior drawer sign</td>
<td>Bending knee at 90° angle, ↑ posterior gliding of tibia due to PCL injury.</td>
</tr>
<tr>
<td>Abnormal passive abduction</td>
<td>Knee either extended or at ~ 30° angle, lateral (valgus) force → medial space widening of tibia → MCL injury.</td>
</tr>
<tr>
<td>Abnormal passive adduction</td>
<td>Knee either extended or at ~ 30° angle, medial (varus) force → lateral space widening of tibia → LCL injury.</td>
</tr>
<tr>
<td>McMurray test</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</td>
</tr>
<tr>
<td></td>
<td>• Pain, “popping” on internal rotation → lateral meniscal tear</td>
</tr>
</tbody>
</table>
Common knee conditions

“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 knee’s largest sac of synovial fluid. Can be caused by repeated trauma or pressure from excessive kneeling.

Baker cyst
Popliteal fluid collection in gastrocnemius-semimembranous bursa commonly communicating with synovial space and related to chronic joint disease.

Rotator cuff muscles
Shoulder muscles that form the rotator cuff:
- 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), assessed by “empty/full can” test.
- Infraspinatus (suprascapular nerve)—laterally rotates arm; pitching injury.
- teres minor (axillary nerve)—adducts and laterally rotates arm.
- Subscapularis (upper and lower subscapular nerves)—medially rotates and adducts arm. Innervated primarily by C5-C6.

SIS (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 bones

Scaphoid, Lunate, Triquetrum, Pisiform, Hamate, Capitate, Trapezoid, Trapezium (So Long To Pinky, Here Comes The Thumb). Scaphoid (palpated in anatomic snuff box) is the most commonly fractured carpal bone (typically from a fall on an outstretched hand) and is prone to avascular necrosis owing to retrograde blood supply. Dislocation of lunate may cause acute carpal tunnel syndrome. A fall on an outstretched hand that damages the hook of the hamate can cause ulnar nerve injury.

Carpal tunnel syndrome

Entrapment of median nerve in carpal tunnel; nerve compression → paresthesia, pain, and numbness in distribution of median nerve (thenar eminence atrophies but sensation spared, because palmar cutaneous branch enters the hand external to carpal tunnel). Associated with pregnancy, rheumatoid arthritis, hypothyroidism, diabetes, dialysis-related amyloidosis; may be associated with repetitive use.

Guyon canal syndrome

Compression of ulnar nerve at wrist or hand. Classically seen in cyclists due to pressure from handlebars.
### 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&lt;br&gt;Loss of arm abduction at shoulder (&gt; 15 degrees)&lt;br&gt;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&lt;br&gt;Loss of sensation over lateral forearm</td>
</tr>
<tr>
<td>Radial (C5-T1)</td>
<td>Midshaft fracture of humerus; compression of axilla, eg, due to crutches or sleeping with arm over chair (“Saturday night palsy”)</td>
<td>Wrist drop: loss of elbow, wrist, and finger extension&lt;br&gt;↓ grip strength (wrist extension necessary for maximal action of flexors)&lt;br&gt;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”&lt;br&gt;Loss of wrist flexion, flexion of lateral fingers, thumb opposition, lumbricals of 2nd and 3rd digits&lt;br&gt;Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 3½ fingers with proximal lesion&lt;br&gt;Tinel sign (tingling on percussion) in carpal tunnel syndrome</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)</td>
<td>“Ulnar claw” on digit extension&lt;br&gt;Radial deviation of wrist upon flexion (proximal lesion)&lt;br&gt;Loss of wrist flexion, flexion of medial fingers, abduction and adduction of fingers (interossei), actions of medial 2 lumbrical muscles&lt;br&gt;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”&lt;br&gt;Loss of thenar muscle group: opposition, abduction, and flexion of thumb&lt;br&gt;No loss of sensation</td>
</tr>
</tbody>
</table>

![Diagram of upper extremity nerves](image)
### Brachial Plexus Lesions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Injury/Effect</th>
<th>Causes</th>
<th>Muscle Deficit</th>
<th>Functional Deficit</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erb Palsy (&quot;waiter's tip&quot;)</td>
<td>Traction or tear of upper &quot;Erb-er&quot; trunk: C5-C6 roots</td>
<td>Infants—lateral traction on neck during delivery. Adults—trauma.</td>
<td>Deltoid, supraspinatus. Infraspinatus.</td>
<td>Total claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints.</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abduction (arm hangs by side).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lateral rotation (arm medially rotated).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biceps brachii, Flexion, supination (arm extended and pronated).</td>
<td></td>
</tr>
<tr>
<td>Klumpke Palsy</td>
<td>Traction or tear of lower trunk: C8-T1 root</td>
<td>Infants—upward force on arm during delivery. Adults—trauma (eg, grabbing a tree branch to break a fall).</td>
<td>Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar.</td>
<td>Same as Klumpke palsy.</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression.</td>
<td></td>
</tr>
<tr>
<td>Thoracic Outlet Syndrome</td>
<td>Compression of lower trunk and subclavian vessels</td>
<td>Cervical rib, Pancoast tumor</td>
<td>Same as Klumpke palsy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winged Scapula</td>
<td>Lesion of long thoracic nerve</td>
<td>Axillary node dissection after mastectomy, stab wounds.</td>
<td>Serratus anterior.</td>
<td>Inability to anchor scapula to thoracic cage; cannot abduct arm above horizontal position.</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
</tr>
</tbody>
</table>
**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><strong>PRESENTATION</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Extending fingers/at rest</td>
<td>Making a fist</td>
</tr>
<tr>
<td>Extending fingers/at rest</td>
<td>Making a fist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CONTEXT</strong></th>
<th>Extending fingers/at rest</th>
<th>Making a fist</th>
<th>Extending fingers/at rest</th>
<th>Making a fist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOCATION OF LESION</strong></td>
<td>Distal ulnar nerve</td>
<td>Proximal median nerve</td>
<td>Distal median nerve</td>
<td>Proximal ulnar nerve</td>
</tr>
<tr>
<td><strong>SIGN</strong></td>
<td>“Ulnar claw”</td>
<td>“Pope’s blessing”</td>
<td>“Median claw”</td>
<td>“OK gesture” (with digits 1–3 flexed)</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.

**Hand muscles**

Thenar (median)—Opponens pollicis, Abductor pollicis brevis, Flexor pollicis brevis, superficial head (deep head by ulnar nerve).

Hypothenar (ulnar)—Opponens digitii minimi, Abductor digitii minimi, Flexor digitii minimi brevis.

Dorsal interossei—abduct the fingers.

Palmar interossei—adduct the fingers.

Lumbricals—flex at the MCP joint, extend PIP and DIP joints.

Both groups perform the same functions: Oppose, Abduct, and Flex (OAF).

DAB = Dorsals Abduct.

PAD = Palmaris Abduct.
Lower extremity nerves

<table>
<thead>
<tr>
<th>NERVE</th>
<th>CAUSE OF INJURY</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obturator (L2–L4)</td>
<td>Pelvic surgery</td>
<td>↓ thigh sensation (medial) and ↓ adduction.</td>
</tr>
<tr>
<td>Femoral (L2–L4)</td>
<td>Pelvic fracture</td>
<td>↓ thigh flexion and leg extension.</td>
</tr>
<tr>
<td>Common peroneal (L4–S2)</td>
<td>Trauma or compression of lateral aspect of leg, fibular neck fracture</td>
<td>Foot drop—inverted and plantarflexed at rest, loss of eversion and dorsiflexion. “Steppage gait.” Loss of sensation on dorsum of foot.</td>
</tr>
<tr>
<td>Tibial (L4–S3)</td>
<td>Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)</td>
<td>Inability to curl toes and loss of sensation on sole of foot. In proximal lesions, foot everted at rest with loss of inversion and plantarflexion.</td>
</tr>
<tr>
<td>Superior gluteal (L4–S1)</td>
<td>Iatrogenic injury during intramuscular injection to upper medial gluteal 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>Inferior gluteal (L5–S2)</td>
<td>Posterior hip dislocation</td>
<td>Difficulty climbing stairs, rising from seated position. Loss of hip extension.</td>
</tr>
</tbody>
</table>

 Superior gluteal nerve innervates gluteus medius, gluteus minimus, and tensor fascia latae. Inferior gluteal nerve innervates gluteus maximus.

PED = Peroneal Everts and Dorsiflexes; if injured, foot drop PED.

TIP = Tibial Inverts and Plantarflexes; if injured, can’t stand on TIP toes.

Sciatic nerve (L4–S3) innervates posterior thigh, splits into common peroneal and tibial nerves.

Pudendal nerve (S2–S4) innervates perineum. Can be blocked with local anesthetic during childbirth using the ischial spine as a landmark for injection.

Choose superolateral gluteal quadrant as intramuscular injection site to avoid nerve injury.
**Signs of lumbosacral radiculopathy**

Paresthesias and weakness in distribution of specific lumbar or sacral spinal nerves. Often due to intervertebral disc herniation in which the nerve associated with the inferior vertebral body is impinged (eg, herniation of L3–L4 disc affects the L4 spinal nerve). 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>DISC 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 plantarflexion, 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 thoracic</td>
<td>Lateral thoracic</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>
Muscle conduction to contraction

T-tubules are extensions of plasma membrane juxtaposed with terminal cisternae of the sarcoplasmic reticulum.

In skeletal muscle, 1 T-tubule + 2 terminal cisternae = triad.
In cardiac muscle, 1 T-tubule + 1 terminal cisterna = dyad.

1. Action potential depolarization opens presynaptic voltage-gated Ca\(^{2+}\) channels, inducing neurotransmitter release.
2. Postsynaptic ligand binding leads to muscle cell depolarization in the motor end plate.
3. Depolarization travels along muscle cell and down the T-tubule.
4. Depolarization of the voltage-sensitive dihydropyridine receptor, mechanically coupled to the ryanodine receptor on the sarcoplasmic reticulum, induces a conformational change in both receptors, causing Ca\(^{2+}\) release from sarcoplasmic reticulum.
5. Released Ca\(^{2+}\) binds to troponin C, causing a conformational change that moves tropomyosin out of the myosin-binding groove on actin filaments.
6. Myosin releases bound ADP and P\(_i\), → displacement of myosin on the actin filament (power stroke). Contraction results in shortening of H and I bands and between Z lines (HIZ shrinkage), but the A band remains the same length (A band is Always the same length).

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.

**Type 2 muscle**

- **Fast twitch; white fibers resulting from**
  - ↓ mitochondria and myoglobin concentration (↑ anaerobic glycolysis). Proportion ↑ after weight/resistance training.
**Smooth muscle contraction**

![Diagram of smooth muscle contraction]

**Bone formation**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endochondral ossification</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Membranous ossification</strong></td>
<td>Bones of calvarium and facial bones. Woven bone formed directly without cartilage. Later remodeled to lamellar bone.</td>
</tr>
</tbody>
</table>

**Cell biology of bone**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteoblast</strong></td>
<td>Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum.</td>
</tr>
<tr>
<td><strong>Osteoclast</strong></td>
<td>Dissolves bone by secreting H⁺ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors.</td>
</tr>
<tr>
<td><strong>Parathyroid hormone</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Estrogen</strong></td>
<td>Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Estrogen deficiency (surgical or postmenopausal), excess cycles of remodeling, and bone resorption lead to osteoporosis.</td>
</tr>
</tbody>
</table>
Achondroplasia

Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is not 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). 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 secondary to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other medical conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes).

Diagnosed by a bone mineral density scan (dual-energy x-ray absorptiometry) with a T-score of ≤−2.5 or by a fragility fracture of hip or vertebra.

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).

Osteopetrosis (marble bone disease)

Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. X-rays show bone-in-bone (“stone” bone) appearance. Can result in cranial nerve impingement and palsies as a result of narrowed foramina. 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 bow legs, bead-like costochondral junctions (rachitic rosary), craniotabes (soft skull). ↑ vitamin D → ↑ serum Ca²⁺ → ↑ PTH secretion → ↑ serum PO₄³⁻. 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 Ca²⁺, phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone (osteocytes with 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

Osteonecrosis (avascular necrosis)
Infarction of bone and marrow, usually very painful. Most common site is femoral head (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 Ca²⁺</th>
<th>PO₄³⁻</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. Ca²⁺ ↓ 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>“Brown tumors” due to fibrous replacement of bone, subperiosteal thinning</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</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 (↓ PO₄³⁻ 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>
### Primary bone tumors

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>EPIDEMIOLOGY/LOCATION</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign tumors</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Malignant tumors</strong></td>
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</tr>
</tbody>
</table>

[Diagram showing various bone lesions: Diaphysis, Epiphysis, Metaphysis, Osteosarcoma, Osteochondroma, Simple bone cyst, Fibrous dysplasia, Round cell lesions, Ewing sarcoma, Myeloma, Osteoid osteoma (nightsime pain, serval node), Giant cell tumor]
**Osteoarthritis and rheumatoid arthritis**

<table>
<thead>
<tr>
<th></th>
<th><strong>Osteoarthritis</strong></th>
<th><strong>Rheumatoid arthritis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATHOGENESIS</strong></td>
<td>Mechanical—wear and tear destroys articular cartilage (“degenerative joint disease”). Chondrocytes mediate degradation and inadequate repair.</td>
<td>Autoimmune—inflammatory cytokines and cells induce pannus (proliferative granulation tissue) formation, which erodes articular cartilage and bone.</td>
</tr>
</tbody>
</table>
| **PREDISPOISING FACTORS**    | Age, female, obesity, joint trauma. | Female, HLA-DR4, smoking, silica exposure.  
|                              |                     | ⊕ rheumatoid factor (anti-IgG antibody; in 80%), anti-cyclic citrullinated peptide antibody (more specific). |
| **JOINT FINDINGS**           | Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid non-inflammatory (WBC < 2000/mm³). Involves DIP (Heberden nodes) and PIP (Bouchard nodes), and 1st CMC; not MCP. | Erosions, juxtaarticular osteopenia, joint space narrowing, soft tissue swelling, subchondral cysts. Deformities include subluxation, fingers with ulnar deviation, swan neck, and boutonniere. Synovial fluid inflammatory (WBC > 2000/mm³). Involves MCP, PIP, wrist; not DIP or 1st CMC. |
| **TREATMENT**                | Acetaminophen, NSAIDs, intra-articular glucocorticoids. | NSAIDs, glucocorticoids, disease-modifying agents (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), biologic agents (eg, TNF-α inhibitors). |

*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.
**Gout**

**FINDINGS**

Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints. More common in males. Associated with hyperuricemia, which can be caused by:

- Underexcretion of uric acid (90% of patients)—largely idiopathic; 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 birefringent under polarized light (yellow under parallel light, blue under perpendicular light).

**SYMPTOMS**

Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid).

**TREATMENT**

Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine.
Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).

---

**Calcium pyrophosphate deposition disease**

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 birefringent under polarized light (blue when parallel to light).

Acute treatment: NSAIDs, colchicine, glucocorticoids.
Prophylaxis: colchicine.
**Sjögren syndrome**

Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates. Predominantly affects females 40–60 years old.

Findings:
- Inflammatory joint pain
- Keratoconjunctivitis sicca (dry tear production and subsequent corneal damage)
- Xerostomia (dry saliva production)
- Presence of antinuclear antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

A common 1st disorder or a 2nd syndrome associated with other autoimmune disorders (eg, rheumatoid arthritis, SLE, systemic sclerosis).

Complications: dental caries; mucosa-associated lymphoid tissue (MALT) lymphoma (may present as parotid enlargement).

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**Septic arthritis**

*Staphylococcus 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 polyarthritis, 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, eg, 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. Seen in fewer than 1/3 of patients with psoriasis.

**Ankylosing spondylitis**
Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation. Bamboo spine (vertebral fusion). More common in males.

**Inflammatory bowel disease**
Crohn disease and ulcerative colitis are often associated with spondyloarthritis.

**Reactive arthritis**
Formerly known as Reiter syndrome. Classic triad:
- Conjunctivitis
- Urethritis
- Arthritis

“Can’t see, can’t pee, can’t bend my knee.” Post-GI (Shigella, Salmonella, Yersinia, Campylobacter) or Chlamydia infections.
Systemic lupus erythematosus

**SYMPTOMS**

Classic presentation: rash, joint pain, and fever, most commonly in a female of reproductive age and African-American descent.

**Libman-Sacks Endocarditis**—nonbacterial, verrucous thrombi usually on mitral or aortic valve (LSE in SLE).

Lupus nephritis (glomerular deposition of anti-DNA immune complexes) can be nephritic or nephrotic (hematuria or proteinuria). Most common and severe type is diffuse proliferative.

Common causes of death in SLE:

- Cardiovascular disease
- Infections
- Renal disease

**FINDINGS**

| Antinuclear antibodies (ANA) | Sensitive, not specific |
| Anti-dsDNA antibodies | Specific, poor prognosis (renal disease) |
| Anti-Smith antibodies | Specific, not prognostic (directed against snRNPs) |
| Antihistone antibodies | Sensitive for drug-induced lupus (eg, hydralazine, procainamide) |

C3, C4, and CH50 due to immune complex formation.

**TREATMENT**

NSAIDs, steroids, immunosuppressants, hydroxychloroquine.

**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, anticardiolipin, anti-β2 glycoprotein antibodies.

Treat with systemic anticoagulation.

Anticardiolipin antibodies and lupus anticoagulant can cause false-positive VDRL/RPR and prolonged PTT.

**Mixed connective tissue disease**

Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).
Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas A, 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 B. CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy C.

Associated with restrictive lung disease (interstitial fibrosis), erythema nodosum, lupus pernio (skin lesions on face resembling lupus), Bell palsy, epithelioid granulomas containing microscopic Schaumann and asteroid bodies, uveitis, hypercalcemia (due to \( \uparrow \) 1α-hydroxylase–mediated vitamin D activation in macrophages).

Treatment: steroids (if symptomatic).

Polymyalgia rheumatica

**SYMPTOMS**
Pain and stiffness in shoulders and 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.

**FINDINGS**
\( \uparrow \) ESR, \( \uparrow \) CRP, normal CK.

**TREATMENT**
Rapid response to low-dose corticosteroids.

Fibromyalgia

Most commonly seen in females 20–50 years old. Chronic, widespread musculoskeletal pain associated with stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance (“fibro fog”).

Treatment: regular exercise, antidepressants (TCAs, SNRIs), anticonvulsants.
Polymyositis/dermatomyositis

† CK, ⊕ ANA, ⊕ anti-Jo-1, ⊕ anti-SRP, ⊕ anti-Mi-2 antibodies. Treatment: steroids followed by long-term immunosuppressant therapy (e.g., methotrexate).

Polymyositis

Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.

Dermatomyositis

Similar to polymyositis, but also involves malar rash (similar to SLE), Gottron papules A, heliotrope (erythematous periorbital) rash B, “shawl and face” rash C, “mechanic’s hands.” † risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.

Neuromuscular junction diseases

**Myasthenia gravis**

FREQUENCY

Most common NMJ disorder

PATHOPHYSIOLOGY

Autoantibodies to postsynaptic ACh receptor

CLINICAL

Ptosis, diplopia, weakness
Worsens with muscle use

ASSOCIATED WITH

Thymoma, thymic hyperplasia

ACHE INHIBITOR ADMINISTRATION

Reverses symptoms (edrophonium to diagnose, pyridostigmine to treat)

**Lambert-Eaton myasthenic syndrome**

FREQUENCY

Uncommon

PATHOPHYSIOLOGY

Autoantibodies to presynaptic Ca2+ channel → ↓ ACh release

CLINICAL

Proximal muscle weakness, autonomic symptoms (dry mouth, impotence)
Improves with muscle use

ASSOCIATED WITH

Small cell lung cancer

ACHE INHIBITOR ADMINISTRATION

Minimal effect

**Myositis ossificans**

Heterotopic ossification of skeletal muscle following muscular trauma A. Most often seen in upper or lower extremity. May present as suspicious “mass” at site of known trauma or as incidental finding on radiography.
**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. Also sclerosis of renal, pulmonary (most common cause of death), cardiovascular, GI systems. 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, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. More benign clinical course. Associated with anti-centromere antibody.

**Raynaud phenomenon**

Blood flow to the 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 (limited form of systemic sclerosis) syndrome. Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with Ca$^{2+}$ channel blockers.

**Skin layers**

Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis). Epidermis layers from surface to base:

- Stratum Corneum (keratin)
- Stratum Lucidum
- Stratum Granulosum
- Stratum Spinosum (desmosomes)
- Stratum Basale (stem cell site)

Californians Like Girls in String Bikinis.
Musculoskeletal, skin, and connective tissue

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 cadherins (Ca²⁺-dependent adhesion proteins). Loss of E-cadherin promotes metastasis.
- **Desmosome** (spot desmosome, macula adherens)—structural support via intermediate filament interactions. Autoantibodies impetigo (bullous pemphigoid). (Desmosomes are down “bullos”).
- **Gap junction**—channel proteins called connexons permit electrical and chemical communication between cells.

**Integrins**—membrane proteins that maintain integrity of basolateral membrane by binding to collagen and laminin in basement membrane.

### Dermatologic macroscopic terms (morphology)

<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>Hyperkeratosis with 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>Disorder</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 areas of complete depigmentation. Caused by autoimmune destruction of melanocytes.</td>
</tr>
</tbody>
</table>
Common skin disorders

**Acne**

Pilosebaceous follicles with sebum, keratin, *Propionibacterium acnes* → obstruction (comedones) and inflammation (papules/pustules, nodules, cysts). Treatment includes retinoids, benzoyl peroxide, antibiotics.

**Atopic dermatitis (eczema)**

Pruritic eruption, commonly on skin flexures. Often associated with other atopic diseases (asthma, allergic rhinitis, food allergies); serum IgE. Usually appears on face in infancy and then antecubital fossae.

**Allergic contact dermatitis**

Type IV hypersensitivity reaction that follows exposure to allergen. Lesions occur at site of contact (eg, nickel, poison ivy, neomycin).

**Melanocytic nevus**

Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular. Junctional nevi are flat macules.

**Psoriasis**

Papules and plaques with silvery scaling, especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. Transient stratum spinosum, stratum granulosum. Auspitz sign (arrow in image)—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Can be associated with nail pitting and psoriatic arthritis.

**Rosacea**

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 (bulbous deformation of nose).

**Seborrheic keratosis**


**Verrucae**


**Urticaria**

Hives. Pruritic wheals that form after mast cell degranulation. Characterized by superficial dermal edema and lymphatic channel dilation.
### Vascular tumors of skin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiosarcoma</td>
<td>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.</td>
</tr>
<tr>
<td>Bacillary angiomatosis</td>
<td>Benign capillary skin papules found in AIDS patients. Caused by <em>Bartonella henselae</em> infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate.</td>
</tr>
<tr>
<td>Cherry hemangioma</td>
<td>Benign capillary hemangioma of the elderly. Does not regress. Frequency ↑ with age.</td>
</tr>
<tr>
<td>Cystic hygroma</td>
<td>Cavernous lymphangioma of the neck. Associated with Turner syndrome.</td>
</tr>
<tr>
<td>Glomus tumor</td>
<td>Benign, painful, red-blue tumor, commonly under fingernails. Arises from modified smooth muscle cells of the thermoregulatory glomus body.</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Endothelial malignancy most commonly of the skin, but also mouth, GI tract, and respiratory tract. Associated with HHV-8 and HIV. Frequently mistaken for bacillary angiomatosis, but has lymphocytic infiltrate.</td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>Polypoid lobulated capillary hemangioma that can ulcerate and bleed. Associated with trauma and pregnancy.</td>
</tr>
<tr>
<td>Strawberry hemangioma</td>
<td>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.</td>
</tr>
</tbody>
</table>
Skin infections

**Bacterial infections**

**Impetigo**  Very superficial skin infection. Usually from *S. aureus* or *S. pyogenes*. Highly contagious. Honey-colored crusting A.

Bullous impetigo B 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 demarcation between infected and normal skin C.

**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 D.

**Abscess**  Collection of pus from a walled-off infection within deeper layers of skin E. Offending organism is almost always *S. aureus*.

**Necrotizing fasciitis**  Deeper tissue injury, usually from anaerobic bacteria or *S. pyogenes*. Results in crepitus from methane and CO₂ production. “Flesh-eating bacteria.” Causes bullae and a purple color to the skin F.

**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 G that heals completely. Nikolsky sign. 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 H (finger).

**Molluscum contagiosum**  Umbilicated papules I 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 J. EBV mediated. Occurs in HIV-positive patients, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).
### Blistering skin disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pemphigus vulgaris</strong></td>
<td>Potentially fatal autoimmune skin disorder with IgG antibody against desmoglein (component of desmosomes). Flaccid intraepidermal bullae caused by acantholysis (keratinocytes in stratum spinosum are connected by desmosomes); oral mucosa also involved. Immunofluorescence reveals antibodies around epidermal cells in a reticular (net-like) pattern. Nikolsky sign (separation of epidermis upon manual stroking of skin).</td>
</tr>
<tr>
<td><strong>Bullous pemphigoid</strong></td>
<td>Less severe than pemphigus vulgaris. 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.</td>
</tr>
<tr>
<td><strong>Dermatitis herpetiformis</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Erythema multiforme</strong></td>
<td>Associated with infections (eg, <em>Mycoplasma pneumoniae</em>, 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).</td>
</tr>
<tr>
<td><strong>Stevens-Johnson syndrome</strong></td>
<td>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 &gt; 30% of the body surface area involved is toxic epidermal necrolysis (TEN). 10–30% involvement denotes SJS-TEN.</td>
</tr>
</tbody>
</table>
### Miscellaneous skin disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acanthosis nigricans</strong></td>
<td>Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck. Associated with insulin resistance (e.g., diabetes, obesity, Cushing syndrome), visceral malignancy (e.g., gastric adenocarcinoma).</td>
</tr>
<tr>
<td><strong>Actinic keratosis</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Erythema nodosum</strong></td>
<td>Painful inflammatory lesions of subcutaneous fat, usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections, leprosy, inflammatory bowel disease.</td>
</tr>
<tr>
<td><strong>Lichen Planus</strong></td>
<td>Pruritic, purple, polygonal papules and plaques are the <strong>6 P’s</strong> of lichen planus. Mucosal involvement manifests as Wickham striae (reticular white lines). Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.</td>
</tr>
<tr>
<td><strong>Pityriasis rosea</strong></td>
<td>“Herald patch” followed days later by other scaly erythematous plaques, often in a “Christmas tree” distribution on trunk. Multiple plaques with collarette scale. Self-resolving in 6–8 weeks.</td>
</tr>
<tr>
<td><strong>Sunburn</strong></td>
<td>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. Can lead to impetigo, skin cancers (basal cell carcinoma, squamous cell carcinoma, melanoma).</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. 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, 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. Associated with chronic draining sinuses. 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; fair-skinned persons are at high risk. Depth of tumor 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. 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

**MEMBRANE PHOSPHOLIPIDS**

Membrane phospholipids are metabolized by phospholipase A₂ to release arachidonic acid, which can then be metabolized via the 5-lipoxygenase pathway or the cyclooxygenase pathway.

**LEUKOTRIENE SYNTHESIS (5-lipoxygenase)**

- Zileuton
- Montelukast
- Zafirlukast

**Leukotrienes**

- LTC₄
- LTD₄
- LTE₄
- LTB₄

**Cyclic endoperoxides**

Cyclic endoperoxides are metabolites of prostaglandins and thromboxane.

**Prostaglandins**

- PGI₂
- PGE₁
- PGE₂
- PGF₂α

- Thromboxane (TXA₂)
- Prostacyclin (PGI₂)
- Prostaglandins (PGE₁, PGE₂, PGF₂α)

**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 VIII). Chronic use can lead to acute renal failure, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated with aspirin for viral infection. Causes respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis.

### Celecoxib

**Mechanism**
Reversibly inhibits specifically the cyclooxygenase (COX) isoform 2, 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. Sufa allergy.

### NSAIDs

Ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, meloxicam, piroxicam.

**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).

### 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

Alendronate, ibandronate, risedronate, zoledronate.

**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 stress fractures.

### Teriparatide

**Mechanism**
Recombinant PTH analog given subcutaneously daily. ↑ osteoblastic activity.

**Clinical Use**
Osteoporosis. Causes ↑ bone growth compared to antiresorptive therapies (eg, bisphosphonates).

**Adverse Effects**
Transient hypercalcemia.
### Gout drugs

**Chronic gout drugs (preventive)**

**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).

**Febuxostat**
- Inhibits xanthine oxidase.

**Febuxostat**
- Recombinant uricase that catalyzes metabolism of uric acid to allantoin (a more water-soluble product).

**Probenecid**
- Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.

**Acute gout drugs**

**NSAIDs**
- Naproxen, indomethacin.
- Do not give salicylates; all but the highest doses depress uric acid clearance. Even high doses (5–6 g/day) have only minor uricosuric activity.

**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 side effects.

### TNF-α inhibitors

All TNF-α inhibitors predispose to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etanercept</strong></td>
<td>Fusion protein (receptor for TNF-α + IgG1 Fc), produced by recombinant DNA. <strong>Etanercept</strong> is a TNF decoy receptor.</td>
<td>Rheumatoid arthritis, psoriasis, ankylosing spondylitis</td>
</tr>
<tr>
<td><strong>Infliximab, adalimumab</strong></td>
<td>Anti-TNF-α monoclonal antibody.</td>
<td>Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis</td>
</tr>
</tbody>
</table>

### Rasburicase

**MECHANISM**
- Recombinant uricase that catalyzes metabolism of uric acid to allantoin.

**CLINICAL USE**
- Prevention and treatment of tumor lysis syndrome.
“Estimated amount of glucose used by an adult human brain each day, expressed in M&Ms: 250.”
—Harper’s Index

“He has two neurons held together by a spirochete.”
—Anonymous

“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
Neural development


Regional specification of developing brain

CNS/PNS origins

Neuroectoderm—CNS neurons, ependymal cells (inner lining of ventricles, make CSF), oligodendroglia, astrocytes. Neural crest—PNS neurons, Schwann cells. Mesoderm—Microglia (like Macrophages).
Neural tube defects
Neuropores fail to fuse (4th week) → persistent connection between amniotic cavity and spinal canal. Associated with low folic acid intake before conception and during pregnancy.
† α-fetoprotein (AFP) in amniotic fluid and maternal serum (except spina bifida occulta).
† acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test (fetal AChE in CSF flows through defect into amniotic fluid).

Spina bifida occulta
Failure of bony spinal canal 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. Normal AFP.

Meningocele
Meninges (but no neural tissue) herniate through bony defect.

Meningomyelocele
Meninges and neural tissue (eg, cauda equina) herniate through bony defect.

Forebrain anomalies
Anencephaly

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 Patau syndrome and fetal alcohol syndrome.

Posterior fossa malformations
Chiari II malformation
Herniation of low-lying cerebellar vermis through foramen magnum with aqueductal stenosis → hydrocephalus. Usually associated with lumbosacral meningomyelocele (paralysis/sensory loss at and below the level of the lesion).

Dandy-Walker syndrome
Agenesis of cerebellar vermis with cystic enlargement of 4th ventricle (fills the enlarged posterior fossa). Associated with noncommunicating hydrocephalus, spina bifida.
**Syringomyelia**

Cystic cavity (syrinx) within central canal of spinal cord (yellow arrow in A). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a “cape-like,” bilateral loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved). Associated with Chiari malformations (red arrow in A), trauma, and tumors.

Syrinx = tube, as in syringe.

Most common at C8–T1.

**Chiari I malformation**—cerebellar tonsillar ectopia > 3–5 mm; congenital, usually asymptomatic in childhood, manifests with headaches and cerebellar symptoms.

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**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.
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 distal to injury and axonal retraction proximally; allows for potential regeneration of axon (if in PNS).

Astrocytes

Microglia
Phagocytic scavenger cells of CNS (mesodermal, mononuclear origin). Activated in response to tissue damage. Not readily discernible by Nissl stain. HIV-infected microglia fuse to form multinucleated giant cells in CNS.

Myelin
Wraps and insulates axons. ↑ conduction velocity via saltatory conduction at the nodes of Ranvier, where there is a high concentration of Na⁺ channels. CNS—oligodendrocytes; PNS—Schwann cells.

Schwann cells
Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration. Derived from neural crest. May be injured in Guillain-Barré syndrome. Vestibular schwannoma—typically located on CN VIII in internal acoustic meatus, may extend to cerebellopontine angle.
Oligodendroglia


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</td>
<td>All skin, epidermis, some viscera</td>
<td>Pain, temperature</td>
</tr>
<tr>
<td></td>
<td>Aδ—fast, myelinated fibers</td>
<td></td>
<td></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 (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).
### Neurotransmitters

<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, SNpc</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>

### 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


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—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

The hypothalamus wears **TAN HATS**—Thirst and water balance, Adenohypophysis control (regulates anterior pituitary), Neurohypophysis releases hormones produced in the hypothalamus, Hunger, Autonomic regulation, Temperature regulation, Sexual urges.

Inputs (areas not protected by blood-brain barrier): OVLT (organum vasculosum of the lamina terminalis; senses change in osmolarity), area postrema (found in medulla, responds to emetics).

Supraoptic nucleus primarily makes ADH.
Paraventricular nucleus primarily makes oxytocin.
Hypothalamus makes ADH and oxytocin. They are carried by neurophysins down axons to posterior pituitary, where they are stored and released.

<table>
<thead>
<tr>
<th>Lateral area</th>
<th>Hunger. Destruction → anorexia, failure to thrive (infants). Stimulated by ghrelin, inhibited by leptin.</th>
<th>If you zap your lateral area, you shrink laterally.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventromedial area</td>
<td>Satiety. Destruction (e.g., craniopharyngioma) → hyperphagia. Stimulated by leptin.</td>
<td>If you zap your ventromedial area, you grow ventrally and medially.</td>
</tr>
<tr>
<td>Anterior hypothalamus</td>
<td>Cooling, parasympathetic.</td>
<td><strong>Anterior</strong> nucleus = cool off (cooling, parasympathetic). <strong>A/C</strong> = <strong>anterior cooling</strong>.</td>
</tr>
<tr>
<td>Posterior hypothalamus</td>
<td>Heating, sympathetic.</td>
<td>Posterior nucleus = get fired up (heating, sympathetic). If you zap your posterior hypothalamus, you become a poikilotherm (cold-blooded, like a snake).</td>
</tr>
<tr>
<td>Suprachiasmatic nucleus</td>
<td>Circadian rhythm.</td>
<td>You need sleep to be charismatic (chiasmatic).</td>
</tr>
</tbody>
</table>
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. Extraocular movements during REM sleep due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center). REM sleep occurs every 90 minutes, and duration ↑ through the night. ↑ ACh in REM.

Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and delta wave sleep; norepinephrine also ↓ REM sleep.

Treat bedwetting (sleep enuresis) with oral desmopressin (ADH analog); preferred over imipramine because of the latter’s adverse effects.

Benzodiazepines are useful for night terrors and sleepwalking.

<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>Alert, active mental concentration</td>
<td>Alpha</td>
</tr>
<tr>
<td>Non-REM sleep</td>
<td>Light sleep</td>
<td>Theta</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 occurs</td>
<td>Sleep spindles and K complexes</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; when dreaming, nightmares, and penile/clitoral tumescence occur; may serve memory processing function</td>
<td>Beta</td>
</tr>
</tbody>
</table>

At night, BATS Drink Blood
### Thalamus

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Input</th>
<th>Senses</th>
<th>Destination</th>
<th>Mnemonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral posterolateral nucleus</td>
<td>Spinothalamic and dorsal columns/medial lemniscus</td>
<td>Pain, temperature; pressure, touch, vibration, proprioception</td>
<td>1st somatosensory cortex</td>
<td></td>
</tr>
<tr>
<td>Ventral postero-Medial nucleus</td>
<td>Trigeminal and gustatory pathway</td>
<td>Face sensation, taste</td>
<td>1st somatosensory cortex</td>
<td>Makeup goes on the face (VPM)</td>
</tr>
<tr>
<td>Lateral geniculate nucleus</td>
<td>CN II</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. Structures include hippocampus (red arrows in A), amygdala, fornix, mammillary bodies, cingulate gyrus (blue arrows in A). Responsible for Feeding, Fleeing, Fighting, Feeling, and Sex. The famous 5 F’s.

### Dopaminergic pathways

Commonly altered by drugs (e.g., antipsychotics) and movement disorders (e.g., 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 (e.g., flat affect, limited speech)</td>
<td>Antipsychotic drugs have limited effect.</td>
</tr>
<tr>
<td>Mesolimbic</td>
<td>↑ activity → “positive” symptoms (e.g., delusions, hallucinations)</td>
<td>Primary therapeutic target of antipsychotic drugs → ↓ positive symptoms (e.g., in schizophrenia).</td>
</tr>
<tr>
<td>Nigrostriatal</td>
<td>↓ activity → extrapyramidal symptoms (e.g., 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.

**Input:**
- Contralateral cortex via middle cerebellar peduncle.
- Ipsilateral proprioceptive information via inferior cerebellar peduncle from spinal cord.

**Output:**
- Sends information to contralateral cortex to modulate movement. Output nerves = Purkinje cells → deep nuclei of cerebellum → contralateral cortex via superior cerebellar peduncle.
- Deep nuclei (lateral → medial)—Dentate, Emboliform, Globose, Fastigial (“Don’t Eat Greasy Foods”).

Lateral lesions—affect voluntary movement of extremities; when injured, propensity to fall toward injured (ipsilateral) side.

Medial lesions—involvement of midline structures (vermal cortex, fastigial nuclei) and/or flocculonodular lobe → truncal ataxia (wide-based cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature.
**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.

\[ D_1 \text{-Receptor} = \text{D1R} \]
\[ \text{Direct pathway} \]
\[ \text{Indirect pathway} = \text{Inhibitory} \]

Excitatory pathway—cortical inputs stimulate the striatum, stimulating the release of GABA, which inhibits GABA release from the GPI, disinhibiting the thalamus via the GPI (↑ motion).
Inhibitory pathway—cortical inputs stimulate the striatum, releasing GABA that disinhibits STN via GPe inhibition, and STN stimulates GPI to inhibit the thalamus (↓ motion).
Dopamine binds to \( D_1 \), stimulating the excitatory pathway, and to \( D_2 \), inhibiting the inhibitory pathway \( \rightarrow \) ↑ motion.
<table>
<thead>
<tr>
<th>Movement disorders</th>
<th>Presentation</th>
<th>Characteristic lesion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athetosis</td>
<td>Slow, writhing movements; especially seen in fingers</td>
<td>Basal ganglia (eg, Huntington)</td>
<td>Writhing, snake-like movement.</td>
</tr>
<tr>
<td>Chorea</td>
<td>Sudden, jerky, purposeless movements</td>
<td>Basal ganglia (eg, Huntington)</td>
<td>Chorea = dancing.</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Sustained, involuntary muscle contractions</td>
<td></td>
<td>Writer’s cramp; blepharospasm (sustained eyelid twitch).</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>High-frequency tremor with sustained posture (eg, outstretched arms),</td>
<td>Contralateral subthalamic nucleus (eg, lacunar stroke)</td>
<td>Often familial. Patients often self-medicate with alcohol, which + tremor amplitude. Treatment: nonselective ( \beta )-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.”</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>Slow, zigzag motion when pointing/extending toward a target</td>
<td>Cerebellar dysfunction</td>
<td>Contralateral lesion.</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),</td>
<td>Parkinson disease</td>
<td>Occurs at rest; “pill-rolling tremor” of Parkinson disease.</td>
</tr>
</tbody>
</table>

**Parkinson disease**

Degenerative disorder of CNS associated with Lewy bodies (composed of \( \alpha \)-synuclein—intracellular eosinophilic inclusions \( \alpha \)) and loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta.

Parkinson **TRAPS** your body:
- Tremor (pill-rolling tremor at rest)
- Rigidity (cogwheel)
- Akinesia (or bradykinesia)
- Postural instability
- Shuffling gait
Huntington disease

Autosomal dominant trinucleotide repeat disorder on chromosome 4. Symptoms manifest between ages 20 and 50; characterized by choreiform movements, aggression, depression, dementia (sometimes initially mistaken for substance abuse). ↑ dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity. Atrophy of caudate and putamen with hydrocephalus ex vacuo.

Expansion of \( \text{CAG} \) repeats (anticipation). Caudate loses ACh and GABA.

Cerebral cortex functions
**Aphasia**

Aphasia—higher-order language deficit (inability to understand/speak/read/write).

Dysarthria—motor inability to speak (movement deficit).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SPEECH FLUIDITY</th>
<th>COMPREHENSION</th>
<th>REPETITION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broca</td>
<td>Nonfluent</td>
<td>Intact</td>
<td>Impaired</td>
<td>Broca = Broken Boca (<em>boca</em> = mouth in Spanish). Broca area in inferior frontal gyrus of frontal lobe.</td>
</tr>
<tr>
<td>Wernicke</td>
<td>Fluent</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Wernicke is Wordy but makes no sense. Wernicke area in superior temporal gyrus of temporal lobe.</td>
</tr>
<tr>
<td>Conduction</td>
<td>Fluent</td>
<td>Intact</td>
<td>Impaired</td>
<td>Can be caused by damage to arcuate fasciculus.</td>
</tr>
<tr>
<td>Global</td>
<td>Nonfluent</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Arcuate fasciculus; Broca and Wernicke areas affected.</td>
</tr>
<tr>
<td>Transcortical motor</td>
<td>Nonfluent</td>
<td>Intact</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>Intact</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>Intact</td>
<td>Broca and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.</td>
</tr>
</tbody>
</table>
### Common brain lesions

<table>
<thead>
<tr>
<th>AREA OF LESION</th>
<th>CONSEQUENCE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala (bilateral)</td>
<td>Klüver-Bucy syndrome—disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality).</td>
<td>Associated with HSV-1 encephalitis.</td>
</tr>
<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>Nondominant parietal cortex</td>
<td>Hemispatial neglect syndrome (agnosia of the contralateral side of the world).</td>
<td></td>
</tr>
<tr>
<td>Dominant parietal cortex</td>
<td>Agraphia, acalculia, finger agnosia, left-right disorientation.</td>
<td>Gerstmann syndrome.</td>
</tr>
<tr>
<td>Reticular activating system (midbrain)</td>
<td>Reduced levels of arousal and wakefulness (eg, coma).</td>
<td></td>
</tr>
<tr>
<td>Mammillary bodies (bilateral)</td>
<td>Wernicke-Korsakoff syndrome—confusion, ophthalmoplegia, ataxia; memory loss (anterograde and retrograde amnesia), confabulation, personality changes.</td>
<td>Associated with thiamine (B₁) deficiency and excessive alcohol use; can be precipitated by giving glucose without B₁ to a B₁-deficient patient. Wernicke problems come in a CAN of beer: Confusion, Ataxia, Nystagmus.</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>Cerebellar hemisphere</td>
<td>Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion.</td>
<td>Degeneration associated with chronic alcohol use. Cerebellar hemispheres are laterally located—affect lateral limbs.</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>Truncal ataxia, dysarthria.</td>
<td>Vermis is centrally located—affects central body.</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>Contralateral hemiballismus.</td>
<td></td>
</tr>
<tr>
<td>Hippocampus (bilateral)</td>
<td>Anterograde amnesia— inability to make new memories.</td>
<td></td>
</tr>
<tr>
<td>Paramedian pontine reticular formation</td>
<td>Eyes look away from side of lesion.</td>
<td></td>
</tr>
<tr>
<td>Frontal eye fields</td>
<td>Eyes look toward lesion.</td>
<td></td>
</tr>
</tbody>
</table>
### Cerebral perfusion

Brain perfusion relies on tight autoregulation. Cerebral perfusion is primarily driven by $\text{PCO}_2$ ($\text{PO}_2$ 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 → ↓ $\text{PCO}_2$ → vasoconstriction → ↓ cerebral blood flow → ↓ intracranial pressure (ICP). May be used to treat acute cerebral edema (e.g., 2° to stroke) unresponsive to other interventions. CPP = MAP – ICP. If CPP = 0, there is no cerebral perfusion → brain death.

---

**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 ↑ cortical representation.
Cerebral arteries—cortical distribution

<table>
<thead>
<tr>
<th>Artery</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral artery</td>
<td>Supplies anteromedial surface</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>Supplies lateral surface</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>Supplies posterior and inferior surfaces</td>
</tr>
</tbody>
</table>

Watershed zones

Between anterior cerebral/middle cerebral, posterior cerebral/middle cerebral arteries. Damage by severe hypotension → upper leg/upper arm weakness, defects in higher-order visual processing.

Circle of Willis

System of anastomoses between anterior and posterior blood supplies to brain.
# 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 and face.</td>
<td>Contralateral paralysis and sensory loss—face and upper limb. Apasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) side.</td>
<td></td>
</tr>
<tr>
<td>Lenticulostriate artery</td>
<td>Striatum, internal capsule.</td>
<td>Contralateral paralysis and/or sensory loss—face and body. Absence of cortical signs (eg, neglect, aphasia, visual field loss).</td>
<td>Common location of lacunar infarcts, 2° to unmanaged hypertension.</td>
</tr>
<tr>
<td><strong>Posterior circulation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior inferior cerebellar artery</td>
<td>Lateral medulla—vestibular nuclei, lateral spinthalamic tract, spinal trigeminal nucleus, nucleus ambiguus, sympathetic fibers, inferior cerebellar peduncle.</td>
<td>Vomiting, vertigo, nystagmus; ↓ pain and temperature sensation from ipsilateral face and contralateral body; dysphagia, hoarseness, ↓ gag reflex; ipsilateral Horner syndrome; ataxia, dysmetria.</td>
<td>Lateral medullary (Wallenberg) syndrome. Nucleus ambiguus effects are specific to PICA lesions. “Don’t pick a (PICA) horse (hoarseness) that can’t eat (dysphagia).”</td>
</tr>
<tr>
<td>Anterior inferior cerebellar artery</td>
<td>Lateral pons—cranial nerve nuclei (vestibular nuclei, facial nucleus, spinal trigeminal nucleus, cochlear nuclei), spinthalamic tract, corticospinal tract, sympathetic fibers. Middle and inferior cerebellar peduncles.</td>
<td>Vomiting, vertigo, nystagmus. Paralysis of face, ↓ lacrimation, salivaion, ↓ taste from anterior 2/3 of tongue. Ipsilateral ↓ pain and temperature of the face, contralateral ↓ pain and temperature of the body. Ataxia, dysmetria.</td>
<td>Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions. “Facial droop means AICA’s pooped.”</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>Pons, medulla, lower midbrain, corticospinal and corticobulbar tracts, ocular cranial nerve nuclei, paramedian pontine reticular formation.</td>
<td>Preserved consciousness, vertical eye movement, blinking; quadriplegia, loss of voluntary facial, mouth, and tongue movements.</td>
<td>“Locked-in syndrome.”</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>Occipital cortex, visual cortex.</td>
<td>Contralateral hemianopia with macular sparing.</td>
<td></td>
</tr>
</tbody>
</table>
Aneurysms | Abnormal dilation of an artery due to weakening of vessel wall.
---|---
Saccular (berry) aneurysm | Occurs at bifurcations in the circle of Willis. Most common site is junction of anterior communicating artery and anterior cerebral artery. Rupture (most common complication) → subarachnoid hemorrhage (“worst headache of my life”) or hemorrhagic stroke. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race (↑ risk in blacks).
Charcot-Bouchard microaneurysm | Common, associated with chronic hypertension; affects small vessels (eg, in basal ganglia, thalamus); not seen on angiogram.

Effects of saccular aneurysms | Usually clinically silent until rupture → subarachnoid hemorrhage (eg, thunderclap headache). Can also cause symptoms via direct compression on surrounding structures by growing aneurysm.
---|---
**ARTERY** | **ASSOCIATED SYMPTOMS**
Anterior communicating artery | Compression may cause bitemporal hemianopia (compression of optic chiasm); visual acuity deficits.
Rupture may cause ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
Posterior communicating artery | Compression may cause ipsilateral CN III palsy → mydriasis (“blown pupil”); may also see ptosis, “down and out” eye.
Middle cerebral artery | Rupture may cause ischemia in MCA distribution → contralateral upper extremity and facial hemiparesis, sensory deficits.

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. Occurs in 10% of stroke patients.
### Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidural Hematoma</strong></td>
<td>Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture. Lucid interval. Rapid expansion under systemic arterial pressure → transtentorial herniation, CN III palsy. CT shows biconvex (lentiform), hyperdense blood collection not crossing suture lines.</td>
</tr>
<tr>
<td><strong>Subdural Hematoma</strong></td>
<td>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 that crosses suture lines (red arrows in C and D). Can cause midline shift (blue arrow in C), findings of “acute on chronic” hemorrhage (blue arrow in D).</td>
</tr>
<tr>
<td><strong>Subarachnoid Hemorrhage</strong></td>
<td>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. 4–10 days after hemorrhage, vasospasm (narrowing of blood vessels) can occur → ischemic infarct; nimodipine used for prevention. ↑ risk of developing communicating and/or obstructive hydrocephalus.</td>
</tr>
<tr>
<td><strong>Intraparenchymal Hemorrhage</strong></td>
<td>Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vasculitis, neoplasm. May be 2° to reperfusion injury in ischemic stroke. Typically occurs in basal ganglia and internal capsule (Charcot-Bouchard aneurysm of lenticulostriate vessels), but can be lobar.</td>
</tr>
</tbody>
</table>

![Images of brain scans](image1.png)
**Ischemic brain disease/stroke**

Irreversible damage begins after 5 minutes of hypoxia. Most vulnerable: hippocampus, neocortex, cerebellum, watershed areas. Irreversible neuronal injury. Ischemic hypoxia—“hypocampus” is most vulnerable.

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>12–48 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>Red neurons</td>
<td>Necrosis + neutrophils</td>
<td>Macrophages (microglia)</td>
<td>Reactive gliosis + 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; 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).

**Transient ischemic attack**

Brief, reversible episode of focal neurologic dysfunction without acute infarction (MR)I), with the majority resolving in < 15 minutes; deficits due to focal ischemia.

**Dural venous sinuses**

Large venous channels that run through the dura. Drain blood from cerebral veins 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 ventricle → 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 is made by ependymal cells of choroid plexus; it is reabsorbed by arachnoid granulations and then drains into dural venous sinuses.

---

**Idiopathic intracranial hypertension (pseudotumor cerebri)**

† ICP with no apparent cause on imaging (eg, hydrocephalus, obstruction of CSF outflow). Risk factors include being a woman of childbearing age, vitamin A excess, danazol, tetracycline.

Findings: headache, diplopia (usually from CN VI palsy), without change in mental status. Papilledema seen on fundoscopy. Lumbar puncture reveals † opening pressure and provides headache relief.

Treatment: weight loss, acetazolamide, topiramate, invasive procedures for refractory cases (eg, repeat lumbar puncture, CSF shunt placement, optic nerve fenestration surgery).

---

**Hydrocephalus**

† CSF volume → ventricular dilation +/- † ICP.

<table>
<thead>
<tr>
<th>Communicating hydrocephalus</th>
<th>↓ CSF absorption by arachnoid granulations (eg, arachnoid scarring post-meningitis) → † ICP, papilledema, herniation.</th>
</tr>
</thead>
<tbody>
<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 urinary incontinence, ataxia, and cognitive dysfunction (sometimes reversible). “Wet, wobbly, and wacky.” Characteristic magnetic gait (feet appear stuck to floor).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Noncommunicating (obstructive)</th>
<th>Caused by structural blockage of CSF circulation within ventricular system (eg, stenosis of aqueduct of Sylvius; colloid cyst blocking foramen of Monro; tumors).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalus mimics</td>
<td>Ex vacuo ventriculomegaly Appearance of † CSF on imaging, but is actually due to decreased brain tissue (neuronal atrophy) (eg, Alzheimer disease, advanced HIV, Pick disease). ICP is normal; triad is not seen.</td>
</tr>
</tbody>
</table>
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. 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.
Spinal tract anatomy and functions

<table>
<thead>
<tr>
<th>Tract and Function</th>
<th>1st-Order Neuron</th>
<th>Synapse 1</th>
<th>2nd-Order Neuron</th>
<th>Synapse 2</th>
<th>3rd-Order Neuron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal column</td>
<td>Sensory nerve ending → cell body in dorsal root ganglion → enters spinal cord, ascends ipsilaterally in dorsal column</td>
<td>Ipsilateral nucleus cuneatus or gracilis (medulla)</td>
<td>Decussates in medulla → ascends contralaterally in medial lemniscus</td>
<td>VPL. (thalamus)</td>
<td>Sensory cortex</td>
</tr>
<tr>
<td>Spinothalamic tract</td>
<td>Sensory nerve ending (Aδ and C fibers) → cell body in dorsal root ganglion → enters spinal cord</td>
<td>Ipsilateral gray matter (spinal cord)</td>
<td>Decussates at anterior white commissure → ascends contralaterally</td>
<td>VPL. (thalamus)</td>
<td>Sensory cortex</td>
</tr>
<tr>
<td>Lateral corticospinal tract</td>
<td>UMN: cell body in 1° motor cortex → descends ipsilaterally (through internal capsule), most fibers decussate at caudal medulla (pyramidal decussation) → descends contralaterally</td>
<td>Cell body of anterior horn (spinal cord)</td>
<td>LMN: leaves spinal cord</td>
<td>NMJ</td>
<td></td>
</tr>
</tbody>
</table>

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.</td>
</tr>
<tr>
<td>Reflexes</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Tone</td>
<td>↑</td>
<td>↓</td>
<td>Fas</td>
</tr>
<tr>
<td>Babinski</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>Complete occlusion of anterior spinal artery</td>
<td>Spares dorsal columns and Lissauer tract; upper thoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below ∼ T8.</td>
<td></td>
</tr>
<tr>
<td>Posterior spinal arteries</td>
<td>Tabes dorsalis</td>
<td>Caused by 3° syphilis. Results from degeneration (demyelination) of dorsal columns and roots → progressive sensory ataxia (impaired proprioception → poor coordination). Associated with Charcot joints, shooting pain, Argyll Robertson pupils. Exam will demonstrate absence of DTRs and ⊕ Romberg sign.</td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral loss of pain and temperature sensation in cape-like distribution; seen with Chiari I malformation; can expand and affect other tracts.</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂ deficiency</td>
<td>Subacute combined degeneration (SCD)—demyelination of Spinocerebellar tracts, lateral Corticospinal tracts, and Dorsal columns. Ataxic gait, paresthesia, impaired position/vibration sense.</td>
<td></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: weakness, hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Signs of infection: malaise, headache, fever, nausea, etc.

CSF shows ↑ WBCs and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

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**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 multiple spinal cord tracts → muscle weakness and loss of DTRs, vibratory sense, proprioception. **Staggering** gait, frequent **falling**, nystagmus, dysarthria, pes cavus, hammer toes, **diabetes mellitus**, **hypertrophic cardiomyopathy** (cause of death). Presents in childhood with kyphoscoliosis 🧲.

Friedreich is Fratastic (frataxin): he’s your favorite frat brother, always staggering and falling but has a sweet, big heart. Ataxic GAAit.

---

**Brown-Séquard syndrome**

Hemisection of spinal cord. Findings:

* Ipsilateral UMN signs below level of lesion (due to corticospinal tract damage)
* Ipsilateral loss of tactile, vibration, proprioception sense below level of lesion (due to dorsal column damage)
* Contralateral pain and temperature loss below level of lesion (due to spinothalamic tract damage)
* Ipsilateral loss of all sensation at level of lesion
* Ipsilateral LMN signs (eg, flaccid paralysis) at level of lesion

If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.
Landmark dermatomes

- **C2**—posterior half of a skull “cap.”
- **C3**—high turtleneck shirt.
- **C4**—low-collar shirt.
- **C6**—includes thumbs.
- **T4**—at the nipple.
- **T7**—at the xiphoid process.
- **T10**—at the umbilicus (important for early appendicitis pain referral).
- **L1**—at the inguinal ligament.
- **L4**—includes the kneecaps.
- **S2, S3, S4**—erection and sensation of penile and anal zones.

Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve.

Thumbs up sign on left hand looks like a six for C6. T4 at the teat pore.

T10 at the belly button.

L1 is IL (Inguinal Ligament). Down on ALL 4’s (L4).

“S2, 3, 4 keep the penis off the floor.”

Clinical reflexes

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Nerve Root</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps</td>
<td>C5 nerve root.</td>
</tr>
<tr>
<td>Triceps</td>
<td>C7 nerve root.</td>
</tr>
<tr>
<td>Patella</td>
<td>L4 nerve root.</td>
</tr>
<tr>
<td>Achilles</td>
<td>S1 nerve root.</td>
</tr>
</tbody>
</table>

Reflexes count up in order:

- S1, 2—“buckle my shoe” (Achilles reflex)
- L3, 4—“kick the door” (patellar reflex)
- C5, 6—“pick up sticks” (biceps reflex)
- C7, 8—“lay them straight” (triceps reflex)

Additional reflexes:

- L1, L2—“testicles move” (cremaster reflex)
- S3, S4—“winks galore” (anal wink reflex)

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
  Babinski sign—presence of this reflex in an adult, which may signify a UMN lesion

- **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
Brain stem—ventral view

4 CN are in above pons (I, II, III, IV).
4 CN are in 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—conjugate vertical gaze center.
Inferior colliculi—auditory.
Parinaud syndrome—paralysis of conjugate vertical gaze due to lesion in superior colliculi (eg, stroke, hydrocephalus, pinealoma).

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

<table>
<thead>
<tr>
<th>Anterior cranial fossa</th>
<th>Cribiform plate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optic canal</td>
</tr>
<tr>
<td></td>
<td>Superior orbital fissure</td>
</tr>
<tr>
<td></td>
<td>Foramen Rotundum</td>
</tr>
<tr>
<td></td>
<td>Foramen Oval</td>
</tr>
<tr>
<td></td>
<td>Foramen spinosum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Middle cranial fossa (through sphenoid bone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal auditory meatus</td>
</tr>
<tr>
<td>Jugular foramen</td>
</tr>
<tr>
<td>Hypoglossal canal</td>
</tr>
<tr>
<td>Foramen magnum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Posterior cranial fossa (through temporal or occipital bone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN I</td>
</tr>
<tr>
<td>CN II Ophthalmic artery</td>
</tr>
<tr>
<td>CN III</td>
</tr>
<tr>
<td>CN IV</td>
</tr>
<tr>
<td>CN VI</td>
</tr>
<tr>
<td>CN VII</td>
</tr>
<tr>
<td>CN VIII</td>
</tr>
<tr>
<td>CN IX</td>
</tr>
<tr>
<td>CN XI</td>
</tr>
<tr>
<td>CN XII</td>
</tr>
<tr>
<td>Brainstem</td>
</tr>
<tr>
<td>Middle meningeal artery</td>
</tr>
<tr>
<td>CN V₁</td>
</tr>
<tr>
<td>CN V₂</td>
</tr>
<tr>
<td>CN V₃</td>
</tr>
</tbody>
</table>

Divisions of CN V exit owing to Standing Room Only
### 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</td>
<td>Motor</td>
<td>Marry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(sphincter pupillae: Edinger-Westphal nucleus, muscarinic receptors), accommodation, eyelid opening (levator palpebrae)</td>
<td></td>
<td></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, lacrimation, salivation (submandibular and sublingual glands), 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 chemo- and baroreceptors, and elevation of pharynx/larynx (stylopharyngus)</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, coughing, parasympathetics to thoracoabdominal viscera, monitoring aortic arch chemo- 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 aMbiguus</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>V₁ ophthalmic (nasociliary branch)</td>
<td>VII (temporal branch: orbicularis oculi)</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>V₁ (loss of reflex does not preclude emotional tears)</td>
<td>VII</td>
</tr>
<tr>
<td>Jaw jerk</td>
<td>V₃ (sensory—muscle spindle from masseter)</td>
<td>V₃ (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>
### Common cranial nerve lesions

<table>
<thead>
<tr>
<th>CN V motor lesion</th>
<th>Jaw deviates <strong>toward</strong> side of lesion due to unopposed force from the opposite pterygoid muscle.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN X lesion</td>
<td>Uvula deviates <strong>away</strong> from side of lesion. Weak side collapses and uvula points away.</td>
</tr>
<tr>
<td>CN XI lesion</td>
<td>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.</td>
</tr>
<tr>
<td>CN XII lesion</td>
<td>LMN lesion. Tongue deviates <strong>toward</strong> side of lesion (“lick your wounds”) due to weakened tongue muscles on affected side.</td>
</tr>
</tbody>
</table>

### Mastication muscles

3 muscles close jaw: **M**asseter, **tM**poralis, **M**edial 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.”

### Facial nerve lesions

<table>
<thead>
<tr>
<th>Upper motor neuron lesion</th>
<th>Destruction of motor cortex or connection between motor cortex and facial nucleus in pons → contralateral paralysis of lower muscles of facial expression. Forehead is spared due to its bilateral UMN innervation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower motor neuron lesion</td>
<td>Destruction of facial nucleus or CN VII anywhere along its course → ipsilateral paralysis of upper and lower muscles of facial expression <strong>A</strong>, hyperacusis, loss of taste sensation to anterior tongue.</td>
</tr>
<tr>
<td>Facial nerve palsy</td>
<td>Clinical syndrome of peripheral CN VII (LMN) lesion. Depending on lesion location and severity, may cause partial or complete loss of function. When idiopathic (most common), called <strong>Bell palsy</strong>. May also be caused by Lyme disease, herpes simplex, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors, diabetes mellitus. Treatment is corticosteroids, acyclovir. Most patients have gradual recovery of function.</td>
</tr>
</tbody>
</table>
Cavernous sinus

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.

CNSs III, IV, V1, VI, and occasionally V2 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.

Auditory physiology

Outer ear
Visible portion of ear (pinna), includes auditory canal and eardrum. Transfers sound waves via vibration of eardrum.

Middle ear
Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from eardrum 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).

Hearing loss

<table>
<thead>
<tr>
<th></th>
<th>Rinne test</th>
<th>Weber test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductive</td>
<td>Abnormal (bone &gt; air)</td>
<td>Localizes to affected ear</td>
</tr>
<tr>
<td>Sensorineural</td>
<td>Normal (air &gt; bone)</td>
<td>Localizes to unaffected ear</td>
</tr>
<tr>
<td>Noise-induced</td>
<td>Damage to stereociliated cells in organ of Corti; loss of high-frequency hearing 1st; sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.</td>
<td></td>
</tr>
</tbody>
</table>
**Cholesteatoma**

Overgrowth of desquamated keratin debris within the middle ear space (A, blue arrows); may erode ossicles, mastoid air cells → conductive hearing loss.

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**NEUROLOGY—OPHTHALMOLOGY**

**Normal eye**

![Normal eye diagram](image)
Aqueous humor pathway

- **Trabecular outflow (90%)**: Drainage through trabecular meshwork → canal of Schlemm → episcleral vasculature (I with M3 agonists)
- **Uveoscleral outflow (10%)**: Drainage into uvea and sclera (I with prostaglandin agonists)

Refractive errors

- **Hyperopia**: Eye too short for refractive power of cornea and lens → light focused behind retina.
- **Myopia**: Eye too long for refractive power of cornea and lens → light focused in front of retina.
- **Astigmatism**: Abnormal curvature of cornea → different refractive power at different axes.
- **Presbyopia**: Age-related impaired accommodation (focusing on near objects), primarily due to lens elasticity. Often necessitates “reading glasses.”

Cataract

Painless, often bilateral, opacification of lens, often resulting in vision. 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), ToRCH infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.
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 the IOP.

Open-angle glaucoma
Associated with \( A \)ge, 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 forward movement of lens against central iris (pupil margin) \( \rightarrow \) obstruction of normal aqueous flow through pupil \( \rightarrow \) 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 \( \rightarrow \) angle closes abruptly. Very painful, red eye \( D \), sudden vision loss, halos around lights, rock-hard eye, frontal headache. Do not give epinephrine because of its mydriatic effect.

Conjunctivitis
Inflammation of the conjunctiva \( \rightarrow \) red eye \( A \). Allergic—itchy eyes, bilateral. Bacterial—pus; treat with antibiotics. Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node; self-resolving.

Uveitis
Inflammation of uvea, specific name based on location within affected eye. Anterior uveitis: iritis; intermediate uveitis: pars planitis; 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 and between Bruch membrane and retinal pigment epithelium (“drusen”) 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, ranibizumab).

Diabetic retinopathy

Retinal damage due to chronic hyperglycemia. Two types:

- Nonproliferative—damaged capillaries leak blood lipid and fluid seep into retina → hemorrhages (blue 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.

Retinal vein occlusion

Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement (blue 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 (e.g., 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 (blue arrows in) 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 (e.g., 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 pupillary sphincter muscles

**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 contract bilaterally (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.

**Marcus Gunn pupil**  
Afferent pupillary defect—due to optic nerve damage or severe retinal injury, ↓ bilateral pupillary constriction when light is shone in affected eye relative to unaffected eye. Tested with “swinging flashlight test.”

**Horner syndrome**  
Sympathetic denervation of face  
- Ptosis (slight drooping of eyelid: superior tarsal muscle)  
- Anhidrosis (absence of sweating) and flushing of affected side of face  
- Miosis (pupil constriction)  
Associated with lesion of spinal cord above T1 (eg, Pancoast tumor, Brown-Séquard syndrome, late-stage syringomyelia). Any interruption results in Horner syndrome.

PAM is horny (Hornet).  
Ptosis, anhidrosis, and miosis (rhyming).
Ocular motility

To test each muscle, ask patient to move his/her eye in the path diagrammed below, from neutral position toward the muscle being tested.

Obliques go Opposite (left SO and IO tested with patient looking right).

IOU: IO tested looking Up.

CN VI innervates the Lateral Rectus.
CN IV innervates the Superior Oblique.
CN III innervates the Rest.
The “chemical formula” LR₆SO₃R₅.
The superior oblique abducts, intorts, and depresses while adducted.
**CN III, IV, VI palsies**

**CN III damage**

CN III has both motor (central) and parasympathetic (peripheral) components. Motor output to ocular 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 1st affected by compression (eg, posterior communicating artery 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 and head tilt toward the side of the lesion (problems going down stairs, may present with compensatory head tilt in the opposite direction).

**CN VI damage**

Medially directed eye that cannot abduct.

**Visual field defects**

1. Right anopia
2. Bitemporal hemianopia (pituitary lesion, chiasm)
3. Left homonymous hemianopia
4. Left upper quadrantic anopia (right temporal lesion, MCA)
5. Left lower quadrantic anopia (right parietal lesion, MCA)
6. Left hemianopia with macular sparing (PCA infarct)
7. Central scotoma (eg, macular degeneration)

Meyer loop—inferior retina; loops around inferior horn of lateral ventricle.

Dorsal optic radiation—superior retina; takes shortest path via internal capsule.

*Note: When an image hits 1° visual cortex, it is upside down and left-right reversed.*
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 fire. 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.

Diagram:
- Medial recti
- Lateral recti
- Nuclei of CN VI
- Medial rectus subnucleus of CN III
- MLF

Right INO (right MLF lesion)
- Impaired adduction (convergence normal)
- Nystagmus

Left gaze
## Dementia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Histologic/Gross Findings</th>
</tr>
</thead>
</table>
| **Alzheimer disease** | Most common cause in elderly. Down syndrome patients have an ↑ risk of developing Alzheimer. Associated with the following altered proteins:  
  * ApoE2: ↑ risk of sporadic form  
  * ApoE4: ↑ risk of sporadic form  
  * APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset | Widespread cortical atrophy. Narrowing of gyri and widening of sulci.  
  ↓ ACh. 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. |
| **Frontotemporal dementia** | Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia). May have associated movement disorders (eg, parkinsonism, ALS-like UMN/LMN degeneration). Previously known as Pick disease. | Frontotemporal lobe degeneration. Inclusions of hyperphosphorylated tau (round Pick bodies; or ubiquitinated TDP-43). |
| **Lewy body dementia** | Initially dementia and visual hallucinations (“hallucinations”) followed by parkinsonian features. | Intracellular Lewy bodies (insoluble aggregates of α-synuclein) primarily in cortex. |
| **Vascular dementia** | Result of multiple arterial infarcts and/or chronic ischemia. Step-wise decline in cognitive ability with late-onset memory impairment. 2nd most common cause of dementia in elderly. | MRI or CT shows multiple cortical and/or subcortical infarcts. |
| **Creutzfeldt-Jakob disease** | Rapidly progressive (weeks to months) dementia with myoclonus (“startle myoclonus”). | Spongiform cortex. Prions (PrPsc → PrPsc sheet |β|-pleated sheet resistant to proteases). |
| **Other causes** | Syphilis; HIV; hypothyroidism; vitamins B1, B3, or B12 deficiency; Wilson disease; normal pressure hydrocephalus. | |

![Image A](image1.png)  ![Image B](image2.png)  ![Image C](image3.png)
**Osmotic demyelination syndrome (central pontine myelinolysis)**


- Correcting serum Na⁺ too fast:
  - “From low to high, your pons will die” (osmotic demyelination syndrome)
  - “From high to low, your brain will blow” (cerebral edema/herniation)

---

**Multiple sclerosis**

- Autoimmune inflammation and demyelination of CNS (brain and spinal cord). Patients can present with optic neuritis (sudden loss of vision resulting in Marcus Gunn pupils), INO, hemiparesis, hemisensory symptoms, bladder/bowel dysfunction. Relapsing and remitting course. Most often affects women in their 20s and 30s; more common in whites living further from equator.

- Charcot triad of MS is a SIN:
  - Scanning speech
  - Intention tremor (also Incontinence and Internuclear ophthalmoplegia)
  - Nystagmus

- **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) with destruction of axons. Multiple white matter lesions separated in space and time.

- **TREATMENT**

  - 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>β</sub> receptor agonists), pain (opioids).
### Acute inflammatory demyelinating polyradiculopathy

Most common subtype of Guillain-Barré syndrome. Autoimmune condition that destroys Schwann cells → inflammation and demyelination of peripheral nerves and motor fibers. Results in symmetric ascending muscle weakness/paralysis beginning in lower extremities. Facial paralysis in 50% of cases. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive; the majority recover completely after weeks to months. Findings: ↑ CSF protein with normal cell count (albuminocytologic dissociation). ↑ protein may cause papilledema. Associated with infections (eg, Campylobacter jejuni, viral) → autoimmune attack of peripheral myelin due to molecular mimicry, inoculations, and stress, but no definitive link to pathogens. Respiratory support is critical until recovery. Additional treatment: plasmapheresis, IV immunoglobulins. No role for steroids.

### Other demyelinating and dysmyelinating diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated (postinfectious) encephalomyelitis</td>
<td>Multifocal periventricular inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth disease</td>
<td>Also known as hereditary motor and sensory neuropathy (HMSN). 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 (pes cavus), lower extremity weakness and sensory deficits.</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>Autosomal recessive lysosomal storage disease due to deficiency of galactocerebrosidase. Buildup of galactocerebroside and psychosine destroys myelin sheath. Findings: peripheral neuropathy, developmental delay, optic atrophy, globoid cells.</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Autosomal recessive lysosomal storage disease, most commonly due to arylsulfatase A deficiency. Buildup of sulfatides → impaired production and destruction of myelin sheath. Findings: central and peripheral demyelination with ataxia, dementia.</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Demyelination of CNS due to destruction of oligodendrocytes. Seen in 2–4% of AIDS patients (reactivation of latent JC virus infection). Rapidly progressive, usually fatal. ↑ risk associated with natalizumab, rituximab.</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>X-linked genetic disorder typically affecting males. Disrupts metabolism of very-long-chain fatty acids → excessive buildup in nervous system, adrenal gland, testes. Progressive disease that can lead to long-term coma/death and adrenal gland crisis.</td>
</tr>
</tbody>
</table>
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. Often preceded by seizure aura; can secondarily generalize. Types:
- **Simple partial** (consciousness intact)—motor, sensory, autonomic, psychic
- **Complex partial** (impaired consciousness)

**Generalized seizures**
Diffuse. Types:
- **Absence** (petit mal)—3 Hz, 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 or recurring seizure(s) that may result in brain injury; defined as > 5 min.
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>Cluster&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unilateral</td>
<td>15 min–3 hr; repetitive</td>
<td>Repetitive brief headaches. Excruciating periorbital pain with lacrimation and rhinorrhea. May present with Horner syndrome.</td>
<td>Acute: sumatriptan, 100% O&lt;sub&gt;2&lt;/sub&gt; Prophylaxis: verapamil</td>
</tr>
<tr>
<td>Tension</td>
<td>Bilateral</td>
<td>&gt; 30 min (typically 4–6 hr); constant</td>
<td>Steady pain. No photophobia or phonophobia. No aura.</td>
<td>Analgesics, NSAIDs, acetaminophen; amitriptyline for chronic pain</td>
</tr>
<tr>
<td>Migraine</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, calcium channel blockers, amitriptyline, topiramate, valproate. <strong>POUND–Pulsatile, One-day duration, Unilateral, Nausea, Disabling</strong></td>
</tr>
</tbody>
</table>

Other causes of headache include subarachnoid hemorrhage (“worst headache of my life”), meningitis, hydrocephalus, neoplasia, arteritis.

<sup>a</sup>Compare with trigeminal neuralgia, which produces repetitive, unilateral, shooting pain in the distribution of CN V that lasts (typically) for < 1 minute.
Vertigo  
Sensation of spinning while actually stationary. Subtype of “dizziness,” but distinct from “light-headedness.”

**Peripheral vertigo**  
More common. Inner ear etiology (e.g., semicircular canal debris, vestibular nerve infection, Menière disease). Positional testing → delayed horizontal nystagmus.

**Central vertigo**  
Brain stem or cerebellar lesion (e.g., stroke affecting vestibular nuclei or posterior fossa tumor). Findings: directional change of nystagmus, skew deviation, diplopia, dysmetria. Positional testing → immediate nystagmus in any direction; may change directions. Focal neurologic findings.

### Neurocutaneous disorders

#### Sturge-Weber syndrome (encephalotrigeminal angiomatosis)
Congenital, non-inherited (somatic), developmental anomaly of neural crest derivatives due to activating mutation of *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 angiooma → 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  
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. ↑ incidence of subependymal astrocytomas and ungual fibromas.

#### Neurofibromatosis type I (von Recklinghausen disease)
Café-au-lait spots; Lisch nodules (pigmented iris hamartomas); optic gliomas, pheochromocytomas. Mutated NF1 tumor suppressor gene (neurofibromin, a negative regulator of RAS) on chromosome 17. Neurofibromas are derived from neural crest cells.

#### von Hippel-Lindau disease
Hemangioblastomas (high vascularity with hyperchromatic nuclei) in retina, brain stem, cerebellum, spine; angiomatosis (e.g., cavernous hemangiomas in skin, mucosa, organs); bilateral renal cell carcinomas; pheochromocytomas.
## Adult primary brain tumors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glioblastoma multiforme (grade IV astrocytoma)</strong></td>
<td>Common, highly malignant 1° brain tumor with ~ 1-year median survival. Found in cerebral hemispheres. Can cross corpus callosum (“butterfly glioma”). “Pseudopalisading” pleomorphic tumor cells—border central areas of necrosis and hemorrhage. Stain astrocytes for GFAP.</td>
</tr>
<tr>
<td><strong>Meningioma</strong></td>
<td>Common, typically benign 1° brain tumor. Most often occurs near surfaces of brain and parasagittal region. Arises from arachnoid cells, is extra-axial (external to brain parenchyma), and may have a dural attachment (“tail”). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery. 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 angiomas. Can produce erythropoietin → 2° polycythemia. Closely arranged, thin-walled capillaries with minimal intervening parenchyma.</td>
</tr>
<tr>
<td><strong>Schwannoma</strong></td>
<td>Classically at the cerebellopontine angle, but can be along any peripheral nerve. Often localized to CN VIII → vestibular schwannoma. Bilateral vestibular schwannomas found in NF-2. Resection or stereotactic radiosurgery. Schwann cell origin. S-100.</td>
</tr>
<tr>
<td><strong>Oligodendroglioma</strong></td>
<td>Relatively rare, slow growing. Most often in frontal lobes. “Chicken-wire” capillary pattern. Oligodendrocytes = “fried egg” cells—round nuclei with clear cytoplasm. Often calcified.</td>
</tr>
<tr>
<td><strong>Pituitary adenoma</strong></td>
<td>Most commonly prolactinoma (lactotroph adenoma) or nonfunctioning adenoma. Bitemporal hemianopia due to pressure on optic chiasm. Hyperplasia of a single type of endocrine cell found in pituitary (ie, lactotroph, gonadotroph, somatotroph, corticotroph).</td>
</tr>
</tbody>
</table>

![Image](image_url)
### Childhood primary brain tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ependymoma</strong></td>
<td>Ependymal cell tumors most commonly found in 4th ventricle. Can cause hydrocephalus. Poor prognosis. Characteristic perivascular rosettes. Rod-shaped blepharoplasts (basal ciliary bodies) found near nucleus.</td>
</tr>
<tr>
<td><strong>Craniopharyngioma</strong></td>
<td>Childhood tumor, may be confused with pituitary adenoma (both can cause bitemporal hemianopia). Most common childhood supratentorial tumor. Derived from remnants of Rathke pouch. Calcification is common. Cholesterol crystals found in “motor oil”–like fluid within tumor.</td>
</tr>
<tr>
<td><strong>Pinealoma</strong></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). Histologically similar to germ cell tumors (eg, testicular seminoma).</td>
</tr>
</tbody>
</table>
Herniation syndromes

1. Cingulate (subfalcine) herniation under falx cerebri
   - Can compress anterior cerebral artery.

2. Downward transtentorial (central) herniation
   - Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal.

3. Uncal herniation
   - Uncus = medial temporal lobe. Compresses ipsilateral CN III (blown pupil, “down-and-out” gaze), ipsilateral PCA (contralateral homonymous hemianopia with macular sparing), contralateral crus cerebri at the Kernohan notch (ipsilateral paresis; a “false localization” sign).

4. Cerebellar tonsillar herniation into the foramen magnum
   - Coma and death result when these herniations compress the brain stem.

### NEUROLOGY—PHARMACOLOGY

**Glaucoma drugs**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (α&lt;sub&gt;1&lt;/sub&gt;), brimonidine (α&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>↓ aqueous humor synthesis via vasoconstriction ↓ aqueous humor synthesis</td>
<td>Mydriasis (α&lt;sub&gt;1&lt;/sub&gt;); do not use in closed-angle glaucoma Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus</td>
</tr>
<tr>
<td><strong>β-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol, betaxolol, carteolol</td>
<td>↓ aqueous humor synthesis</td>
<td>No pupillary or vision changes</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>↓ aqueous humor synthesis via inhibition of carbonic anhydrase</td>
<td>No pupillary or vision changes</td>
</tr>
<tr>
<td><strong>Cholinomimetics (M&lt;sub&gt;3&lt;/sub&gt;)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct (pilocarpine, carbachol)</td>
<td>↑ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork</td>
<td>Miosis (contraction of pupillary sphincter muscles) and cyclospasm (contraction of ciliary muscle)</td>
</tr>
<tr>
<td>Indirect (physostigmine, echothiophate)</td>
<td>Use pilocarpine in emergencies—very effective at opening meshwork into canal of Schlemm</td>
<td></td>
</tr>
<tr>
<td><strong>Prostaglandin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bimatoprost, latanoprost (PGF&lt;sub&gt;2α&lt;/sub&gt;)</td>
<td>↑ outflow of aqueous humor</td>
<td>Darkens color of iris (browning), eyelash growth</td>
</tr>
</tbody>
</table>
### Opioid Analgesics

<table>
<thead>
<tr>
<th><strong>Morphine, fentanyl, codeine, loperamide, methadone, meperidine, dextromethorphan, diphenoxylate, pentazocine.</strong></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>

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### Pentazocine

<table>
<thead>
<tr>
<th><strong>κ-opioid receptor agonist and μ-opioid receptor antagonist.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
</tr>
</tbody>
</table>

---

### Butorphanol

<table>
<thead>
<tr>
<th><strong>κ-opioid receptor agonist and μ-opioid receptor partial agonist; produces analgesia.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
</tr>
</tbody>
</table>

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### Tramadol

<table>
<thead>
<tr>
<th><strong>Very weak opioid agonist; also inhibits 5-HT and norepinephrine reuptake (works on multiple neurotransmitters—“tram it all” in with tramadol).</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
</tr>
</tbody>
</table>
# Epilepsy Drugs

<table>
<thead>
<tr>
<th></th>
<th>Partial (Focal)</th>
<th>Generalized</th>
<th>Mechanism</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethosuximide</strong></td>
<td>Simple ✗</td>
<td>✓</td>
<td>Blocks thalamic T-type Ca(^{2+}) channels</td>
<td>Gl, fatigue, headache, urticaria, Stevens-Johnson syndrome. <strong>EFCHJ</strong> — Ethosuximide causes Fatigue, GI distress, Headache, Itching, and Stevens-Johnson syndrome</td>
<td>Sucks to have Silent (absence) Seizures</td>
</tr>
<tr>
<td><strong>Benzodiazepines (eg, diazepam, lorazepam, midazolam)</strong></td>
<td>Simple ✓</td>
<td>Tonic-Clonic <strong>✓</strong></td>
<td>GABA(_\alpha) action</td>
<td>Sedation, tolerance, dependence, respiratory depression</td>
<td>Also for eclampsia seizures (1st line is MgSO(_4))</td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td>✓</td>
<td>✓</td>
<td>GABA(_\alpha) action</td>
<td>Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression</td>
<td>1st line in neonates</td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>✗</td>
<td>✓</td>
<td>Blocks Na(^+) channels</td>
<td>Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450, SIADH, Stevens-Johnson syndrome</td>
<td>1st line for trigeminal neuralgia</td>
</tr>
<tr>
<td><strong>Valproic acid</strong></td>
<td>✓</td>
<td>✓</td>
<td>Na(^+) channel inactivation, GABA concentration by inhibiting GABA transaminase</td>
<td>Gl 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></td>
<td>GABA by irreversibly inhibiting GABA transaminase</td>
<td>GABA by irreversibly inhibiting GABA transaminase</td>
<td></td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>✓</td>
<td></td>
<td>Primarily inhibits high-voltage-activated Ca(^{2+}) channels, designed as GABA analog</td>
<td>Sedation, ataxia</td>
<td>Also used for peripheral neuropathy, postherpetic neuralgia</td>
</tr>
<tr>
<td><strong>Topiramate</strong></td>
<td>✓</td>
<td></td>
<td>Blocks Na(^+) channels, GABA action</td>
<td>Sedation, mental dulling, kidney stones, weight loss</td>
<td>Also used for migraine prevention</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>✓</td>
<td>✓</td>
<td>Blocks voltage-gated Na(^+) channels</td>
<td>Stevens-Johnson syndrome (must be titrated slowly)</td>
<td></td>
</tr>
<tr>
<td><strong>Levetiracetam</strong></td>
<td>✓</td>
<td>✓</td>
<td>Unknown; may modulate GABA and glutamate release</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tiagabine</strong></td>
<td>✓</td>
<td></td>
<td>GABA by inhibiting reuptake</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = 1st line; ** = 1st line for acute; *** = 1st line for prophylaxis.
### Barbiturates

**Phenobarbital, pentobarbital, thiopental, secobarbital.**

**Mechanism**
Facilitate GABA<sub>A</sub> action by ↑ duration of Cl<sup>-</sup> channel opening, thus ↓ neuron firing (barbiturates ↑ duration). Contraindicated in porphyria.

**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).

---

### Benzodiazepines

Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

**Mechanism**
Facilitate GABA<sub>A</sub> action by ↑ frequency of Cl<sup>-</sup> channel opening. ↓ REM sleep. Most have long half-lives and active metabolites (exceptions: Alprazolam, Triazolam, Oxazepam, and Midazolam are short acting → higher addictive potential).

**Clinical Use**
Anxiety, spasticity, status epilepticus (lorazepam and diazepam), eclampsia, detoxification (especially alcohol withdrawal–DTs), 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. “All ZZZs put you to sleep.”**

**Mechanism**
Act via the BZ1 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.
**Anesthetics—general principles**

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported. Drugs with $\downarrow$ solubility in blood = rapid induction and recovery times.

Drugs with $\uparrow$ solubility in lipids = $\uparrow$ potency $= \frac{1}{\text{MAC}}$.

$\text{MAC} = \text{Minimal Alveolar Concentration}$ (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (eg, skin incision).

Examples: nitrous oxide ($\text{N}_2\text{O}$) has $\downarrow$ blood and lipid solubility, and thus fast induction and low potency. Halothane, in contrast, has $\uparrow$ lipid and blood solubility, and thus high potency and slow induction.

### Inhaled anesthetics

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Desflurane, halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, $\text{N}_2\text{O}$.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects</td>
<td>Myocardial depression, respiratory depression, nausea/emesis, $\uparrow$ cerebral blood flow (↓ cerebral metabolic demand).</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), expansion of trapped gas in a body cavity ($\text{N}_2\text{O}$).</td>
</tr>
</tbody>
</table>

**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 cause $\uparrow$ $\text{Ca}^{2+}$ release from sarcoplasmic reticulum. Treatment: dantrolene, a ryanodine receptor antagonist.

### Intravenous anesthetics

**The Mighty King Proposes Foolishly to Oprah.**

- **Barbiturates (Thiopental)**
  - High potency, high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by rapid redistribution into tissue and fat, $\downarrow$ cerebral blood flow.

- **Benzodiazepines (Midazolam)**
  - Used for endoscopy; used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, $\downarrow$ BP (treat overdose with flumazenil), anterograde amnesia.

- **Arylcyclohexylamines (Ketamine)**
  - PCP analogs that act as dissociative anesthetics. Block NMDA receptors. Cardiovascular stimulants. Cause disorientation, hallucination, bad dreams. $\uparrow$ cerebral blood flow.

- **Propofol**
  - Used for sedation in ICU, rapid anesthesia induction, short procedures. Less postoperative nausea than thiopental. Potentiates GABA$_A$.

- **Opioids**
  - Morphine, fentanyl used with other CNS depressants during general anesthesia.
### Local anesthetics

| Esters—procaine, cocaine, tetracaine, benzocaine. |
| Amides—lidocaine, mepivacaine, bupivacaine (amides have 2 Is in name). |

**MECHANISM**

Block Na⁺ 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 motor (vs autonomic) nicotinic receptor.**

#### Depolarizing

Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction.

Reversal of blockade:

- 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

Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rocuronium—competitive antagonists—compete with ACh for receptors.

Reversal of blockade—neostigmine (must be given with atropine to prevent muscarinic effects such as bradycardia), edrophonium, and other cholinesterase inhibitors.

### Dantrolene

**MECHANISM**

Prevents release of Ca²⁺ from the sarcoplasmic reticulum of skeletal muscle by binding to the ryanodine receptor.

**CLINICAL USE**

Malignant hyperthermia and neuroleptic malignant syndrome (a toxicity of antipsychotic drugs).

### Baclofen

**MECHANISM**

Activates GABA₉ receptors at spinal cord level, inducing skeletal muscle relaxation.

**CLINICAL USE**

Muscle spasms (eg, acute low back pain).

### Cyclobenzaprine

**MECHANISM**

Centrally acting skeletal muscle relaxant. Structurally related to TCAs, similar anticholinergic side effects.

**CLINICAL USE**

Muscle spasms.
Parkinson disease

Drugs

Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity. Bromocriptine, Amantadine, Levodopa (with carbidopa), Selegiline (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</td>
</tr>
<tr>
<td></td>
<td>Non-ergot (preferred)—pramipexole, ropinirole</td>
</tr>
<tr>
<td>1 dopamine availability</td>
<td>Amantadine (1—dopamine release and 1—dopamine reuptake); toxicity = ataxia, livedo reticularis.</td>
</tr>
<tr>
<td>1 l-DOPA availability</td>
<td>Agents prevent peripheral (pre-BBB) l-dopa degradation → ↑ l-DOPA entering CNS → ↑ central l-DOPA available for conversion to dopamine.</td>
</tr>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>Entacapone, tolcapone—prevent peripheral l-dopa degradation to 3-O-methylldopa (3-OMD) by inhibiting COMT.</td>
</tr>
<tr>
<td>Prevent dopamine</td>
<td>Agents act centrally (post-BBB) to inhibit breakdown of dopamine.</td>
</tr>
<tr>
<td>breakdown</td>
<td>Selegiline—blocks conversion of dopamine into DOPAC by selectively inhibiting MAO-B.</td>
</tr>
<tr>
<td></td>
<td>Tolcapone—blocks conversion of dopamine to 3-OMD by inhibiting central COMT.</td>
</tr>
<tr>
<td>Curb excess cholinergic activity</td>
<td>Benztropine (Antimuscarinic; improves tremor and rigidity but has little effect on bradykinesia in Parkinson disease). Park your Mercedes-Benz.</td>
</tr>
</tbody>
</table>

![Diagram of dopamine pathways and drugs]
### L-dopa (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**
Arrhythmias 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.

### Alzheimer drugs

**Memantine**

**MECHANISM**
NMDA receptor antagonist; helps prevent excitotoxicity (mediated by Ca2+).

**ADVERSE EFFECTS**
Dizziness, confusion, hallucinations.

**Donepezil, galantamine, rivastigmine, tacrine**

**MECHANISM**
AChE inhibitors.

**ADVERSE EFFECTS**
Nausea, dizziness, insomnia.

### Huntington disease drugs

Tetrabenazine and reserpine—inhibit vesicular monoamine transporter (VMAT) → † dopamine vesicle packaging and release.

Haloperidol—D2 receptor antagonist.

### Riluzole

Treatment for ALS that modestly † survival by † glutamate excitotoxicity via an unclear mechanism. For Lou Gehrig disease, give riluzole.

### Triptans

**Sumatriptan**

**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.

A SUMo wrestler TRIPs ANd falls on your head.
HIGH-YIELD PRINCIPLES IN

Psychiatry

“A Freudian slip is when you say one thing but mean your mother.”
—Anonymous

“Men will always be mad, and those who think they can cure them are the maddest of all.”
—Voltaire

“Anyone who goes to a psychiatrist ought to have his head examined.”
—Samuel Goldwyn

“Words of comfort, skillfully administered, are the oldest therapy known to man.”
—Louis Nizer
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).

Punishment: Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior.

Extinction: Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.

Transference and countertransference

Transference: Patient projects feelings about formative or other important persons onto physician (eg, psychiatrist is seen as parent).

Countertransference: Doctor projects feelings about formative or other important persons onto patient (eg, patient reminds physician of younger sibling).

Ego defenses: Mental processes (unconscious or conscious) used to resolve conflict and prevent undesirable feelings (eg, 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>Tantrums.</td>
</tr>
<tr>
<td>Denial</td>
<td>Avoiding the awareness of some painful reality.</td>
<td>A common reaction in newly diagnosed AIDS and cancer patients.</td>
</tr>
<tr>
<td>Displacement</td>
<td>Transferring avoided ideas and feelings to a neutral person or object (vs projection).</td>
<td>Mother yells at her child, because her husband yelled at her.</td>
</tr>
<tr>
<td>Dissociation</td>
<td>Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress.</td>
<td>Extreme forms can result in dissociative identity disorder (multiple personality disorder).</td>
</tr>
<tr>
<td>Fixation</td>
<td>Partially remaining at a more childish level of development (vs regression).</td>
<td>Adults fixating on video games.</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>Modeling behavior after another person who is more powerful (though not necessarily admired).</td>
<td>Abused child later becomes a child abuser.</td>
</tr>
</tbody>
</table>
### Ego defenses (continued)

<table>
<thead>
<tr>
<th>Ego Defense</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immature defenses</strong></td>
<td></td>
<td></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>Failing to meet the needs/expectations of others as an indirect show of opposition.</td>
<td>Disgruntled employee is repeatedly late to work.</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 by an (unconsciously derived) emphasis on its opposite (vs sublimation).</td>
<td>A patient with libidinous thoughts enters a monastery.</td>
</tr>
<tr>
<td>Regression</td>
<td>Involuntarily 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 when hospitalized).</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>
<tr>
<td><strong>Mature defenses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublimation</td>
<td>Replacing an unacceptable wish with a course of action that is similar to the wish but does not conflict with one’s value system (vs reaction formation).</td>
<td>Teenager’s aggression toward his father is redirected to perform well in sports.</td>
</tr>
<tr>
<td>Altruism</td>
<td>Alleviating negative feelings via unsolicited generosity.</td>
<td>Mafia boss makes large donation to charity.</td>
</tr>
<tr>
<td>Suppression</td>
<td>Intentionally withholding an idea or feeling from conscious awareness (vs repression); temporary.</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>
<td>Nervous medical student jokes about the boards.</td>
</tr>
</tbody>
</table>

**Mature adults wear a SASH.**
### Psychiatric genetics

Both genetic and environmental factors are involved in development of most psychiatric disorders. For example, in bipolar disorder and schizophrenia, lifetime risk in general population (~1%) < parent or sibling of someone affected (~10%) < monozygotic twin of someone affected (~50%).

### 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)

The 4 W's: Weak, Wordless, Wanting (socially), Wary.

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. During exam, children often avoid eye contact.</td>
</tr>
<tr>
<td><strong>ABUSER</strong></td>
<td>Usually biological mother.</td>
</tr>
<tr>
<td><strong>EPIDEMIOLOGY</strong></td>
<td>40% of deaths 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. Limited attention span and 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. Continues into adulthood in as many as 50% of individuals. 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.

**Rett syndrome**
X-linked dominant disorder seen almost exclusively in girls (affected males die in utero or shortly after birth). Symptoms usually become apparent around ages 1–4, including regression characterized by loss of development, loss of verbal abilities, intellectual disability, ataxia, stereotyped hand-wringing.

**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, many of these patients will meet criteria for diagnosis of antisocial personality disorder. Treatment for both: psychotherapy such as 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**
Common onset at 7–9 years. Overwhelming fear of separation from home or loss of attachment figure. May lead to factitious physical complaints to avoid going to or staying at 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 10–20% of patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics, high-potency antipsychotics (eg, fluphenazine, pimozide), tetrabenazine, guanfacine, and clonidine may be used.

**Neurotransmitter changes with disease**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>NEUROTRANSMITTER CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>↓ ACh</td>
</tr>
<tr>
<td></td>
<td>↑ glutamate</td>
</tr>
<tr>
<td>Anxiety</td>
<td>↑ norepinephrine</td>
</tr>
<tr>
<td></td>
<td>↓ GABA, ↓ 5-HT</td>
</tr>
<tr>
<td>Depression</td>
<td>↓ norepinephrine</td>
</tr>
<tr>
<td></td>
<td>↓ 5-HT, ↑ dopamine</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>↓ GABA, ↑ ACh</td>
</tr>
<tr>
<td></td>
<td>↑ dopamine</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>↓ dopamine</td>
</tr>
<tr>
<td></td>
<td>↑ ACh</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>↑ dopamine</td>
</tr>
</tbody>
</table>

Understanding these changes can help guide pharmacologic treatment choice.
### 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.

Order of loss: 1st—time; 2nd—place; last—person.

### Amnesias

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrograde amnesia</strong></td>
<td>Inability to remember things that occurred before a CNS insult.</td>
</tr>
<tr>
<td><strong>Anterograde amnesia</strong></td>
<td>Inability to remember things that occurred after a CNS insult (acquisition of new memory).</td>
</tr>
<tr>
<td><strong>Korsakoff syndrome</strong></td>
<td>Amnesia (anterograde &gt; retrograde) 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>
<tr>
<td><strong>Dissociative amnesia</strong></td>
<td>Inability to recall important personal information, usually subsequent to severe trauma or stress. May be accompanied by dissociative fugue (abrupt travel or wandering during a period of dissociative amnesia, associated with traumatic circumstances).</td>
</tr>
</tbody>
</table>

### Dissociative disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dissociative identity disorder</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Depersonalization/ derealization disorder</strong></td>
<td>Persistent feelings of detachment or estrangement from one’s own body, thoughts, perceptions, and actions (depersonalization) or one’s environment (derealization).</td>
</tr>
</tbody>
</table>

### 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. Usually 2° to other illness (eg, CNS disease, infection, trauma, substance abuse/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention). Most common presentation of altered mental status in inpatient setting. Commonly, diffuse slowing EEG. Treatment is aimed at identifying and addressing underlying condition. Haloperidol may be used as needed. Use benzodiazepines for alcohol withdrawal.

Delirium = changes in sensorium. May be caused by medications (eg, anticholinergics), especially in the elderly. Reversible.

T-A-DA approach (Tolerate, Anticipate, Don’t Agitate) helpful for management.
Dementia

In intellectual function without affecting level of consciousness. Characterized by memory deficits, apraxia, aphasia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment. A patient with dementia can develop delirium (eg, patient with Alzheimer disease who develops pneumonia is at risk for delirium). Irreversible causes: Alzheimer disease, Lewy body dementia, Huntington disease, Pick disease, cerebral infarct, Creutzfeldt-Jakob disease, chronic substance abuse (due to neurotoxicity of drugs). Reversible causes: hypothyroidism, depression, vitamin B12 deficiency, normal pressure hydrocephalus, neurosyphilis. Incidence with age. EEG usually normal.

Psychosis

Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thinking. Can occur in patients with medical illness, psychiatric illness, or both.

Delusions

Unique, false beliefs that persist despite the facts (eg, thinking aliens are communicating with you). Types include persecutory, referential, grandiose, erotomanic, somatic.

Disorganized thought

Speech may be incoherent (“word salad”), tangential, or derailed (“loose associations”).

Hallucinations

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:

- Visual—more commonly a feature of medical illness (eg, drug intoxication) than psychiatric illness.
- Auditory—more commonly a feature of psychiatric illness (eg, schizophrenia) than medical illness.
- Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors.
- Gustatory—rare, but seen in epilepsy.
- Tactile—common in alcohol withdrawal and stimulant use (eg, cocaine, amphetamines), delusional parasitosis, “cocaine crawlies.”
- Hypnagogic—occurs while going to sleep. Sometimes seen in narcolepsy.
- Hypnopompic—occurs while waking from sleep (“pompous upon awakening”). Sometimes seen in narcolepsy.
**Schizophrenia**

Chronic mental disorder with periods of psychosis, disturbed behavior and thought, and decline in functioning **lasting > 6 months**. Associated with ↑ dopaminergic activity, ↑ dendritic branching.

Diagnosis requires at least 2 of the following, 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**—**lasting < 1 month**, usually stress related.

**Schizophrreniform disorder**—**lasting 1–6 months**.

**Schizoaffective disorder**—> 2 weeks of hallucinations or delusions without major mood episode (major depression or mania), plus periods of concurrent major mood episode with schizophrenic symptoms.

---

**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).

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**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 disorder, bipolar disorder, dysthymic disorder, and cyclothymic disorder. Episodic superimposed psychotic features (delusions or hallucinations) may be present.

---

**Manic episode**

Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently ↑ activity or energy **lasting at least 1 week**. Often disturbing to patient.

Diagnosis requires hospitalization or at least 3 of the following (manics **DIG FAST**):

- Distractibility
- Irresponsibility—seeks pleasure without regard to consequences (hedonistic)
- Grandiosity—Inflated self-esteem
- Flight of ideas—racing thoughts
- ↑ in 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 are at ↑ risk for suicide.

Ventriculomegaly on brain imaging. Treatment: atypical antipsychotics (eg, risperidone) are first line.
Hypomanic episode

Like 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 at least 4 consecutive days.

Bipolar disorder

Bipolar I defined by presence of at least 1 manic episode +/- a hypomanic or depressive episode. Bipolar II defined by presence of a hypomanic and a depressive episode. Patient’s mood and functioning usually return to normal between episodes. Use of antidepressants can precipitate mania. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics.

Cyclothymic disorder—milder form of bipolar disorder lasting at least 2 years, fluctuating between mild depressive and hypomanic symptoms.

Major depressive disorder

May be self-limited disorder, with major depressive episodes usually lasting 6–12 months. Episodes characterized by at least 5 of the following 9 symptoms for 2 or more weeks (symptoms must include patient-reported depressed mood or anhedonia). Treatment: CBT and SSRIs are first line. SNRIs, mirtazapine, bupropion can also be considered. Electroconvulsive therapy (ECT) in select patients.

Persistent depressive disorder (dysthymia)—depression, often milder, lasting at least 2 years.

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:
- \( \downarrow \) slow-wave sleep
- \( \uparrow \) REM latency
- \( \uparrow \) REM early in sleep cycle
- \( \uparrow \) total REM sleep
- Repeated nighttime awakenings
- Early-morning wakening (terminal insomnia)

Depression with atypical features

Differs from classical forms of depression. Characterized by mood reactivity (being 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.
Postpartum mood disturbances

Onset 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. 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

Normal grief is characterized by shock, denial, guilt, sadness, anxiety, yearning, and somatic symptoms. Hallucinations of the deceased person are common. Duration varies widely; usually < 6 months. Pathologic grief is persistent and causes functional impairment. Can meet criteria for major depressive episode.

Electroconvulsive therapy

Used mainly for treatment-refractory depression, depression with psychotic symptoms, and acutely suicidal patients. Produces grand mal seizure in an anesthetized patient. Adverse effects include disorientation, temporary headache, partial anterograde/retrograde amnesia usually resolving in 6 months. Safe in pregnancy.

Risk factors for suicide completion

Sex (male)  
Age (young adult or elderly)  
Depression  
Previous attempt  
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 1 risk of suicide completion.  
Women try more often; men succeed more often.

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. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism. Treatment: CBT, SSRIs, SNRIs.
Panic disorder

Defined by recurrent panic attacks (periods of intense fear and discomfort peaking in 10 minutes with at least 4 of the following):
- Palpitations
- Paresthesias
- Personalization or derealization
- Abdominal distress or Nausea
- Intense fear of dying
- Intense fear of losing control or “going crazy,”
- Light-headedness
- Chest pain
- Chills
- Choking
- Sweating
- Shaking
- Shortness of breath. Strong genetic component. Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.

Specific phobia

Severe, persistent fear or anxiety due to presence or anticipation of a specific object or situation. Person recognizes fear is excessive. Can be treated with systematic desensitization.

Social anxiety disorder—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For only occasional anxiety-inducing situations, benzodiazepine or β-blocker.

Agoraphobia—exaggerated fear of open or enclosed places, using public transportation, being in line or in crowds, or leaving home alone. Associated with panic disorder. Treatment: CBT, SSRIs, MAO inhibitors.

Generalized anxiety disorder

Anxiety lasting > 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.

Adjustment disorder—emotional symptoms (anxiety, depression) causing impairment following an identifiable psychosocial stressor (eg, divorce, illness) and lasting < 6 months (> 6 months in presence of chronic stressor). Treatment: CBT, SSRIs.

Obsessive-compulsive disorder

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). Associated with Tourette syndrome. Treatment: CBT, SSRIs, and clomipramine are first line.

Body dysmorphic disorder—preoccupation with minor or imagined defect in appearance → significant emotional distress or impaired functioning; patients often repeatedly seek cosmetic treatment. Treatment: CBT.

Post-traumatic stress disorder

Exposure to prior trauma (eg, witnessing death, experiencing serious injury or rape) → intrusive reexperiencing of the event (nightmares, flashbacks), avoidance of associated stimuli, changes in cognition or mood (fear, horror), and persistently † arousal. Disturbance lasts > 1 month with significant distress or impaired social-occupational functioning. Treatment: CBT, SSRIs, and venlafaxine are first line.

Acute stress disorder—lasts between 3 days and 1 month. Treatment: CBT; pharmacotherapy is usually not indicated.

PANICS.

Diagnosis requires attack followed by 1 month (or more) of 1 (or more) of the following:
- Persistent concern of additional attacks
- Worrying about consequences of attack
- Behavioral change related to attacks

Symptoms are the systemic manifestations of fear.
<table>
<thead>
<tr>
<th>Malingering</th>
<th>Patient <strong>consciously</strong> fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific (2^\circ) <strong>(external) gain</strong> (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factitious disorders</strong></td>
<td>Patient <strong>consciously</strong> creates physical and/or psychological symptoms in order to assume “sick role” and to get medical attention (1^\circ) <strong>(internal) gain</strong>.</td>
</tr>
<tr>
<td>Factitious disorder imposed on self (Munchausen syndrome)</td>
<td><strong>Chronic</strong> factitious disorder with predominantly physical signs and symptoms. Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures.</td>
</tr>
<tr>
<td>Factitious disorder imposed on another (Munchausen syndrome by proxy)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Somatic symptom and related disorders</strong></td>
<td>Category of disorders characterized by physical symptoms causing significant distress and impairment. Both illness production and motivation are <strong>unconscious</strong> drives. Symptoms not intentionally produced or feigned. More common in women.</td>
</tr>
<tr>
<td>Somatic symptom disorder</td>
<td>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.</td>
</tr>
<tr>
<td>Conversion disorder</td>
<td>Loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient is aware of but sometimes indifferent toward symptoms (“la belle indifférence”); more common in females, adolescents, and young adults.</td>
</tr>
<tr>
<td>Illness anxiety disorder</td>
<td>Excessive preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal somatic symptoms.</td>
</tr>
<tr>
<td>Pseudocyesis</td>
<td>False, nondelusional belief of being pregnant. May have signs and symptoms of pregnancy but is not pregnant.</td>
</tr>
</tbody>
</table>

**Personality**

<table>
<thead>
<tr>
<th>Personality trait</th>
<th>An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and oneself.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personality disorder</td>
<td>Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem. Usually presents by early adulthood. Three clusters, A, B, and C; remember as <strong>Weird</strong>, <strong>Wild</strong>, and <strong>Worried</strong> based on symptoms.</td>
</tr>
</tbody>
</table>

**Somatic symptom and related disorders**

<table>
<thead>
<tr>
<th>Category of disorders characterized by physical symptoms causing significant distress and impairment. Both illness production and motivation are <strong>unconscious</strong> drives. Symptoms not intentionally produced or feigned. More common in women.</th>
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<tbody>
<tr>
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<td>Loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient is aware of but sometimes indifferent toward symptoms (“la belle indifférence”); more common in females, adolescents, and young adults.</td>
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<td>Excessive preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal somatic symptoms.</td>
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<tr>
<td>False, nondelusional belief of being pregnant. May have signs and symptoms of pregnancy but is not pregnant.</td>
</tr>
<tr>
<td><strong>Cluster A personality disorders</strong></td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>Paranoid</strong></td>
</tr>
<tr>
<td><strong>Schizoid</strong></td>
</tr>
<tr>
<td><strong>Schizotypal</strong></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” (Bad to the Bone).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antisocial</strong></td>
<td>Disregard for and violation of rights of others, 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.</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.</td>
</tr>
<tr>
<td><strong>Histrionic</strong></td>
<td>Excessive emotionality and excitability, attention seeking, sexually provocative, overly concerned with appearance.</td>
<td></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></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” (Cowardly, 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></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>Submissive and clingy, excessive need to be taken care of, low self-confidence.</td>
<td>Patients often get stuck in abusive relationships.</td>
</tr>
</tbody>
</table>
### Eating disorders

**Anorexia nervosa**
- Excessive dieting, exercise, or binge eating/purging with BMI < 18.5 kg/m²; intense fear of gaining weight; and distortion or overvaluation of body image. Associated with ↓ bone density, severe weight loss, metatarsal stress fractures, amenorrhea (due to loss of pulsatile GnRH secretion), lanugo, anemia, electrolyte disturbances. Commonly coexists with depression. Psychotherapy and nutritional rehabilitation are first line. Refeeding syndrome (↑ insulin → hypophosphatemia → cardiac complications) 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, alkalosis, dorsal hand calluses from induced vomiting (Russell sign). Treatment: psychotherapy, nutritional rehabilitation, antidepressants.

**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.

### Gender dysphoria
- Strong, persistent cross-gender identification that leads to persistent discomfort with sex assigned at birth, causing significant distress and/or impaired functioning. Transgender individuals may have gender dysphoric disorder.
  - **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:
  - Drugs (eg, antihypertensives, neuroleptics, SSRIs, ethanol)
  - Diseases (eg, depression, diabetes, STIs)
  - Psychological (eg, performance anxiety)

### Sleep terror disorder
- Periods of terror with screaming in the middle of the night; occurs during slow-wave/deep (stage N3) sleep. Most common in children. Occurs during non-REM sleep (no memory of arousal) as opposed to nightmares that occur during REM sleep (memory of a scary dream). Cause unknown, but triggers include emotional stress, fever, or lack of sleep. Usually self limited.
Narcolepsy
Disordered regulation of sleep-wake cycles; 1st characteristic is excessive daytime sleepiness (awaken feeling rested).
Caused by ↓ hypocretin (orexin) production in lateral hypothalamus.
Also associated with:
- Hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep.
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter) in some patients.
Strong genetic component. Treatment: 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:
- Tolerance—need more to achieve same effect
- Withdrawal
- 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 because of substance use
- 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 due to use
- Social or interpersonal conflicts related to substance use

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 behavior changes
6. Relapse—returning to old behaviors and abandoning new changes
# 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 ( \gamma )-glutamyltransferase (GGT) — sensitive indicator of alcohol use. AST value is twice ALT value.</td>
<td>Mild alcohol withdrawal: symptoms similar to other depressants. Severe alcohol withdrawal can cause autonomic hyperactivity and DTs (5–15% mortality rate). Treatment for DTs: benzodiazepines.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Low safety margin, marked respiratory depression. Treatment: symptom management (eg, assist respiration, ( \uparrow ) 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>
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</tr>
<tr>
<td>Cocaine</td>
<td>Impaired judgment, pupillary dilation, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death. Treatment: ( \alpha )-blockers, benzodiazepines. ( \beta )-blockers not recommended.</td>
<td>Non-specific: headache, difficulty concentrating, muscle twitching, vivid nightmares.</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Restlessness, ( \downarrow ) 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>
<tr>
<td>Psychotropic Drug</td>
<td>Intoxication</td>
<td>Withdrawal</td>
</tr>
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<td>-------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Hallucinogens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Violence, impulsivity, psychomotor agitation, nystagmus, tachycardia, hypertension, analgesia, psychosis, delirium, seizures. Trauma is most common complication. Treatment: benzodiazepines, rapid-acting antipsychotic.</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 (tetrahydrocannabinol isomer): used as antiemetic (chemotherapy) and appetite stimulant (in AIDS).</td>
<td>Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite. Generally detectable in urine for up to 1 month.</td>
</tr>
<tr>
<td>MDMA (ecstasy)</td>
<td>Hallucinogenic stimulant: euphoria, disinhibition, hyperactivity. Life-threatening effects include hypertension, tachycardia, hyponatremia, serotonin syndrome.</td>
<td>Depression, fatigue, change in appetite, difficulty concentrating, anxiety.</td>
</tr>
<tr>
<td><strong>Heroin addiction</strong></td>
<td>Users at ↑ risk for hepatitis, HIV, abscesses, bacteraemia, right-heart endocarditis. Treatment is described below.</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Long-acting oral opiate used for heroin detoxification or long-term maintenance.</td>
<td></td>
</tr>
<tr>
<td>Naloxone + buprenorphine</td>
<td>Antagonist + partial agonist. Naloxone is not orally bioavailable, so withdrawal symptoms occur only if injected (lower abuse potential).</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Long-acting opioid antagonist used for relapse prevention once detoxified.</td>
<td></td>
</tr>
<tr>
<td><strong>Alcoholism</strong></td>
<td>Physiologic tolerance and dependence with symptoms of withdrawal (tremor, tachycardia, hypertension, malaise, nausea, DTs) 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, supportive care. Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family.</td>
<td></td>
</tr>
<tr>
<td>Wernicke-Korsakoff syndrome</td>
<td>Caused by vitamin B&lt;sub&gt;1&lt;/sub&gt; (thiamine) deficiency. Triad of confusion, ophthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff syndrome). Associated with periventricular hemorrhage/necrosis of mammillary bodies. Treatment: IV vitamin B&lt;sub&gt;1&lt;/sub&gt;.</td>
<td></td>
</tr>
<tr>
<td>Mallory-Weiss syndrome</td>
<td>Partial thickness tear at gastroesophageal junction caused by excessive/forceful vomiting. Often presents with hematemesis and misdiagnosed as ruptured esophageal varices.</td>
<td></td>
</tr>
</tbody>
</table>
Delirium tremens

Life-threatening alcohol withdrawal syndrome that peaks 2–4 days after last drink. Characterized by autonomic hyperactivity (eg, tachycardia, tremors, anxiety, seizures). Classically occurs in hospital setting (eg, 2–4 days postsurgery) in alcoholics not able to drink as inpatients. Treatment: benzodiazepines. Alcoholic hallucinosis is a distinct condition characterized by visual hallucinations 12–48 hours after last drink. Treatment: benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam).

**CNS stimulants**

| MECHANISM | Stimulates release of catecholamines in the synaptic cleft, especially norepinephrine and dopamine. |
| CLINICAL USE | ADHD, narcolepsy, appetite control. |
## Antipsychotics (neuroleptics)

| MECHANISM | All typical antipsychotics block dopamine $D_2$ receptors (↑[cAMP]). |
| CLINICAL USE | Schizophrenia (primarily positive symptoms), psychosis, bipolar disorder, delirium, Tourette syndrome, Huntington disease, OCD. |
| ADVERSE EFFECTS | Highly lipid soluble and stored in body fat; thus, very slow to be removed from body. Extrapyramidal system side effects (eg, dyskinesias). Treatment: benztropine, diphenhydramine, benzodiazepines. Endocrine side effects (eg, dopamine receptor antagonism $→$ hyperprolactinemia $→$ galactorrhea, oligomenorrhea, gynecomastia). Side effects arising from blocking muscarinic (dry mouth, constipation), $\alpha_1$ (orthostatic hypotension), and histamine (sedation) receptors. Can cause QT prolongation. |
| OTHER TOXICITIES | Neuroleptic malignant syndrome (NMS) — rigidity, myoglobinuria, autonomic instability, hyperpyrexia. Treatment: dantrolene, $D_2$ agonists (eg, bromocriptine). Tardive dyskinesia — orofacial chorea as a result of long-term antipsychotic use. |

### High potency: Trifluoperazine, Fluphenazine, Haloperidol (Try to Fly High)—neurologic side effects (eg, extrapyramidal symptoms [EPS]).

### Low potency: Chlorpromazine, Thioridazine (Cheating Thieves are low)—non-neurologic side effects (anticholinergic, antihistamine, and $\alpha_1$-blockade effects).

- Chlorpromazine — Corneal deposits;
- Thioridazine — reTinal deposits; haloperidol — NMS, tardive dyskinesia.

Onset of EPS: ADAPT

* Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyrice crisis)
* Days to months: Akathisia (restlessness) and Parkinsonism (bradykinesia).
* Months to years: Tardive dyskinesia

For NMS, think FEVER:

- Fever
- Encephalopathy
- Vitals unstable
- Enzymes ↑
- Rigidity of muscles

## Atypical antipsychotics

| MECHANISM | Not completely understood. Most are $D_2$ antagonists; aripiprazole is $D_2$ partial agonist. Varied effects on 5-HT$_2$, dopamine, and $\alpha$- and H$_1$-receptors. |
| CLINICAL USE | Schizophrenia — both positive and negative symptoms. Also used for bipolar disorder, OCD, anxiety disorder, depression, mania, Tourette syndrome. |
| 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 WBC weekly). Risperidone — hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia). Must watch bone marrow closely with clozapine. |

Olanzapine $→$ Obesity
Lithium

**MECHANISM**
Not established; possibly related to inhibition of phosphoinositol cascade.

**CLINICAL USE**
Mood stabilizer for bipolar disorder; blocks relapse and acute manic events.

**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+. Thiazide use is implicated in lithium toxicity in bipolar patients.

LMNOP—Lithium side effects:
- Movement (tremor)
- Nephrogenic diabetes insipidus
- Hypothyroidism
- Pregnancy problems

Buspirone

**MECHANISM**
Stimulates 5-HT$_{1A}$ 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

NORADRENERGIC

- MAO inhibitors
- NE reuptake
- TCA, SNRIs
- NE receptor
- Metabolites
- MAO

SEROTONERGIC

- MAO inhibitors
- NE reuptake
- TCA, SSRIs, SNRIs, trazodone
- Metabolites
- MAO
- 5-HT receptor
- 5-HT reuptake
- 5-HT

POSTSYNAPTIC NEURON
<table>
<thead>
<tr>
<th>Selective serotonin reuptake inhibitors</th>
<th>Fluoxetine, paroxetine, sertraline, citalopram.</th>
<th>Flashbacks paralyze senior citizens.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECHANISM</td>
<td>5-HT–specific reuptake inhibitors.</td>
<td>It normally takes 4–8 weeks for antidepressants to have an effect.</td>
</tr>
<tr>
<td>CLINICAL USE</td>
<td>Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.</td>
<td></td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Fewer than TCAs. GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serotonin-norepinephrine reuptake inhibitors</th>
<th>Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECHANISM</td>
<td>Inhibit 5-HT and norepinephrine reuptake.</td>
</tr>
<tr>
<td>CLINICAL USE</td>
<td>Depression, general anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>↑ BP most common; also stimulant effects, sedation, nausea.</td>
</tr>
</tbody>
</table>

| Serotonin syndrome                          | Can occur with any drug that ↑ 5-HT (eg, MAO inhibitors, SNRIs, TCAs). Characterized by 3 As: neuromuscular Activity (clonus, hypertonia, tremor, seizure), Autonomic stimulation (hyperthermia, diaphoresis, diarrhea), and Agitation. Treatment: cyproheptadine (5-HT₂ receptor antagonist). |

<table>
<thead>
<tr>
<th>Tricyclic antidepressants</th>
<th>Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECHANISM</td>
<td>Block reuptake of norepinephrine and 5-HT.</td>
</tr>
<tr>
<td>CLINICAL USE</td>
<td>Major depression, OCD (clomipramine), peripheral neuropathy, chronic pain, migraine prophylaxis.</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>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 elderly due to anticholinergic side effects (use nortriptyline). Treatment: NaHCO₃ to prevent arrhythmia.</td>
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</tbody>
</table>

Tri-C’s: Convulsions, Coma, Cardiotoxicity (arrhythmia due to Na⁺ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline). Treatment: NaHCO₃ to prevent arrhythmia.
### Monoamine oxidase inhibitors

**Tranylcypromine, Phenelzine, Isocarboxazid, Selegiline** (selective MAO-B inhibitor). *(MAO Takes Pride In Shanghai)*.

**MECHANISM**
Nonselective MAO inhibition ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).

**CLINICAL USE**
Atypical depression, anxiety.

**ADVERSE EFFECTS**
Hypertensive crisis (most notably with ingestion of tyramine, which is found in many foods such as aged cheese and wine); CNS stimulation. 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

**Bupropion**
↑ norepinephrine and dopamine via unknown mechanism. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in anorexic/bulimic patients. No sexual side effects.

**Mirtazapine**
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.

**Trazodone**
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 trazZZobone due to sedative and male-specific side effects.

**Varenicline**
Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance.
“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
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 32–36 weeks of gestation.
- Ureteric bud—derived from caudal end of mesonephric duct; gives rise to ureter, pelvises, 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
Ureteropelvic junction—last to canalize → most common site of obstruction (hydronephrosis) in fetus.

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)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Horseshoe kidney</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Unilateral renal agenesis</strong></td>
<td>Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter. Often diagnosed prenatally via ultrasound.</td>
</tr>
<tr>
<td><strong>Multicystic dysplastic kidney</strong></td>
<td>Ureteric bud fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Often diagnosed prenatally via ultrasound.</td>
</tr>
<tr>
<td><strong>Duplex collecting system</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Congenital solitary functioning kidney</strong></td>
<td>Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common.</td>
</tr>
</tbody>
</table>
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.

Ureters: course

Ureters pass under uterine artery or under vas deferens (retroperitoneal).
Gynecologic procedures (eg, ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.

“Water (ureters) under the bridge (uterine artery, 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)
- ~14 kg (20% of 70 kg)
- Interstitial fluid = 75% ECF ~ 10.5 L = 10.5 kg
- Blood volume ~ 6 L
  - Plasma = 25% ECF = 3.5 L = 3.5 kg

#### Intracellular fluid (ICF)
- ~28 kg (40% of 70 kg)

HIKIN: High K+ Intracellularly.

60–40–20 rule (% of body weight for average person):
- 60% total body water
- 40% ICF
- 20% ECF

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 net charge.

- Fenestrated capillary endothelium (size barrier)
- Fused basement membrane with heparan sulfate (negative charge and size barrier)
- Epithelial layer consisting of podocyte foot processes (negative charge barrier)

Charge barrier is lost in nephrotic syndrome → albuminuria, hypoproteinemia, generalized edema, hyperlipidemia.

---

**Renal clearance**

\[ C_x = \frac{U_x \cdot V}{P_x} \]

- \( C_x \) = volume of plasma from which the substance is completely cleared per unit time.
- If \( C_x < GFR \), net tubular reabsorption of X.
- If \( C_x > GFR \), net tubular secretion of X.
- If \( C_x = GFR \), no net secretion or reabsorption.

\( C_x \) = clearance of X (mL/min).
\( U_x \) = urine concentration of X (eg, mg/mL).
\( P_x \) = plasma concentration of X (eg, mg/mL).
\( V \) = 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.

\[
GFR = \frac{U_{\text{inulin}} \times V}{P_{\text{inulin}}} = C_{\text{inulin}} = K_f \left( \frac{P_{\text{GC}} - P_{\text{BS}}}{\pi_{\text{GC}} - \pi_{\text{BS}}} \right)
\]

(GC = glomerular capillary; BS = Bowman space.)

\(\pi_{\text{BS}}\) normally equals zero; \(K_f\) = filtration constant.

Normal GFR \(\approx 100\) 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 because between filtration and secretion there is nearly 100% excretion of all PAH that enters the kidney.

\[
eRPF = \frac{U_{\text{PAH}} \times V}{P_{\text{PAH}}} = C_{\text{PAH}}.
\]

Renal blood flow (RBF) = RPF/(1 - Hct).

Plasma = 1 - hematocrit.

eRPF underestimates true renal plasma flow (RPF) slightly.
**Filtration**

Filtration fraction (FF) = GFR/RPF.

- Normal FF = 20%.
- Filtered load (mg/min) = GFR (mL/min) x plasma concentration (mg/mL).
- GFR can be estimated with creatinine clearance.
- RPF is best estimated with PAH clearance.

**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>

**Calculation of reabsorption and secretion rate**

- Filtered load = GFR x P_x.
- Excretion rate = V x U_x.
- Reabsorption = filtered – excreted.
- Secretion = excreted – filtered.

\[
\text{FE}_{\text{Na}} = \frac{\text{Na}^+ \text{excreted}/\text{Na}^+ \text{filtered}}{\text{V} \times \text{GFR} \times \text{P}_{\text{Na}}} = \frac{\text{P}_{\text{G}} \times \text{U}_{\text{Na}}}{\text{P}_{\text{Na}}}
\]

\[
\text{GFR} = \text{U}_{\text{Cr}} \times \frac{\text{V}}{\text{P}_{\text{G}}}
\]
Glucose clearance

Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by 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 (Tm).

Normal pregnancy may decrease ability of PCT to reabsorb glucose and amino acids → glucosuria and aminoaciduria.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay is the region of substance clearance between threshold and Tm; due to the heterogeneity of nephrons.
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 acts as a buffer for secreted 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.


Thick ascending loop of Henle—reabsorbs Na⁺, K⁺, and Cl⁻. Indirectly induces paracellular reabsorption of Mg²⁺ and Ca²⁺ through β lumen potential generated by K⁺ backleak. Impermeable to H₂O. Makes urine less concentrated as it ascends.
10–20% Na⁺ reabsorbed.

Collecting tubule—reabsorbs Na⁺ in exchange for secreting K⁺ and H⁺ (regulated by aldosterone).
Aldosterone—acts on mineralocorticoid receptor → mRNA → protein synthesis. In principal cells: ↑ apical K⁺ conductance, ↑ Na⁺/K⁺ pump, ↑ epithelial Na⁺ channel (ENaC) activity → lumen negativity → K⁺ secretion. In α-intercalated cells: lumen negativity → ↑ H⁺ ATPase activity → ↑ H⁺ secretion → ↑ HCO₃⁻/Cl⁻ exchanger activity.
ADH—acts at V₂ receptor → insertion of aquaporin H₂O channels on apical side.
3–5% Na⁺ reabsorbed.
<table>
<thead>
<tr>
<th>Renal tubular defects</th>
<th>Fanconi syndrome is first (PCT), the rest are in alphabetic order.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi syndrome</td>
<td>Generalized reabsorptive defect in PCT.</td>
</tr>
<tr>
<td></td>
<td>Associated with ↑ excretion of nearly all amino acids, glucose, HCO$_3^-$, and PO$_4^{3-}$. May result in metabolic acidosis (proximal renal tubular acidosis).</td>
</tr>
<tr>
<td></td>
<td>Causes include hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease, cystinosis), ischemia, multiple myeloma, nephrotoxins/drugs (eg, ifosfamide, cisplatin, tenofovir, expired tetracyclines), lead poisoning.</td>
</tr>
<tr>
<td>Gitelman syndrome</td>
<td>Reabsorptive defect of NaCl in DCT. Similar to using lifelong thiazide diuretics. Autosomal recessive. Less severe than Bartter syndrome. Leads to hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria.</td>
</tr>
<tr>
<td>Liddle syndrome</td>
<td>Gain of function mutation → ↑ Na$^+$ reabsorption in collecting tubules (↑ activity of epithelial Na$^+$ channel). Presents like hyperaldosteronism, but aldosterone is nearly undetectable. Autosomal dominant. Results in hypertension, hypokalemia, metabolic alkalosis, ↓ aldosterone. Treatment: Amiloride.</td>
</tr>
<tr>
<td>Syndrome of Apparent Mineralocorticoid Excess</td>
<td>Hereditary deficiency of 11β-hydroxysteroid dehydrogenase, which normally converts cortisol (can activate mineralocorticoid receptors) to cortisone (inactive on mineralocorticoid receptors) in cells containing mineralocorticoid receptors. Excess cortisol in these cells from enzyme deficiency → ↑ mineralocorticoid receptor activity → hypertension, hypokalemia, metabolic alkalosis. Low serum aldosterone levels. Can acquire disorder from glycyrrhetinic acid (present in licorice), which blocks activity of 11β-hydroxysteroid dehydrogenase. Treatment: corticosteroids (exogenous corticosteroids ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation). Cortisol tries to be the SAME as aldosterone.</td>
</tr>
</tbody>
</table>
Relative concentrations along proximal convoluted tubules

\[ \frac{[T]}{[P]} > 1 \] when solute is reabsorbed less quickly than water.

\[ \frac{[T]}{[P]} = 1 \] when solute and water are reabsorbed at the same rate.

\[ \frac{[T]}{[P]} < 1 \] 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-angiotensin-aldosterone system

**Renin**
- Secreted by JG cells in response to ↓ renal arterial pressure and ↑ renal sympathetic discharge (β₁ effect).

**AT II**
- Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects. Helps maintain blood volume and blood pressure.

**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 osmolarity; also responds to low blood volume states.

**Aldosterone**
- Primarily regulates ECF volume and Na⁺ content; responds to low blood volume states.

---

**Juxtaglomerular apparatus**
- Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole) and the macula densa (NaCl sensor, part of DCT). 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. 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.

**Caciferol**
- PCT cells convert 25-OH vitamin D₃ to 1,25-(OH)₂ vitamin D₃ (calcitriol, active form).

**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**

**Atrial natriuretic peptide**

**Angiotensin II**
- Synthesized in response to ↓ blood pressure. Causes ↓ GFR and ↓ Na⁺ filtration but with compensatory Na⁺ reabsorption in proximal and distal nephron. Net effect: preservation of renal function (↑ FF) in low-volume state with simultaneous Na⁺ reabsorption (both proximal and distal) to maintain circulating volume.

**Parathyroid hormone**
- Secreted in response to ↓ plasma [Ca²⁺], ↑ plasma [PO₄³⁻], or ↓ plasma 1,25-(OH)₂ vitamin D₃.
- Causes ↑ Ca²⁺ reabsorption (DCT), ↑ PO₄³⁻ reabsorption (PCT), and ↑ 1,25-(OH)₂ vitamin D₃ production (↑ Ca²⁺ and PO₄³⁻ absorption from gut via vitamin D₃).

**Aldosterone**
- Secreted in response to ↓ blood volume (via AT II) 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⁺ Out of Cell (Causing Hyperkalemia)</th>
<th>Shifts K⁺ Into Cell (Causing Hypokalemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis (blocks Na⁺/K⁺ ATPase)</td>
<td>Hypo-osmolarity</td>
</tr>
<tr>
<td>Hyperosmolarity</td>
<td>Lysis of cells (eg, crush injury, rhabdomyolysis, tumor lysis syndrome)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Alkalosis</td>
</tr>
<tr>
<td>ß-blocker</td>
<td>ß-adrenergic agonist (↑ Na⁺/K⁺ ATPase)</td>
</tr>
<tr>
<td>High blood Sugar (insulin deficiency)</td>
<td>Insulin (↑ Na⁺/K⁺ ATPase)</td>
</tr>
<tr>
<td>Patient with hyperkalemia? DO LABS.</td>
<td>Insulin shifts K⁺ into cells</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), but not necessarily calciuria</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>Tetany, torsades de pointes, hypokalemia</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</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>
Acid-base physiology

<table>
<thead>
<tr>
<th></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: ↑ 1° disturbance; ↓ = compensatory response.

Henderson-Hasselbalch equation:  
\[
pH = 6.1 + \log \frac{[HCO₃⁻]}{0.03 \text{Pco₂}}
\]

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured Pco₂ > predicted Pco₂ → concomitant respiratory acidosis; if measured Pco₂ < predicted Pco₂ → concomitant respiratory alkalosis:

\[
Pco₂ = 1.5 [HCO₃⁻] + 8 ± 2
\]

Acidosis/alkalosis

Check arterial pH

pH < 7.35

- Acidemia: 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
    - Check anion gap = Na⁺ – (Cl⁻ + HCO₃⁻) > 12 mEq/L

- Normal anion gap
  - MUDPILES:
    - Methanol (formic acid)
    - Uremia
    - Diabetic ketoacidosis
    - Propylene glycol
    - Iron tablets or INH
    - Lactic acidosis
    - Ethylene glycol (↔ oxalic acid)
    - Salicylates (late)

pH > 7.45

- Atelexia: Pco₂ < 36 mm Hg, HCO₃⁻ > 28 mEq/L
  - Metabolic alkalosis
    - Hyperventilation
      - Hysteria
      - Hypoxemia (eg, high altitude)
      - Salicylates (early)
      - Tumor
      - Pulmonary embolism

- Normal anion gap
  - HARDASS:
    - Hyperalimentation
    - Addison disease
    - Renal tubular acidosis
    - Diarrhea
    - Acetazolamide
    - Speronolactone
    - Saline infusion

- Mixed acidosis
  - Pco₂ = 40 mm Hg

- Mixed alkalosis

- Buffer line
Renal tubular acidosis
A disorder of the renal tubules that leads to normal anion gap (hyperchloremic) metabolic acidosis.

<table>
<thead>
<tr>
<th>Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal renal tubular acidosis (type 1)</td>
<td>Urine pH &gt; 5.5. Defect in ability of ( \alpha )-intercalated cells to secrete ( H^+ ) ( \rightarrow ) no new ( HCO_3^- ) is generated ( \rightarrow ) metabolic acidosis. Associated with hypokalemia, ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover). Causes: amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract.</td>
</tr>
<tr>
<td>Proximal renal tubular acidosis (type 2)</td>
<td>Urine pH &lt; 5.5. Defect in PCT ( HCO_3^- ) reabsorption ( \rightarrow ) ↓ excretion of ( HCO_3^- ) in urine and subsequent metabolic acidosis. Urine is acidified by ( \alpha )-intercalated cells in collecting tubule. Associated with hypokalemia, ↑ risk for hypophosphatemic rickets. Causes: Fanconi syndrome and carbonic anhydrase inhibitors.</td>
</tr>
<tr>
<td>Hyperkalemic renal tubular acidosis (type 4)</td>
<td>Urine pH &lt; 5.5. Hypoaldosteronism ( \rightarrow ) hyperkalemia ( \rightarrow ) ↓ ( NH_4^+ ) synthesis in PCT ( \rightarrow ) ↑ ( NH_4^+ ) excretion. Causes: ↓ 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>
</tr>
</tbody>
</table>

**Casts in urine**

Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin. Bladder cancer, kidney stones \( \rightarrow \) hematuria, no casts. Acute cystitis \( \rightarrow \) pyuria, no casts.

- RBC casts
  - Glomerulonephritis, malignant hypertension.
- WBC casts
  - Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.
- Fatty casts ("oval fat bodies")
  - Nephrotic syndrome. Associated with “Maltese cross” sign.
- Granular ("muddy brown") casts
  - Acute tubular necrosis.
- Waxy casts
  - End-stage renal disease/chronic renal failure.
- Hyaline casts
  - Nonspecific, can be a normal finding, often seen in concentrated urine samples.

**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>A 1st disease of the kidney specifically impacting the glomeruli</td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>Secondary glomerular disease</td>
<td>A 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

<table>
<thead>
<tr>
<th>GRAMS OF PROTEIN EXCRETED PER DAY (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
</tr>
<tr>
<td>3.5</td>
</tr>
<tr>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Renal Pathology</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Nephritic syndrome</strong></td>
</tr>
<tr>
<td><strong>Acute poststreptococcal glomerulonephritis</strong></td>
</tr>
<tr>
<td><strong>Rapidly progressive (crescentic) glomerulonephritis</strong></td>
</tr>
<tr>
<td><strong>Diffuse proliferative glomerulonephritis</strong></td>
</tr>
<tr>
<td><strong>IgA nephropathy (Berger disease)</strong></td>
</tr>
<tr>
<td><strong>IgA nephropathy (Berger disease)</strong></td>
</tr>
</tbody>
</table>

---

**Notes:**
- Renal pathology of Henoch-Schönlein purpura.
- SLE: Systemic Lupus Erythematosus.
- PR3-ANCA/c-ANCA: Proteinase 3–antineutrophil cytoplasmic antibody.
- MPO-ANCA/p-ANCA: Myeloperoxidase–antineutrophil cytoplasmic antibody.
### Nephritic syndrome (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Relevant symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alport syndrome</strong></td>
<td>Mutation in type IV collagen → thinning and splitting of glomerular basement membrane. Most commonly X-linked dominant.</td>
<td>Eye problems (eg, retinopathy, lens dislocation), glomerulonephritis, sensorineural deafness; “can’t see, can’t pee, can’t hear a bee.” “Basket-weave” appearance on EM.</td>
</tr>
<tr>
<td><strong>Membrano-proliferative glomerulonephritis (MPGN)</strong></td>
<td>Type I—subendothelial immune complex (IC) deposits with granular IF; “tram-track” appearance on PAS stain and H&amp;E stain due to GBM splitting caused by mesangial ingrowth. Type II—also called dense deposit disease.</td>
<td>MPGN is a nephritic syndrome that often copresents with nephrotic syndrome. Type I may be 2° to hepatitis B or C infection. May also be idiopathic. Type II is associated with C3 nephritic factor (stabilizes C3 convertase → ↓ serum C3 levels).</td>
</tr>
</tbody>
</table>

LM = light microscopy; EM = electron microscopy; IF = immunofluorescence.
### Nephrotic syndrome

Nephrotic syndrome—massive proteinuria (> 3.5 g/day) with hypoalbuminemia, resulting edema, hyperlipidemia. Frothy urine with fatty casts. Due to podocyte damage disrupting glomerular filtration charge barrier. May be 1° (eg, direct sclerosis of podocytes) or 2° (systemic process [eg, diabetes] secondarily damages podocytes). Associated with hypercoagulable state (eg, thromboembolism) due to antithrombin (AT) III loss in urine and risk of infection (due to loss of immunoglobulins in urine and soft tissue compromise by edema).

Severe nephritic syndrome may present with nephrotic syndrome features (nephritic-nephrotic syndrome) if damage to GBM is severe enough to damage charge barrier.

<table>
<thead>
<tr>
<th>Minimal change disease (lipoid nephrosis)</th>
<th>LM—normal glomeruli (lipid may be seen in PCT cells).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IF ⊗.</td>
</tr>
<tr>
<td></td>
<td>EM—effacement of foot processes [1].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Focal segmental glomerulosclerosis</th>
<th>LM—segmental sclerosis and hyalinosis [2].</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IF—often ⊗, but may be ⊕ for nonspecific focal deposits of IgM, C3, C1..</td>
</tr>
<tr>
<td></td>
<td>EM—effacement of foot process similar to minimal change disease.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Membranous nephropathy (membranous glomerulonephritis)</th>
<th>LM—diffuse capillary and GBM thickening [3].</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IF—granular as a result of immune complex deposition. Nephrotic presentation of SLE.</td>
</tr>
<tr>
<td></td>
<td>EM—“spike and dome” appearance with subepithelial deposits.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Membranous nephropathy (membranous glomerulonephritis)</th>
<th>Most common cause of 1° nephrotic syndrome in Caucasian adults. Can be 1° (idiopathic) or 2° to drugs (eg, NSAIDs, penicillamine), infections (eg, HBV, HCV), SLE, or solid tumors. 1° disease has poor response to steroids. May progress to chronic renal disease.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Amyloidosis</th>
<th>LM—Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Diabetic glomerulonephropathy</th>
<th>LM—mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions, arrows in [9]).</th>
</tr>
</thead>
</table>

Most common cause of end-stage renal disease in the United States.
Kidney stones

Can lead to severe complications such as hydronephrosis, pyelonephritis. 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 oxalate: hypocitraturia</td>
<td>Radiopaque</td>
<td>Radiopaque</td>
<td>Shaped like envelope or dumbbell</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>
<td></td>
</tr>
</tbody>
</table>

Calcium phosphate: ↓ pH | Radiopaque | Radiopaque | Wedge-shaped prism | Treatment: thiazides. |

Ammonium magnesium phosphate | ↑ pH | Radiopaque | Radiopaque | Coffin lid | 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. |

Uric acid | ↓ pH | Radiolucent | Minimally visible | Rhomboid or rosettes | About 5% of all stones. Risk factors: ↓ urine volume, arid climates, acidic pH. Visible on ultrasound. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↓ cell turnover, such as leukemia. Treatment: alkalinization of urine, allopurinol. |

Cystine | ↑ pH | Radiolucent | Sometimes visible | Hexagonal | 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. |

A  B  C  D  E
Hydronephrosis

Distention/dilation of renal pelvis and calyces. Usually caused by urinary tract obstruction (e.g., renal stones, BPH, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated only if obstruction is bilateral or if patient has only one kidney. Leads to compression and possible atrophy of renal cortex and medulla.

Renal cell carcinoma

Originates from PCT cells → polygonal clear cells filled with accumulated lipids and carbohydrates. Often golden-yellow due to lipid content. Most common in men 50–70 years old. ↑ incidence with smoking and obesity. Manifests clinically with hematuria, palpable mass, 2° polycythemia, flank pain, fever, weight loss. Invades renal vein then IVC and spreads hematogenously; metastasizes to lung and bone.

Treatment: resection if localized disease. Immunotherapy (e.g., aldesleukin) or targeted therapy for advanced/metastatic disease. Resistant to chemotherapy and radiation therapy.

Renal oncocytoma

Benign epithelial cell tumor arising from collecting ducts (arrows 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 (e.g., renal cell carcinoma).
Wilms tumor (nephroblastoma)

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 WTI 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: Wilms tumor, early-onset nephrotic syndrome, male pseudohermaphroditism (WT1 mutation)
- Beckwith-Wiedemann: Wilms tumor, macroglossia, organomegaly, hemihypertrophy (WT2 mutation)

Transitional cell carcinoma

Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder). Painless hematuria (no casts) suggests bladder cancer. Associated with problems in your Pec 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

<table>
<thead>
<tr>
<th>Incontinence Type</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stress incontinence</strong></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>Urgency incontinence</strong></td>
<td>Overactive bladder (detrusor instability) → leak with urge to void immediately. Treatment: Kegel exercises, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin).</td>
<td></td>
</tr>
<tr>
<td><strong>Mixed incontinence</strong></td>
<td>Features of both stress and urgency incontinence.</td>
<td></td>
</tr>
<tr>
<td><strong>Overflow incontinence</strong></td>
<td>Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling. ↑ post-void residual (urinary retention) on catheterization or ultrasound. Treatment: catheterization, relieve obstruction (eg, α-blockers for BPH).</td>
<td></td>
</tr>
</tbody>
</table>
Urinary tract infection (acute bacterial cystitis)

- Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency.
- Systemic signs (e.g., 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, especially *E. coli*). 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; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages.

Diffuse cortical necrosis

- Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC.
- Associated with obstetric catastrophes (e.g., abruptio placentae), septic shock.
### Renal Osteodystrophy
Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic renal disease → 2° hyperparathyroidism. Hyperphosphatemia also independently ↓ serum Ca\(^{2+}\) by causing tissue calcifications, whereas ↓ 1,25-(OH)\(_2\)D\(_3\) → ↓ intestinal Ca\(^{2+}\) absorption. Causes subperiosteal thinning of bones.

### Acute Kidney Injury (Acute Renal Failure)
Acute kidney injury is defined as an abrupt decline in renal function as measured by ↑ creatinine and ↑ BUN.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal Azotemia</td>
<td>Due to ↓ RBF (eg, hypotension) → ↓ GFR. Na(^+)/H(_2)O and BUN retained by kidney in an attempt to conserve volume → ↑ BUN/creatinine ratio (BUN is reabsorbed, creatinine is not) and ↑ FENa.</td>
</tr>
<tr>
<td>Intrinsic Renal Failure</td>
<td>Generally due to acute tubular necrosis or ischemia/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. BUN reabsorption is impaired → ↑ BUN/creatinine ratio.</td>
</tr>
<tr>
<td>Postrenal Azotemia</td>
<td>Due to outflow obstruction (stones, BPH, neoplasia, congenital anomalies). Develops only with bilateral obstruction.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Prerenal</th>
<th>Intrinsic Renal</th>
<th>Postrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Osmolality (mOsm/kg)</td>
<td>&gt; 500</td>
<td>&lt; 350</td>
<td>&lt; 350</td>
</tr>
<tr>
<td>Urine Na(^+) (mEq/L)</td>
<td>&lt; 20</td>
<td>&gt; 40</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>FENa</td>
<td>&lt; 1%</td>
<td>&gt; 2%</td>
<td>&gt; 1% (mild)</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
Inability to make urine and excrete nitrogenous wastes.

Consequences (MAD HUNGER):
- Metabolic Acidosis
- Dyslipidemia (especially ↑ triglycerides)
- Hyperkalemia
- Uremia—clinical syndrome marked by ↑ BUN:
  - Nausea and anorexia
  - Pericarditis
  - Asterixis
  - Encephalopathy
  - Platelet dysfunction
- Na\(^+\)/H\(_2\)O retention (HF, pulmonary edema, hypertension)
- Growth retardation and developmental delay
- Erythropoietin failure (anemia)
- Renal osteodystrophy

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 haptons, 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, and costovertebral angle tenderness, but can be asymptomatic. Remember these P’s:
- P-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. ↑ FENa.

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

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, radiographic contrast agents, lead, cisplatin), crush injury (myoglobinuria), hemoglobinuria. PCT is particularly susceptible to injury.

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</th>
<th>Description</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant Polycystic Kidney Disease</strong></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.</td>
<td>Death from complications of chronic kidney disease or hypertension (caused by renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts.</td>
</tr>
<tr>
<td><strong>Autosomal Recessive Polycystic Kidney Disease</strong></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>
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</tr>
<tr>
<td><strong>Medullary Cystic Disease</strong></td>
<td>Inherited disease causing tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; shrunken kidneys on ultrasound. Poor prognosis.</td>
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</tr>
<tr>
<td><strong>Simple vs Complex Renal Cysts</strong></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>
<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>
Diuretics: site of action

1. Mannitol
2. Acetazolamide
3. Loop diuretics
4. Thiazide
5. K⁺ sparing diuretics

- Glomerulus
- Proximal convoluted tubule
- Distal convoluted tubule
- Loop of Henle
- Collecting duct
### Mannitol

**MECHANISM**
Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure.

**CLINICAL USE**
Drug overdose, elevated intracranial/intraocular pressure.

**ADVERSE EFFECTS**
Pulmonary edema, dehydration.
Contraindicated in anuria, HF.

### Acetazolamide

**MECHANISM**
Carbonic anhydrase inhibitor. Causes self-limited NaHCO₃ diuresis and ↑ total body HCO₃⁻ stores.

**CLINICAL USE**
Glaucoma, urinary alkalization, metabolic alkalosis, altitude sickness, pseudotumor cerebri.

**ADVERSE EFFECTS**
Proximal renal tubular acidosis, paresthesias, NH₃ toxicity, sulfa allergy.

“ACID”azolamide causes ACIDosis.

### Loop diuretics

#### Furosemide, bumetanide, torsemide

**MECHANISM**
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⁺.

**CLINICAL USE**
Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.

**ADVERSE EFFECTS**
OTotoxicity, Hypokalemia, Dehydration, Allergy (sulfa)/metabolic Alkalosis, Nephritis (interstitial), Gout.

**Ethacrynic acid**

**MECHANISM**
Nonsulfonamide inhibitor of cotransport system (Na⁺/K⁺/2Cl⁻) of thick ascending limb of loop of Henle.

**CLINICAL USE**
Diuresis in patients allergic to sulfa drugs.

**ADVERSE EFFECTS**
Similar to furosemide, but more ototoxic. Loop earrings hurt your ears.
<table>
<thead>
<tr>
<th><strong>Thiazide diuretics</strong></th>
<th>Hydrochlorothiazide, chlorthalidone, metolazone.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Inhibit NaCl reabsorption in early DCT → ↓ diluting capacity of nephron. ↓ Ca(^{2+}) excretion.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Hypokalemic metabolic alkalosis, hyponatremia, hyperGLUC. hypGLycaemia, hyperLipidemia, hyperURicemia, hyperCalcemia. Sulfur allergy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Potassium-sparing diuretics</strong></th>
<th>Spironolactone and eplerenone; Triamterene, and Amiloride.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Hyperaldosteronism, K(^{+}) depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride).</td>
</tr>
<tr>
<td><strong>ADVERSE EFFECTS</strong></td>
<td>Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).</td>
</tr>
</tbody>
</table>

**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. ↓ HCO\(_{3}^{-}\) 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. |
| **Urine Ca\(^{2+}\)** | ↑ with loop diuretics: ↓ paracellular Ca\(^{2+}\) reabsorption → hypocalcemia. ↓ with thiazides: enhanced Ca\(^{2+}\) reabsorption. |
### Angiotensin-converting enzyme inhibitors

Captopril, enalapril, lisinopril, ramipril.

| MECHANISM | 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 (due to ↑ bradykinin; contraindicated in CI 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. |

In diabetic nephropathy, ↓ intraglomerular pressure, slowing GBM thickening.

Captopril’s CATCHH.

### Angiotensin II receptor blockers

Losartan, candesartan, valsartan.

| MECHANISM | Selectively block binding of angiotensin II to AT₁ receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin. |
| CLINICAL USE | Hypertension, HF, proteinuria, or diabetic nephropathy with intolerance to ACE inhibitors (eg, cough, angioedema). |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension; teratogen. |

### Aliskiren

| MECHANISM | Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. |
| CLINICAL USE | Hypertension. |
| ADVERSE EFFECTS | Hyperkalemia, ↓ GFR, hypotension. Relatively contraindicated in patients already taking ACE inhibitors or ARBs. |
“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. Knlo
## Important genes of embryogenesis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function and Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sonic hedgehog gene</strong></td>
<td>Produced at base of limbs in zone of polarizing activity. Involved in patterning along anteroposterior axis and CNS development; mutation can cause holoprosencephaly.</td>
</tr>
<tr>
<td><strong>Wnt-7 gene</strong></td>
<td>Produced at apical ectodermal ridge (thickened ectoderm at distal end of each developing limb). Necessary for proper organization along dorsal-ventral axis.</td>
</tr>
<tr>
<td><strong>FGF gene</strong></td>
<td>Produced at apical ectodermal ridge. Stimulates mitosis of underlying mesoderm, providing for lengthening of limbs.</td>
</tr>
<tr>
<td><strong>Homeobox (Hox) genes</strong></td>
<td>Involved in segmental organization of embryo in a craniocaudal direction. Code for transcription factors. Hox mutations → appendages in wrong locations.</td>
</tr>
</tbody>
</table>

## Early fetal development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within week 1</strong></td>
<td>hCG secretion begins around the time of implantation of blastocyst.</td>
</tr>
<tr>
<td><strong>Within week 2</strong></td>
<td>Bilaminar disc (epiblast, hypoblast).</td>
</tr>
<tr>
<td><strong>Within week 3</strong></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><strong>Weeks 3–8 (embryonic period)</strong></td>
<td>Neural tube formed by neuroectoderm and closes by week 4. Organogenesis.</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>Heart begins to beat. Upper and lower limb buds begin to form.</td>
</tr>
<tr>
<td><strong>Week 6</strong></td>
<td>Fetal cardiac activity visible by transvaginal ultrasound.</td>
</tr>
<tr>
<td><strong>Week 8</strong></td>
<td>Fetal movements start.</td>
</tr>
<tr>
<td><strong>Week 10</strong></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; epidermis; anal canal below the pectinate line; parotid, sweat, mammary glands.</td>
</tr>
<tr>
<td><strong>Neuroectoderm</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>PNS (dorsal root ganglia, cranial nerves, autonomic ganglia, Schwann cells), melanocytes, chromaffin cells of adrenal medulla, parafollicular (C) cells of thyroid, pia and arachnoid, bones of the skull, odontoblasts, aorticopulmonary septum, endocardial cushions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mesoderm</th>
<th>Middle/“meat” layer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle</strong></td>
<td>Muscle, bone, connective tissue, serous linings of body cavities (eg, peritoneum), 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>Bone</strong></td>
<td>Mesodermal defects = VACTERL: Vertebral defects</td>
</tr>
<tr>
<td><strong>Connective tissue</strong></td>
<td>Anal atresia</td>
</tr>
<tr>
<td><strong>Serous linings of body cavities</strong></td>
<td>Cardiac defects</td>
</tr>
<tr>
<td><strong>Spleen</strong></td>
<td>Tracheo-Esophageal fistula</td>
</tr>
<tr>
<td><strong>Cardiovascular structures</strong></td>
<td>Renal defects</td>
</tr>
<tr>
<td><strong>Lymphatics</strong></td>
<td>Limb defects (bone and muscle)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endoderm</th>
<th>“External” layer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>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).</strong></td>
<td></td>
</tr>
</tbody>
</table>

## Types of errors in organ 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>Medications</th>
<th>Effects on Fetus</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<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 happy 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 | 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, neural tube defects, macrosomia |
| 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 vermilion 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.

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).
Placenta

1st site of nutrient and gas exchange between mother and fetus.

| Fetal component | | | | |
|-----------------|-----------------|-----------------|-----------------|
| **Cytotrophoblast** | Inner layer of chorionic villi. | Cytotrophoblast makes **Cells**. | |
| **Syncytiotrophoblast** | 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. | |

| Maternal component | | | | |
|-------------------|-----------------|-----------------|-----------------|
| **Decidua basalis** | Derived from endometrium. Maternal blood in lacunae. | | |

![Diagram of placenta showing maternal and fetal circulation](image-url)
### 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.

![Image of umbilical cord](image-url)

### 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.

- **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. Can lead to infection, adenocarcinoma.
- **Vesicourachal diverticulum**: Slight failure of urachus to obliterate → outpouching of bladder.

![Images of urachus](image-url)

### Vitelline duct

7th week—obliteration of vitelline duct (omphalo-mesenteric 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.

![Images of vitelline duct](image-url)
Aortic arch derivatives

1st: Part of maxillary artery (branch of external carotid). 1st arch is maximal.
2nd: Stapedial artery and hyoid artery. Second = Stapedial.
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 (pharyngeal) 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. Immobile during swallowing.
### 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 arch | Maxillary process  
→ Maxilla, zygomatic bone  
Mandibular process  
→ Meckel cartilage  
→ Mandible, Malleus and incus, sphenomandibular ligament | Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini | CN V₂ and V₃  
chew | Pierre Robin sequence—micrognathia, glossoptosis, cleft palate, airway obstruction  
Treacher Collins syndrome—neural crest dysfunction  
→ mandibular hypoplasia, facial abnormalities |
| 2nd 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 arch | Greater horn of hyoid | Stylopharyngeus (think of stylopharyngeus innervated by glosso pharyngeal nerve) | CN IX (stylopharyngeus)  
swallow stylishly | |
| 4th–6th 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)  
6th arch: CN X (recurrent laryngeal branch)  
simply swallow  
speak | Arches 3 and 4 form posterior ⅓ 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 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 (top = superior parathyroids).</td>
</tr>
<tr>
<td>2nd pouch</td>
<td>Epithelial lining of palatine tonsil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd pouch</td>
<td>Dorsal wings → inferior parathyroids. Ventral wings → 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 pouch</td>
<td>Dorsal wings → superior parathyroids. Ventral wings → ultimobranchial body → parafollicular (C) cells of thyroid.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### DiGeorge Syndrome

Chromosome 22q11 deletion. Aberrant development of 3rd and 4th pouches → 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 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 → 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). In females, remnant of mesonephric duct → Gartner duct.

**SRY gene**

1. No Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia
2. 5α-reductase deficiency—inability to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when ↑ testosterone levels cause masculinization)
Uterine (Müllerian duct) anomalies

- **Septate uterus**: Common anomaly vs normal uterus. Incomplete resorption of septum. † fertility. Treat with septoplasty.

- **Bicornuate uterus**: Incomplete fusion of Müllerian ducts. † risk of complicated pregnancy.

- **Uterus didelphys**: Complete failure of fusion → double uterus, vagina, and cervix. 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 paraurethral glands (of Skene)
  - Labia minora
  - Labia majora

---

- **Normal**
- **Septate**
- **Bicornuate**
- **Didelphys**
Congenital penile abnormalities

**Hypospadias**
Abnormal opening of penile urethra on ventral surface of penis due to failure of urethral folds to fuse.

**Epispadias**
Abnormal opening of penile urethra on dorsal surface of penis due to faulty positioning of genital tubercle.

Hypospadias is more common than epispadias. Associated with inguinal hernia and cryptorchidism. **Hypo is below.**

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></th>
<th>MALE REMNANT</th>
<th>FEMALE REMNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gubernaculum (band of fibrous tissue)</strong></td>
<td>Anchors testes within scrotum.</td>
<td>Ovarian ligament + round ligament of uterus.</td>
</tr>
<tr>
<td><strong>Processus vaginalis (evagination of peritoneum)</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/cervix/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 (suspensory ligament of the ovary)</td>
<td>Ovaries to lateral pelvic wall</td>
<td>Ovarian vessels</td>
<td>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 (not labeled)</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.</td>
</tr>
<tr>
<td>Round ligament of the uterus</td>
<td>Uterine fundus 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 lateral uterus</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

Urethral injury
Suspect if blood seen at urethral meatus.
Posterior urethra—membranous urethra prone to injury from pelvic fracture. Injury can cause urine to leak into retropubic space.
Anterior urethra—bulbar and penile urethra at risk of damage due to perineal straddle injury. Can cause urine to leak beneath deep fascia of Buck. If fascia is torn, urine escapes into superficial perineal space.

Autonomic innervation of the male sexual response
Erection—Parasympathetic nervous system (pelvic nerve):
* NO $\rightarrow$ cGMP $\rightarrow$ smooth muscle relaxation $\rightarrow$ vasodilation $\rightarrow$ proerectile.
* Norepinephrine $\rightarrow$ $\frac{1}{2}$ $[Ca^{2+}]_{in}$ $\rightarrow$ smooth muscle contraction $\rightarrow$ vasoconstriction $\rightarrow$ antierectile.

Emission—Sympathetic nervous system (hypogastric nerve).

Ejaculation—visceral and Somatic nerves (pudendal nerve).

Point, Squeeze, and Shoot.
PDE-5 inhibitors (eg, sildenafil) $\downarrow$ cGMP breakdown.
### Seminiferous tubules

<table>
<thead>
<tr>
<th>CELL</th>
<th>FUNCTION</th>
<th>LOCATION/NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spermatogonia (germ cells)</td>
<td>Maintain germ pool and produce 1° spermatocytes.</td>
<td>Line seminiferous tubules A</td>
</tr>
<tr>
<td>Sertoli cells (non–germ cells)</td>
<td>Secrete inhibit B → inhibit FSH.</td>
<td>Line seminiferous tubules</td>
</tr>
<tr>
<td></td>
<td>Secrete androgen-binding protein → maintain local levels of testosterone.</td>
<td>Convert testosterone and androstenedione to estrogens via aromatase</td>
</tr>
<tr>
<td></td>
<td>Produce MIF.</td>
<td>Sertoli cells Support Sperm Synthesis</td>
</tr>
<tr>
<td></td>
<td>Tight junctions between adjacent Sertoli cells form blood-testis barrier → isolate gametes from autoimmune attack.</td>
<td>Homolog of female granulosa cells</td>
</tr>
<tr>
<td></td>
<td>Support and nourish developing spermatozoa.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regulate spermatogenesis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temperature sensitive; ↓ sperm production and ↑ inhibit B with ↑ temperature.</td>
<td>↑ temperature seen in varicocele, cryptorchidism</td>
</tr>
<tr>
<td>Leydig cells (endocrine 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>Homolog of female theca interna cells</td>
</tr>
</tbody>
</table>

#### Diagram

- **Hypothalamus**
  - GnRH
    - Anterior pituitary
      - LH
      - FSH
      - Inhibit B
      - Sertoli cell
      - Leydig cell
      - Testosterone
      - Capillary

- **Spermatogonium**
- **Spermatocyte**
- **Spermatid**
- **Spermatozoon**

- **Sertoli cell nucleus**
- **Lumen of seminiferous tubule**

- **Spermatogenesis**
- **Seminiferous tubule**
- **Germinal cells (Sertoli cells)**
- **1° spermatocytes**
- **1° spermatids**
- **1° spermatozoa**
- **Interstitial cells (Leydig cells)**

- **Blood testis barrier**: Isolate gametes from autoimmune attack.
### Estrogen

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th>Ovary (17β-estradiol), placenta (estriol), adipose tissue (estrone via aromatization).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNCTION</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th>Corpus luteum, placenta, adrenal cortex, testes.</th>
</tr>
</thead>
</table>

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 met a sperm.” If fertilization does not occur within 1 day, the 2° oocyte degenerates.

<table>
<thead>
<tr>
<th>Oogonium</th>
<th>Diploid (2N, 2C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° oocyte</td>
<td>Diploid (2N, 4C)</td>
</tr>
<tr>
<td>2° oocyte</td>
<td>Haploid (1N, 2C)</td>
</tr>
<tr>
<td>Ovum</td>
<td>Haploid (1N, 1C)</td>
</tr>
</tbody>
</table>

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.

Dysmenorrhea
Pain with menses; often associated with endometriosis.

Oligomenorrhea
> 35-day cycle.

Polymenorrhea
< 21-day cycle.

Metrorrhagia
Frequent or irregular menstruation.

Menorrhagia
Heavy menstrual bleeding; > 80 mL blood loss or > 7 days of menses.

Menometrorrhagia
Heavy, irregular menstruation.
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 renal perfusion)
- Anemia (↑ plasma, ↑ RBCs → ↓ viscosity)
- Hypercoagulability (to ↓ blood loss at delivery)
- Hyperventilation (eliminate fetal CO₂)

hCG

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 estriol 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, Edward syndrome, and Patau syndrome.

Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks.
Apgar score

<table>
<thead>
<tr>
<th></th>
<th>Score 2</th>
<th>Score 1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Pink</td>
<td>Extremities blue</td>
<td>Pale or blue</td>
</tr>
<tr>
<td>Pulse</td>
<td>&gt; 100 bpm</td>
<td>&lt; 100 bpm</td>
<td>No pulse</td>
</tr>
<tr>
<td>Grimace</td>
<td>Cries and pulls away</td>
<td>Grimaces or weak cry</td>
<td>No response to stimulation</td>
</tr>
<tr>
<td>Activity</td>
<td>Active movement</td>
<td>Arms, legs flexed</td>
<td>No movement</td>
</tr>
<tr>
<td>Respiration</td>
<td>Strong cry</td>
<td>Slow, irregular</td>
<td>No breathing</td>
</tr>
</tbody>
</table>

Assessment of newborn vital signs following labor 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.

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 labor, the ↓ in progesterone and estrogen disinhibits lactation. Suckling is required to maintain milk production, 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 (confering 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. Exclusively breastfed infants require vitamin D 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 (testis), Androstenedione (ADrenal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNCTION</td>
<td>Testosterone:</td>
</tr>
<tr>
<td></td>
<td>▪ Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate).</td>
</tr>
<tr>
<td></td>
<td>▪ Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs.</td>
</tr>
<tr>
<td></td>
<td>▪ Deepening of voice.</td>
</tr>
<tr>
<td></td>
<td>▪ Closing of epiphyseal plates (via estrogen converted from testosterone).</td>
</tr>
<tr>
<td></td>
<td>▪ Libido.</td>
</tr>
<tr>
<td></td>
<td>DHT:</td>
</tr>
<tr>
<td></td>
<td>▪ Early—differentiation of penis, scrotum, prostate.</td>
</tr>
<tr>
<td></td>
<td>▪ Late—prostate growth, balding, sebaceous gland activity.</td>
</tr>
</tbody>
</table>

Potency: DHT > testosterone > androstenedione.

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 → azoospermia.
**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)

46 sister chromatids (sex= X-X)

23 sister chromatids (sex= X-Y)

**Replication (interphase)**

**Meiosis II**

23 single (sex= X)

23 single (sex= Y)

23 sister chromatids (sex= Y-Y)

**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
  - Pre-pubertal
- **Stage II**: Pubic hair appears
  - Pubarche
  - Testicular enlargement
  - Breast bud forms (thelarche)
  - Adult
- **Stage III**: Coarsening of pubic hair
  - Testes increase in size and length
  - Breast enlarges, mound forms
  - Adult
- **Stage IV**: Coarse hair across pubis, sparing thigh
  - Penis width/guard
  - Breast enlarges, raised areola, mound on mound
  - Adult
- **Stage V**: Coarse hair across pubis and medial thigh
  - Penis and testes enlarge to adult size
  - Adult breast contour, areola flattens
  - Adult
## REPRODUCTIVE—PATHOLOGY

### Sex chromosome disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Features</th>
<th>Laboratory Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Klinefelter syndrome</strong>&lt;br&gt; <strong>[male] (47,XXY)</strong></td>
<td>Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution</td>
<td>Dysgenesis of seminiferous tubules → ↓ inhibin B → ↑ FSH. Abnormal Leydig cell function → ↓ testosterone → ↑ LH → ↓ estrogen.</td>
</tr>
<tr>
<td><strong>Turner syndrome</strong>&lt;br&gt; <strong>[female] (45,XO)</strong></td>
<td>Short stature (if untreated), ovarian dysgenesis (streak ovary), shield chest, bicuspid aortic valve, coarctation (femoral &lt; brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney</td>
<td>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).</td>
</tr>
<tr>
<td><strong>Double Y males (XYY)</strong></td>
<td>Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.</td>
<td></td>
</tr>
<tr>
<td><strong>Ovotesticular disorder of sex development</strong>&lt;br&gt; 46,XX &gt; 46,XY.</td>
<td>Both ovarian and testicular tissue present (ovotestis); ambiguous genitalia. Previously called true hermaphroditism.</td>
<td></td>
</tr>
</tbody>
</table>
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>1° hypogonadism</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>Hypogonadotropic hypogonadism</td>
</tr>
</tbody>
</table>

Other disorders of sex development

Disagreement between the phenotypic (external genitalia) and gonadal (testes vs ovaries) sex. Include 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).

Placental aromatase deficiency

Inability to synthesize estrogens from androgens. Masculinization of female (46,XX) infants (ambiguous genitalia), ↑ serum testosterone and androstenedione. Can present with maternal virilization during pregnancy (fetal androgens cross the placenta).

Androgen insensitivity syndrome (46,XY)

Defect in androgen receptor resulting in normal-appearing female; female external genitalia with scant sexual 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). 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

Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of GnRH cells and formation of olfactory bulb; ↓ synthesis of GnRH in the hypothalamus; anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).
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>KARYOTYPE</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XX; 46,XY</td>
<td>69,XXX; 69,XXY; 69,XYY</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMPONENTS</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA)</td>
<td>2 sperm + 1 egg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FETAL PARTS</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes (partial = fetal parts)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UTERINE SIZE</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>⬆</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>hCG</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓↓↓↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMAGING</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Honeycombed” uterus or “clusters of grapes”</td>
<td>Fetal parts</td>
<td></td>
</tr>
<tr>
<td>“snowstorm” on ultrasound</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RISK OF MALIGNANCY (GESTATIONAL TROPHOBLASTIC NEOPLASIA)</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–20%</td>
<td>&lt; 5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RISK OF CHORIOCARCINOMA</th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

Choriocarcinoma

Rare; can develop during or after pregnancy in mother or baby. Malignancy of trophoblastic tissue (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.
### Pregnancy complications

#### Placental abruption (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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>with apparent hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>with concealed hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

#### Placenta accreta/increta/percreta
Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section, inflammation, placenta previa. 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. 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.
### 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**  
Most often in ampulla of fallopian tube (A shows 10-mm embryo in oviduct at 7 weeks of gestation). 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.

**Risk factors:**  
- Prior ectopic pregnancy  
- History of infertility  
- Salpingitis (PID)  
- Ruptured appendix  
- Prior tubal surgery

### Amniotic fluid abnormalities

**Polyhydramnios**  
Too much amniotic fluid; 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> (pregnancy-induced hypertension)</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, (\alpha)-Methyldopa, Labetalol, Nifedipine), deliver at 37–39 weeks. Hypertensive Moms Love Nifedipine.</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). May proceed to eclampsia (+ seizures) and/or HELLP syndrome. Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. Incidence 1 in patients with pre-existing hypertension, diabetes, chronic renal disease, autoimmune disorders. Complications: placental abruption, coagulopathy, renal failure, uteroplacental insufficiency, eclampsia.</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. Worst prognosis—ovarian > endometrial > cervical.
### Vaginal tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>Usually 2nd to cervical SCC; 1st vaginal carcinoma rare.</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>Affects women who had exposure to DES in utero.</td>
</tr>
<tr>
<td>Sarcoma botryoides (embryonal rhabdomyosarcoma variant)</td>
<td>Affects girls &lt; 4 years old; spindle-shaped cells; desmin. Presents with clear, grape-like, polypoid mass emerging from vagina.</td>
</tr>
</tbody>
</table>

### Cervical pathology

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia and carcinoma in situ</td>
<td>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 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 suppressor gene) and E7 gene product (inhibits RB suppressor gene). 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, starting sexual intercourse at young age, HIV infection.</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes) before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → renal failure.</td>
</tr>
</tbody>
</table>

### Premature ovarian failure

Premature atresia of ovarian follicles in women of reproductive age. Patients present with signs of menopause after puberty but before age 40.

### 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.

### Polycystic ovarian syndrome (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 subfertility in women. Enlarged, bilateral cystic ovaries presents with amenorrhea/oligomenorrhea, hirsutism, acne, ↓ fertility. Associated with obesity. ↑ risk of endometrial cancer 2nd to unopposed estrogen from repeated anovulatory cycles.

Treatment: weight reduction, OCPs, clomiphene citrate, ketoconazole, spironolactone.
### 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 (BRCA-1 or BRCA-2 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).

### Benign ovarian neoplasms

<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 (ectopic endometrial tissue) 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>
<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 2° to ovarian enlargement or torsion. A monodermal form with thyroid tissue (struma ovarii) uncommonly presents with hyperthyroidism.</td>
</tr>
<tr>
<td>Brenner tumor</td>
<td>Looks like bladder. Solid tumor that is pale yellow-tan and appears encapsulated. “Coffee bean” nuclei on H&amp;E stain.</td>
</tr>
<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>
### Ovarian neoplasms (continued)

#### Malignant ovarian neoplasms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</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).</td>
</tr>
<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>Pseudomyxoma peritonei—intraperitoneal accumulation of mucinous material from ovarian or appendiceal tumor.</td>
</tr>
<tr>
<td><strong>Immature teratoma</strong></td>
<td>Aggressive, contains fetal tissue, neuroectoderm. Commonly diagnosed after menopause. Typically represented by immature/embryonic-like neural tissue.</td>
</tr>
<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>Yolk sac (endodermal sinus) tumor</strong></td>
<td>Aggressive, in ovaries or testes (boys) 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>
<tr>
<td><strong>Krukenberg tumor</strong></td>
<td>GI malignancy that metastasizes to ovaries → mucin-secreting signet cell adenocarcinoma.</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

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. Treatment: gentamicin + clindamycin +/− ampicillin.

Endometriosis
Non-neoplastic endometrial 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 cyst”). 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, OCPs, progestins, GnRH agonists, danazol, laparoscopic removal.
Breast pathology

Benign breast disease

**Fibroadenoma**  
Most common in women under 35 years. Small, well-defined, mobile mass. ↑ size and tenderness with ↑ estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased.

**Fibrocystic changes**  
Most common in premenopausal women > 35 years. Presents 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.

**Sclerosing adenosis**  
↑ acini and stromal fibrosis, associated with calcifications. Slight (1.5–2×) ↑ risk for cancer.

**Intraductal papilloma**  
Small papillary tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight (1.5–2×) ↑ risk for cancer.

**Epithelial hyperplasia**  
↑ cells in terminal ductal or lobular epithelium. ↑ risk of carcinoma with atypical cells.

**Phyllodes tumor**  
Large mass of connective tissue and cysts with “leaf-like” lobulations. Most common in 5th decade. Some may become malignant.

**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**  
During breastfeeding, ↑ risk of bacterial infection through cracks in nipple. *S aureus* is most common pathogen. Treat with antibiotics and continue breastfeeding.

**Gynecomastia**  
Breast enlargement in males due to ↑ estrogen compared with androgen activity. Physiologic (not pathologic) 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, Ketoconazole: “Some Hormones Create Knockers”).
Malignant breast tumors

Commonly postmenopausal. Usually arise from terminal duct lobular unit. Overexpression of estrogen/progesterone receptors or c-erbB2 (HER-2, an EGF receptor) is common; triple negative (ER ⊘, PR ⊘, and Her2/Neu ⊘) 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 upperouter quadrant of breast.

<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 D. Grossly, see classic “stellate” infiltration.</td>
<td>Most common (~ 75% of all breast cancers).</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>Orderly row of cells (“Indian file” E), 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 (breast skin resembles orange peel F); 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>
Malignant breast tumors (continued)

Penile pathology

Peyronie disease

Ischemic priapism
Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs get trapped in 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 (cancer of glans, presents as erythroplakia), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with HPV and lack of circumcision.

Cryptorchidism
Undescended testis (one or both); impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are unaffected by temperature); associated with ↑ risk of germ cell tumors. Prematurity ↑ risk of cryptorchidism. ↑ inhibit B, ↑ FSH, ↑ LH; testosterone ↓ in bilateral cryptorchidism, normal in unilateral.

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 (distension on inspection and “bag of worms” on palpation) or ultrasound with Doppler A; does not transilluminate. Treatment: varicocelectomy, embolization.
### Extrapelvic 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 in infants, due to incomplete obliteration of processus vaginalis. Transilluminating swelling.

### Acquired hydrocele

Scrotal fluid collection usually 2º to infection, trauma, tumor. If bloody → hematocoele.

### 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. Testicular mass that does not transilluminate.

#### 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. Radiosensitive. Late metastasis, excellent prognosis.

#### Yolk sac (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 (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

Golden brown color; contains Reinke crystals (eosinophilic cytoplasmic inclusions). Produce androgens or estrogens → gynecomastia in men, precocious puberty in boys.

#### Sertoli cell

Androblastoma from sex cord stroma.

#### Testicular lymphoma

Most common testicular cancer in older men. Not a 1º 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; 5\( \alpha \)-reductase inhibitors (eg, finasteride); tadalafil.

Prostatitis

Dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate. Acute: bacterial (eg, \( E \) coli); chronic: bacterial or abacterial.

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

Anterior pituitary

LH
FSH

Clomiphene
GnRH antagonists
GnRH agonists

LH
FSH

Oral contraceptives
Danazol

Ketoconazole
Danazol

Anastrozole

Estriol
Estrone
Estradiol

Selective estrogen-receptor modulators

Gene expression in estrogen-responsive cells

Gene expression in androgen-responsive cells

Ovary

LH
FSH

Testis

Testosterone
5α-reductase
Dihydrotestosterone
Androgen-receptor complex

Flutamide
Cyproterone
Spironolactone

Anastrozole

P-450c17
Aromatase

Androstenedione
Testosterone

Estriol
Estrone
Estradiol

Ketoconazole
Danazol

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Dihydrotestosterone
Androgen-receptor complex

Flutamide
Cyproterone
Spironolactone

### Leuprolide

**MECHANISM**
GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion (downregulates GnRH receptor in pituitary to ↓ FSH/LH).

**Leuprolide can be used in lieu of GnRH.**

**CLINICAL USE**
Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility.

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### Estrogens

Ethinyl estradiol, DES, mestranol.

**MECHANISM**
Bind estrogen receptors.

**CLINICAL USE**
Hypogonadism or ovarian failure, menstrual abnormalities, hormone replacement therapy in postmenopausal women; use in men with androgen-dependent prostate cancer.

**ADVERSE EFFECTS**
† risk of endometrial cancer, 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.

---

### 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). 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, so progesterone 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 (e.g., 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.

### Copper intrauterine device
**MECHANISM**
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).

### Terbutaline, ritodrine
$\beta_2$-agonists that relax the uterus; used to ↓ contraction frequency in women during labor.

### Danazol
**MECHANISM**
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.
### 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**
- Causes 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

- **Testosterone $\alpha_5$-reductase**
  - DHT (more potent).
- **Finasteride**
  - $5\alpha$-reductase inhibitor (↑ conversion of testosterone to DHT). Used for BPH and male-pattern baldness.
- **Flutamide**
  - Nonsteroidal competitive inhibitor at androgen receptors. Used for prostate carcinoma.
- **Ketoconazole**
  - Inhibits steroid synthesis (inhibits 17,20-desmolase).
  - Used for polycystic ovarian syndrome to reduce androgenic symptoms. Both have side effects of gynecomastia and amenorrhea.
- **Spironolactone**
  - Inhibits steroid binding, 17α-hydroxylase, and 17,20-desmolase.

### Tamsulosin

- $\alpha_1$-antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for $\alpha_{1A,D}$ receptors (found on prostate) vs vascular $\alpha_{1B}$ receptors.

### Phosphodiesterase type 5 inhibitors

- **Sildenafil, vardenafil, tadalafil.**
  - Inhibit PDE-5 → ↑ cGMP → prolonged smooth muscle relaxation in response to NO → ↑ blood flow in corpus cavernosum of penis, ↓ pulmonary vascular resistance.
  - Sildenafil, vardenafil, and tadalafil fill the penis.

**Clinical Use**
- Erectile dysfunction, pulmonary hypertension, BPH (tadalafil only).

**Adverse Effects**
  - “Hot and sweaty,” but then Headache, Heartburn, Hypotension.

### Minoxidil

**Mechanism**
- Direct arteriolar vasodilator.

**Clinical Use**
- Androgenetic alopecia; severe refractory hypertension.
“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

“Mars is essentially in the same orbit. Somewhat the same distance from the Sun, which is very important. We have seen pictures where there are canals, we believe, and water. If there is water, that means there is oxygen. If there is oxygen, that means we can breathe.”

—Former Vice President Dan Quayle

“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.”

—Hitch
**Lung development**

Occurs in five periods. Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4. Lung bud divides into two bronchial buds that branch off into bronchi.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>IMPORTANT TERMS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic (weeks 4–7)</td>
<td>Lung bud → trachea → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.</td>
<td>Errors at this stage can lead to TE fistula.</td>
</tr>
<tr>
<td>Pseudoglandular (weeks 5–16)</td>
<td>Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.</td>
<td>Respiration impossible, incompatible with life.</td>
</tr>
<tr>
<td>Canalicular (weeks 16–26)</td>
<td>Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.</td>
<td>Airways increase in diameter. Respiration capable at 25 weeks.</td>
</tr>
<tr>
<td>Alveolar (weeks 32–8 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.</td>
<td>At birth, fluid gets replaced with air → ↓ in pulmonary vascular resistance.</td>
</tr>
</tbody>
</table>

**Congenital lung malformations**

**Pulmonary hypoplasia**
Poorly developed bronchial tree with abnormal histology usually involving right lung. Associated with congenital diaphragmatic hernia, bilateral renal agenesis (Potter sequence [syndrome]).

**Bronchogenic cysts**
Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined and air-filled densities on CXR. Drain poorly and cause chronic infections.
Pneumocytes

Type I cells  
97% of alveolar surfaces. Line the alveoli. Squamous; thin for optimal gas diffusion.

Type II cells  
Secrete pulmonary surfactant \(\rightarrow\) ↓ alveolar surface tension, prevents alveolar collapse, ↓ lung recoil, and ↑ compliance. Cuboidal and clustered A. Also serve as precursors to type I cells and other type II cells. Type II cells proliferate during lung damage.

Club cells  
Nonciliated; low-columnar/cuboidal with secretory granules. Secrete component of surfactant; degrade toxins; act as reserve cells.

Collapsing pressure \(P = \frac{2\text{ (surface tension)}}{\text{radius}}\)

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.

Surfactant synthesis begins around week 26 of gestation, but mature levels are not achieved until around week 35.

Neonatal respiratory distress syndrome

Surfactant deficiency \(\rightarrow\) ↑ surface tension \(\rightarrow\) alveolar collapse (“ground-glass” appearance of lung fields) A. 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 test, surfactant-albumin ratio. Persistently low O₂ tension \(\rightarrow\) risk of PDA.

Risk factors: prematurity, maternal diabetes (due to ↑ fetal insulin), C-section delivery (↓ release of fetal glucocorticoids).

Complications: metabolic acidosis, PDA, necrotizing enterocolitis.

Treatment: maternal steroids before birth; artificial surfactant for infant.

Therapeutic supplemental O₂ can result in Retinopathy of prematurity, Intraventricular hemorrhage, Bronchopulmonary dysplasia (RIB).
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 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.

<table>
<thead>
<tr>
<th>GROSS</th>
<th>HISTOLOGIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conducting zone</strong></td>
<td><strong>Conducting zone</strong></td>
</tr>
<tr>
<td>Trachea</td>
<td>Basal cell</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Goblet cell</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>Ciliated cell</td>
</tr>
<tr>
<td>Terminal bronchioles</td>
<td>Pseudostratified ciliated columnar epithelium</td>
</tr>
<tr>
<td>Respiratory zone</td>
<td>Smooth muscle</td>
</tr>
<tr>
<td>Respiratory bronchioles</td>
<td>Cartilage</td>
</tr>
<tr>
<td>Alveolar sacs</td>
<td>Simple ciliated columnar epithelium</td>
</tr>
<tr>
<td></td>
<td>Smooth muscle</td>
</tr>
<tr>
<td></td>
<td><strong>Respiratory zone</strong></td>
</tr>
<tr>
<td></td>
<td>Club cell</td>
</tr>
<tr>
<td></td>
<td>Ciliated cell</td>
</tr>
<tr>
<td></td>
<td>Cuboidal ciliated cells</td>
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<tr>
<td></td>
<td>Club cell</td>
</tr>
<tr>
<td></td>
<td>Squamous cell</td>
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<tr>
<td></td>
<td>Respiratory epithelium</td>
</tr>
<tr>
<td></td>
<td>Smooth muscle</td>
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<tr>
<td></td>
<td>Type I pneumocyte</td>
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<tr>
<td></td>
<td>Type II pneumocyte</td>
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<tr>
<td></td>
<td>Alveolar macrophage</td>
</tr>
<tr>
<td></td>
<td>Capillary</td>
</tr>
</tbody>
</table>
**Lung relations**

Right lung has 3 lobes; **Left has Less Lobes (2)** and Lingula (homolog of right middle lobe). Right lung is more common site for inhaled foreign body because the right main stem bronchus is wider and more vertical than the left.

If you aspirate a peanut:
- While upright—enters inferior segment of right inferior lobe.
- While supine—enters superior segment of right inferior lobe.

Instead of a middle lobe, the left lung has a space occupied by the heart. The relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS—Right Anterior; Left Superior**.

---

**Diaphragm structures**

Structures perforating diaphragm:
- At T8: IVC
- At T10: esophagus, vagus (CN 10; 2 trunks)
- At T12: aorta (red), thoracic duct (white), azygos vein (blue) (“At T-1-2 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>Volume Type</th>
<th>Description</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; cannot be measured on spirometry</td>
</tr>
<tr>
<td>Inspiratory capacity</td>
<td>IRV + TV</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>RV + ERV</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>TV + IRV + ERV</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>IRV + TV + ERV + RV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung capacity</td>
<td>Volume of gas present in lungs after a maximal inspiration; includes RV, cannot be measured by spirometry</td>
</tr>
</tbody>
</table>

### Determination of Physiologic Dead Space

\[
V_D = V_T \times \frac{P_{aCO_2} - P_{Eco_2}}{P_{aCO_2}}
\]

- \(V_D\) = 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 PCO₂.
- \(P_{Eco_2}\) = expired air PCO₂.

### Ventilation

<table>
<thead>
<tr>
<th>Volume Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation ((V_E))</td>
<td>Total volume of gas entering lungs per minute (V_E = V_T \times RR)</td>
</tr>
<tr>
<td>Alveolar ventilation ((V_A))</td>
<td>Volume of gas per unit time that reaches alveoli (V_A = (V_T - V_D) \times RR)</td>
</tr>
</tbody>
</table>

- Normal values:
  - Respiratory rate (RR) = 12–20 breaths/min
  - \(V_T\) = 500 mL/breath
  - \(V_D\) = 150 mL/breath

**Taco, Paco, Peco, Paco** (refers to order of variables in equation)

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with V/Q defects.

Pathologic dead space—when part of the respiratory zone becomes unable to perform gas exchange. Ventilated but not perfused.
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. Elastic properties of both chest wall and lungs determine their combined volume. At FRC, airway and alveolar pressures are 0, and intrapleural pressure is negative (prevents pneumothorax). PVR is at minimum.

Compliance—change in lung volume for a change in pressure; expressed as $\Delta V/\Delta P$ and is inversely proportional to wall stiffness. High compliance = lung easier to fill, lower compliance = lung harder to fill. * in pulmonary fibrosis, pneumonia, pulmonary edema; † in emphysema, normal aging. 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.

Hemoglobin

Hemoglobin (Hb) is composed of 4 polypeptide subunits (2 $\alpha$ and 2 $\beta$) and exists in 2 forms: * T (taut; deoxygenated) form has low affinity for $O_2$, thus promoting release/unloading of $O_2$. † R (relaxed; oxygenated) form has high affinity for $O_2$ (300×). Hb exhibits positive cooperativity and negative allostery.

† CF, H+, CO₂, 2,3-BPG, and temperature favor taut form over relaxed form (shifts dissociation curve right → † $O_2$ unloading). Fetal Hb (2α and 2γ subunits) has a higher affinity for $O_2$ than adult Hb, driving diffusion of oxygen across the placenta from mother to fetus. † $O_2$ affinity results from † affinity of HbF for 2,3-BPG.

Taut in Tissues. Relaxed in Respiratory area. Hemoglobin acts as buffer for H+ ions.
Hemoglobin modifications

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methemoglobin</td>
<td>Oxidized form of Hb (ferric, Fe³⁺) that does not bind O₂ as readily, but has ↑ affinity for cyanide. Iron in Hb is normally in a reduced state (ferrous, Fe²⁺). Methemoglobinemia may present with cyanosis and chocolate-colored blood. Induced methemoglobinemia (using nitrates, followed by thiosulfate) may be used to treat cyanide poisoning. Methemoglobinemia can be treated with methylene blue and vitamin C. Nitrites (eg, from dietary intake or polluted/high altitude H₂O) and benzocaine cause poisoning by oxidizing Fe²⁺ to Fe³⁺. Fe³⁺ binds O₂.</td>
</tr>
<tr>
<td>Carboxyhemoglobin</td>
<td>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. Treat with 100% O₂ and hyperbaric O₂.</td>
</tr>
</tbody>
</table>

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. When curve shifts to the right, ↓ affinity of Hb for O₂ (facilitates unloading of O₂ to tissue). An ↑ in all factors (including H⁺) causes a shift of the curve to the right. A ↓ in all factors (including H⁺) causes a left shift → ↓ O₂ unloading → renal hypoxia → ↑ EPO synthesis → compensatory erythrocytosis. Lower = L. Fetal Hb has higher affinity for O₂ than adult Hb, so its dissociation curve is shifted left.
**Oxygen content of blood**

\[ O_2 \text{ content} = (1.34 \times \text{Hb} \times \text{Sao}_2) + (0.003 \times \text{Pao}_2) \]

- Hb = hemoglobin level
- Sao2 = arterial O2 saturation
- Pao2 = partial pressure of O2

Normally 1 g Hb can bind 1.34 mL O2; normal Hb amount in blood is 15 g/dL.

O2 binding capacity \( \approx 20.1 \text{ mL O}_2/\text{dL blood}\).

With ↓ Hb there is ↓ O2 content of arterial blood, but no change in O2 saturation and Pao2.

O2 delivery to tissues = cardiac output \( \times \) 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\text{O}_2 and P\text{CO}_2 exert opposite effects on pulmonary and systemic circulation. A ↓ in P\text{O}_2 causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—O2 (normal health), CO\text{2}, N\text{2}O. Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.

Diffusion limited—O2 (emphysema, fibrosis), 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 (jugular venous distention, edema, hepatomegaly).

Diffusion: \( V_{\text{gas}} = A \times D_k \times \frac{P_1 - P_2}{T} \) where

- \( A \) = area,
- \( T = \) alveolar wall thickness,
- \( D_k(P_1 - P_2) = \) difference in partial pressures:
  - \( A \) ↓ in emphysema.
  - \( T \) ↑ in pulmonary fibrosis.

\( DLCO \) is the extent to which oxygen passes from air sacs of lungs into blood.

\( P_a \) = partial pressure of gas in pulmonary capillary blood
\( P_{alveolus} \) = partial pressure of gas in alveolar air
Pulmonary vascular resistance

\[ P_{\text{V,R}} = \frac{P_{\text{pulm artery}} - P_{\text{L,atrium}}}{\text{cardiac output}} \]

\[ R = \text{resistance} \]
\[ P_{\text{pulm artery}} = \text{pressure in pulmonary artery} \]
\[ P_{\text{L,atrium}} = \text{pulmonary capillary wedge pressure} \]

Remember: \( \Delta P = Q \times R \), so \( R = \Delta P / Q \)

\[ R = \frac{8\eta l}{\pi r^4} \]

\( \eta = \text{viscosity of blood;} \ l = \text{vessel length;} \ r = \text{vessel radius} \)

Alveolar gas equation

\[ P_{\text{A,PO}_2} = P_{\text{I,PO}_2} - \frac{P_{\text{A,CO}_2}}{R} \]

\[ \approx 150 \text{ mm Hg} - \frac{P_{\text{A,CO}_2}}{0.8} \]

(at sea level breathing room air)

\( P_{\text{A,PO}_2} = \text{alveolar PO}_2 \text{ (mm Hg)} \)
\( P_{\text{I,PO}_2} = \text{PO}_2 \text{ in inspired air (mm Hg)} \)
\( P_{\text{A,CO}_2} = \text{arterial PCO}_2 \text{ (mm Hg)} \)
\( R = \text{respiratory quotient} = \text{CO}_2 \text{ produced/O}_2 \text{ consumed} \)

A-a gradient = \( P_{\text{A,PO}_2} - P_{\text{A,PO}_2} = 10-15 \text{ mm Hg} \)

↑ A-a gradient may occur in hypoxemia; causes include shunting, \( V/Q \) mismatch, fibrosis (impairs diffusion)

Oxygen deprivation

<table>
<thead>
<tr>
<th>Hypoxia (↓ O(_2) delivery to tissue)</th>
<th>Hypoxemia (↓ P(_{\text{A,PO}_2}))</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>

\( V/Q \) 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 \( O_2 \) (eg, TB) flourish in the apex.

\( V/Q = 0 \) = “airway” obstruction (shunt). In shunt, 100% \( O_2 \) does not improve \( P_{\text{A,PO}_2} \) (eg, foreign body aspiration).

\( V/Q = \infty \) = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% \( O_2 \) improves \( P_{\text{A,PO}_2} \) (eg, pulmonary embolus).
**CO₂ transport**

CO₂ is transported from tissues to lungs in 3 forms:
- HCO₃⁻ (90%).
- Carbaminohemoglobin or HbCO₂ (5%). CO₂ bound to Hb at N-terminus of globin (not heme). CO₂ binding favors taut form (O₂ unloaded).
- Dissolved CO₂ (5%).

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 → ↑ hematocrit and Hb (chronic hypoxia).
↑ 2,3-BPG (binds to Hb 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 Paco₂ 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 maxillary sinuses, which drain into the middle meatus, in adults). Most common acute cause is viral URI; may cause superimposed bacterial infection, most commonly *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*.

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).

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.

Deep venous thrombosis

Blood clot within a deep vein → swelling, redness, warmth, pain. Predisposed by Virchow triad (SHE):
- Stasis (e.g., post-op, long drive/flight)
- Hypercoagulability (e.g., defect in coagulation cascade proteins, such as factor V Leiden)
- 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.

Homan sign—dorsiflexion of foot → calf pain.

Use unfractionated heparin or low-molecular-weight heparins (e.g., enoxaparin) for prophylaxis and acute management.

Use oral anticoagulants (e.g., warfarin, rivaroxaban) for treatment (long-term prevention).

Imaging test of choice is compression ultrasound.
Pulmonary emboli

V/Q mismatch → hypoxemia → respiratory alkalosis. Sudden-onset dyspnea, chest pain, tachypnea, tachycardia. Large emboli or saddle embolus may cause sudden death. 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.

Amniotic fluid emboli—can lead to DIC, especially postpartum.

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).

CT pulmonary angiography is imaging test of choice for PE (look for filling defects).

An embolus moves like a FAT BAT.
### Obstructive lung diseases

Obstruction of air flow resulting in air trapping in lungs. Airways close prematurely at high lung volumes → ↑ RV and ↑ FRC, ↑ TLC. PFTs: ↓ FEV, ↓ FVC → ↓ FEV/FVC ratio (hallmark), V/Q mismatch. Chronic, hypoxic pulmonary vasoconstriction can lead to cor pulmonale.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PATHOLOGY</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic bronchitis</strong></td>
<td>Hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) &gt; 50%.</td>
<td>Productive cough for &gt; 3 (not necessarily consecutive) months per year for &gt; 2 consecutive years. Findings: wheezing, crackles, cyanosis (early-onset hypoxemia due to shunting), late-onset dyspnea, CO₂ retention (hypercapnia), 2° polycythemia. Chronic complications: pulmonary hypertension, cor pulmonale.</td>
</tr>
</tbody>
</table>
| **Emphysema** ("pink puffer") | Enlargement of air spaces, ↓ recoil, ↓ compliance, ↓ diffusing capacity for CO resulting from destruction of alveolar walls (arrow in [A]). Two types:  
  - Centriacinar—associated with smoking [B] [C]. Frequently in upper lobes.  
| **Asthma**             | Bronchial hyperresponsiveness causes reversible bronchoconstriction. Smooth muscle hypertrophy, Curschmann spirals [E] (shed epithelium forms whorled mucus plugs), and Charcot-Leyden crystals (eosinophilic, hexagonal, double-pointed, needle-like crystals formed from breakdown of eosinophils in sputum). | Can be triggered by viral URIs, allergens, stress. Clinical diagnosis can be supported by spirometry and methacholine challenge. Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↑ inspiratory/expiratory ratio, pulsus paradoxus, mucus plugging [F]. Peribronchial cuffing on CXR. |
| **Bronchiectasis**     | Chronic necrotizing infection of bronchi → permanently dilated airways, purulent sputum, recurrent infections, hemoptysis, digital clubbing. | Associated with bronchial obstruction, poor ciliary motility (eg, smoking, Kartagener syndrome), cystic fibrosis [G], allergic bronchopulmonary aspergillosis. |
Restrictive lung diseases

Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs: FEV₁/FVC ratio ≥ 80%.

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):
  - Acute respiratory distress syndrome (ARDS)
  - Neonatal respiratory distress syndrome (NRDS; hyaline membrane disease)
  - Pneumoconioses (eg, anthracosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca²⁺
  - Idiopathic pulmonary fibrosis A (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 (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate)

Flow volume loops

Obstructive lung volumes > normal (↑ TLC, ↑ FRC, ↑ RV); restrictive lung volumes < normal. In both obstructive and restrictive, FEV₁ and FVC are reduced. In obstructive, however, FEV₁ is more dramatically reduced compared to FVC, resulting in a ↓ FEV₁/FVC ratio.

Hypersensitivity pneumonitis

Mixed type III/IV hypersensitivity reaction to environmental antigen → dyspnea, cough, chest tightness, headache. Often seen in farmers and those exposed to birds.
### Pneumoconioses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coal workers’ pneumoconiosis, silicosis, and asbestos</td>
<td>→ ↑ risk of cor pulmonale, cancer, and Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).</td>
</tr>
<tr>
<td>Asbestosis</td>
<td>Associated with shipbuilding, roofing, plumbing. “Ivory white,” calcified, supradiaphragmatic and pleural plaques [\text{A},\text{B}] are pathognomonic of asbestosis. Risk of bronchogenic carcinoma &gt; risk of mesothelioma.</td>
</tr>
<tr>
<td></td>
<td>Affects lower lobes. Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells [\text{C}], found in alveolar septum sputum sample, visualized using Prussian blue stain, often obtained by bronchoalveolar lavage. ↑ risk of pleural effusions.</td>
</tr>
<tr>
<td>Berylliosis</td>
<td>Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous on histology and therefore occasionally responsive to steroids.</td>
</tr>
<tr>
<td></td>
<td>Affects upper lobes.</td>
</tr>
<tr>
<td>Coal workers’ pneumoconiosis</td>
<td>Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis. Also known as black lung disease.</td>
</tr>
<tr>
<td></td>
<td>Affects upper lobes. Anthracosis—asymptomatic condition found in many urban dwellers exposed to sooty air.</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Associated with foundries, sandblasting, 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>
</tr>
<tr>
<td></td>
<td>Affects upper lobes. “Eggshell” calcification of hilar lymph nodes. 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).</td>
</tr>
</tbody>
</table>
# Acute respiratory distress syndrome
Clinical syndrome characterized by acute onset respiratory failure, bilateral lung opacities, ↓ PaO₂/FiO₂, no evidence of HF/fluid overload.

**SPARTAS:** Sepsis, Pancreatitis, Pneumonia, Aspiration, Remia, Trauma, Amniotic fluid embolism, Shock. Endothelial damage → ↑ alveolar capillary permeability → protein-rich leakage into alveoli → diffuse alveolar damage and noncardiogenic pulmonary edema (normal PCWP) → Results in formation of intra-alveolar hyaline membranes.[A]

Initial damage due to release of neutrophilic substances toxic to alveolar wall, activation of coagulation cascade, and oxygen-derived free radicals.

Management: mechanical ventilation with low tidal volumes, address underlying cause.

---

# Sleep apnea
Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. 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
No respiratory effort due to CNS injury/toxicity, HF, opioids.

### Obesity hypoventilation syndrome
Obesity (BMI ≥ 30 kg/m²) → hypoventilation (↓ respiratory rate) → ↓ PaO₂ and ↑ PaCO₂ during sleep; ↑ PaCO₂ during waking hours (retention).
**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. Course: severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.

<table>
<thead>
<tr>
<th>Etiologies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary arterial hypertension</strong></td>
<td>Idiopathic PAH. Heritable PAH—often due to an inactivating mutation in BMPR2 gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.</td>
</tr>
<tr>
<td><strong>Left heart disease</strong></td>
<td>Causes include systolic/diastolic dysfunction and valvular disease (eg, mitral lung).</td>
</tr>
<tr>
<td><strong>Lung diseases or hypoxia</strong></td>
<td>Destruction of lung parenchyma (eg, COPD), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).</td>
</tr>
<tr>
<td><strong>Chronic thromboembolic</strong></td>
<td>Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.</td>
</tr>
<tr>
<td><strong>Multifactorial</strong></td>
<td>Causes include hematologic, systemic, and metabolic disorders.</td>
</tr>
</tbody>
</table>

### 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>— or 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>—</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>Bronchial breath sounds; late inspiratory crackles</td>
<td>Dull</td>
<td>↑</td>
<td>—</td>
</tr>
</tbody>
</table>
### Pleural effusions
Excess accumulation of fluid between pleural layers. Can be treated with thoracentesis to remove fluid.  

<table>
<thead>
<tr>
<th>Transudate</th>
<th>Protein content. Due to hydrostatic pressure (eg, HF) or oncotic pressure (eg, nephrotic syndrome, cirrhosis).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exudate</td>
<td>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.</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; triglycerides.</td>
</tr>
</tbody>
</table>

### Pneumothorax
Accumulation of air in pleural space. Unilateral chest pain and dyspnea, unilateral chest expansion, tactile fremitus, hyperresonance, diminished breath sounds, all on the affected side.  

<table>
<thead>
<tr>
<th>Primary spontaneous pneumothorax</th>
<th>Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males.</th>
</tr>
</thead>
<tbody>
<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) or penetrating (eg, gunshot) trauma.</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>Can be any of the above. Air enters pleural space but cannot exit. Increasing trapped air barotrauma. Trachea deviates away from affected lung. Needs immediate needle decompression and chest tube placement.</td>
</tr>
</tbody>
</table>
## Pneumonia

<table>
<thead>
<tr>
<th>TYPE</th>
<th>TYPICAL ORGANISMS</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar</td>
<td><em>S. pneumoniae</em> most frequently, also <em>Legionella</em>, <em>Klebsiella</em></td>
<td>Intra-alveolar exudate → consolidation A; may involve entire lobe B or lung.</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td><em>S. pneumoniae</em>, <em>S. aureus</em>, <em>H. influenzae</em>, <em>Klebsiella</em></td>
<td>Acute inflammatory infiltrates C from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe D.</td>
</tr>
<tr>
<td>Interstitial (atypical) pneumonia</td>
<td><em>Mycoplasma</em>, <em>Chlamydia</em>, <em>Legionella</em>, viruses (RSV, CMV, influenza, adenovirus)</td>
<td>Diffuse patchy inflammation localized to interstitial areas at alveolar walls; diffuse distribution involving ≥ 1 lobe E. Generally follows a more indolent course (“walking” pneumonia).</td>
</tr>
</tbody>
</table>

### Lung abscess

Localized collection of pus within parenchyma A. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcoholics, epileptics]) or bronchial obstruction (eg, cancer). Treatment: clindamycin.

Air-fluid levels B 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:

- Upright → basal segments of right lower lobe
- Supine → posterior segments of right upper lobe or superior segment of right lower lobe

### Mesothelioma

Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening.

Psammoma bodies seen on histology. Cytokeratin and calretinin ⊕ in almost all mesotheliomas, ⊖ in most carcinomas. Smoking not a risk factor.
**Pancoast tumor**  
*(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
- Superior cervical ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Sensorimotor deficit

**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, Pancoast tumor) and thrombosis from indwelling catheters. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, 1 risk of aneurysm/rupture of intracranial arteries.
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 syndrome
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 Sentinel (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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cell (oat cell)</td>
<td>Central</td>
<td>Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), SIADH, or Antibodies against presynaptic Ca²⁺ channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, 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 ⊗.</td>
</tr>
<tr>
<td>Non–small cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Peripheral</td>
<td>Most common lung cancer in nonsmokers and overall (except for metastases). Activating mutations include KRAS, EGFR, and ALK. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis. Bronchial carcinoid and bronchioloalveolar cell carcinoma have lesser association with smoking.</td>
<td>Glandular pattern on histology, often stains mucin ⊕. Bronchioalveolar subtype: grows along alveolar septa → apparent “thickening” of alveolar walls. Tall, columnar cells containing mucus.</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>Central</td>
<td>Hilar mass arising from bronchus; Cavitation; Cigarettes; hyperCalcemia (produces PTHrP).</td>
<td>Keratin pearls D and intercellular bridges.</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large cell</td>
<td>Peripheral</td>
<td>Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically.</td>
<td>Pleomorphic giant cells. Can secrete β-hCG.</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial carcinoid</td>
<td>—</td>
<td>Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).</td>
<td>Nests of neuroendocrine cells; chromogranin A ⊕.</td>
</tr>
<tr>
<td>tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Antihistamines

- **Reversible inhibitors of H₁ histamine receptors.**
- **First generation**
  - Diphenhydramine, dimenhydrinate, chlorpheniramine.
  - CLINICAL USES: Allergy, motion sickness, sleep aid.
  - ADVERSE EFFECTS: Sedation, antimuscarinic, anti-α-adrenergic.
- **Second generation**
  - Loratadine, fexofenadine, desloratadine, cetirizine.
  - CLINICAL USES: Allergy.
  - ADVERSE EFFECTS: Far less sedating than 1st generation because of reduced entry into CNS.
  - Names usually end in “-adine.”
  - Names contain “-en/-ine” or “-en/-ate.”

### Expectorants

- **Guaifenesin**
  - Expectorant—thins respiratory secretions; does not suppress cough reflex.
- **N-acetylcysteine**
  - Mucolytic—liquefies mucus in COPD patients 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

- α-adrenergic agonists, used as nasal decongestants.
- CLINICAL USE
  - Reduce hyperemia, edema, nasal congestion; open obstructed eustachian tubes. Pseudoephedrine also illicitly used to make methamphetamine.
- ADVERSE EFFECTS: Hypertension. 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>BosEΝTan</td>
<td>Competitively antagonizes ENdothelin-1 receptors → ↓ pulmonary vascular resistance</td>
<td>Hepatotoxic (monitor LFTs).</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Inhibits cGMP PDE-5 and prolongs vasodilatory effect of nitric oxide</td>
<td>Also used to treat erectile dysfunction.</td>
</tr>
<tr>
<td>Epoprostenol, iloprost</td>
<td>PGI₂ (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.</td>
<td>Side effects: flushing, jaw pain.</td>
</tr>
</tbody>
</table>
Asthma drugs

Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.

β₂-agonists


Salmeterol, 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.

Muscarinic antagonists

Ipratropium—competitively blocks muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.

Antileukotrienes

Montelukast, zafirlukast—block leukotriene receptors (CysLT1). Especially good for aspirin-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.

Methacholine

Muscarinic receptor (M₁) 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 serve as a quick review before the exam to tune your senses to commonly tested cases.
<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>DIAGNOSIS/DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain, ascites, hepatomegaly</td>
<td>Budd-Chiari syndrome (posthepatic venous thrombosis)</td>
</tr>
<tr>
<td>Abdominal pain, diarrhea, leukocytosis, recent antibiotic use</td>
<td><em>Clostridium difficile</em> infection</td>
</tr>
<tr>
<td>Achilles tendon xanthoma</td>
<td>Familial hypercholesterolemia (1 LDL receptor signaling)</td>
</tr>
<tr>
<td>Adrenal hemorrhage, hypotension, DIC</td>
<td>Waterhouse-Friderichsen syndrome (meningococcemia)</td>
</tr>
<tr>
<td>Anaphylaxis following blood transfusion</td>
<td>IgA deficiency</td>
</tr>
<tr>
<td>Anterior “drawer sign” ⊕</td>
<td>Anterior cruciate ligament injury</td>
</tr>
<tr>
<td>Arachnodactyly, lens dislocation (upward), aortic dissection, hyperflexible joints</td>
<td>Marfan syndrome (fibrillin defect)</td>
</tr>
<tr>
<td>Athlete with polycythemia</td>
<td>2° to erythropoietin injection</td>
</tr>
<tr>
<td>Back pain, fever, night sweats</td>
<td>Pott disease (vertebral TB)</td>
</tr>
<tr>
<td>Bilateral acoustic schwannomas</td>
<td>Neurofibromatosis type 2</td>
</tr>
<tr>
<td>Bilateral hilar adenopathy, uveitis</td>
<td>Sarcoidosis (noncaseating granulomas)</td>
</tr>
<tr>
<td>Black eschar on face of patient with diabetic ketoacidosis</td>
<td><em>Mucor</em> or <em>Rhizopus</em> fungal infection</td>
</tr>
<tr>
<td>Blue sclera</td>
<td>Osteogenesis imperfecta (type I collagen defect)</td>
</tr>
<tr>
<td>Bluish line on gingiva</td>
<td>Burton line (lead poisoning)</td>
</tr>
<tr>
<td>Bone pain, bone enlargement, arthritis</td>
<td>Paget disease of bone († osteoblastic and osteoclastic activity)</td>
</tr>
<tr>
<td>Bounding pulses, wide pulse pressure, diastolic heart murmur, head bobbing</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>“Butterfly” facial rash and Raynaud phenomenon in a young female</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Café-au-lait spots, Lisch nodules (iris hamartoma), cutaneous neurofibromas, pheochromocytomas, optic gliomas</td>
<td>Neurofibromatosis type I</td>
</tr>
<tr>
<td>Café-au-lait spots (unilateral), polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities</td>
<td>McCune-Albright syndrome (mosaic G-protein signaling mutation)</td>
</tr>
<tr>
<td>Calf pseudohypertrophy</td>
<td>Muscular dystrophy (most commonly Duchenne, due to X-linked recessive frameshift mutation of dystrophin gene)</td>
</tr>
<tr>
<td>Cervical lymphadenopathy, desquamating rash, coronary aneurysms, red conjunctivae and tongue, hand-foot changes</td>
<td>Kawasaki disease (treat with IVIG and aspirin)</td>
</tr>
<tr>
<td>“Cherry-red spots” on macula</td>
<td>Tay-Sachs (ganglioside accumulation) or Niemann-Pick ( sphingomyelin accumulation), central retinal artery occlusion</td>
</tr>
<tr>
<td>Chest pain on exertion</td>
<td>Angina (stable: with moderate exertion; unstable: with minimal exertion or at rest)</td>
</tr>
<tr>
<td>Chest pain, pericardial effusion/friction rub, persistent fever following MI</td>
<td>Dressler syndrome (autoimmune-mediated post-MI fibrinous pericarditis, 2 weeks to several months after acute episode)</td>
</tr>
<tr>
<td>Chest pain with ST depressions on EKG</td>
<td>Unstable angina (⊕ troponins) or NSTEMI (⊕ troponins)</td>
</tr>
<tr>
<td>Child uses arms to stand up from squat</td>
<td>Duchenne muscular dystrophy (Gowers sign)</td>
</tr>
<tr>
<td>Child with fever later develops red rash on face that spreads to body</td>
<td>Erythema infectiosum/fifth disease (“slapped cheeks” appearance, caused by parvovirus B19)</td>
</tr>
<tr>
<td>Chorea, dementia, caudate degeneration</td>
<td>Huntington disease (autosomal dominant CAG repeat expansion)</td>
</tr>
<tr>
<td>Chorioretinitis, hydrocephalus, intracranial calcifications</td>
<td>Congenital toxoplasmosis</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Diagnosis/Disease</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Chronic exercise intolerance with myalgia, fatigue, painful cramps, myoglobinuria</td>
<td>McArdle disease (skeletal muscle glycogen phosphorylase deficiency)</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Conjugate horizontal gaze palsy, horizontal diplopia</td>
<td>Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral)</td>
</tr>
<tr>
<td>Continuous “machine-like” heart murmur</td>
<td>PDA (close with indomethacin; keep open with PGE analogs)</td>
</tr>
<tr>
<td>Cutaneous/dermal edema due to connective tissue deposition</td>
<td>Myxedema (caused by hypothyroidism, Graves disease [pretibial])</td>
</tr>
<tr>
<td>Cutaneous flushing, diarrhea, bronchospasm</td>
<td>Carcinoid syndrome (right-sided cardiac valvular lesions, ↑ 5-HIAA)</td>
</tr>
<tr>
<td>Dark purple skin/mouth nodules in a patient with AIDS</td>
<td>Kaposi sarcoma, associated with HHV-8</td>
</tr>
<tr>
<td>Deep, labored breathing/hyperventilation</td>
<td>Diabetic ketoacidosis (Kussmaul respirations)</td>
</tr>
<tr>
<td>Dermatitis, dementia, diarrhea</td>
<td>Pellagra (niacin [vitamin B6] deficiency)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy, edema, alcoholism or malnutrition</td>
<td>Wet beriberi (thiamine [vitamin B1] deficiency)</td>
</tr>
<tr>
<td>Dog or cat bite resulting in infection</td>
<td>Pasteurella multocida (cellulitis at inoculation site)</td>
</tr>
<tr>
<td>Dry eyes, dry mouth, arthritis</td>
<td>Sjögren syndrome (autoimmune destruction of exocrine glands)</td>
</tr>
<tr>
<td>Dysphagia (esophageal webs), glossitis, iron deficiency anemia</td>
<td>Plummer-Vinson syndrome (may progress to esophageal squamous cell carcinoma)</td>
</tr>
<tr>
<td>Elastic skin, hypermobility of joints, ↑ bleeding tendency</td>
<td>Ehlers-Danlos syndrome (type V collagen defect, type III collagen defect seen in vascular subtype of ED)</td>
</tr>
<tr>
<td>Enlarged, hard left supraclavicular node</td>
<td>Virchow node (abdominal metastasis)</td>
</tr>
<tr>
<td>Episodic vertigo, tinnitus, hearing loss</td>
<td>Meniere disease</td>
</tr>
<tr>
<td>Erythroderma, lymphadenopathy, hepatosplenomegaly, atypical T cells</td>
<td>Mycosis fungoides (cutaneous T-cell lymphoma) or Sézary syndrome (mycosis fungoides + malignant T cells in blood)</td>
</tr>
<tr>
<td>Facial muscle spasm upon tapping</td>
<td>Chvostek sign (hypocalcaemia)</td>
</tr>
<tr>
<td>Fat, female, forty, and fertile</td>
<td>Cholelithiasis (gallstones)</td>
</tr>
<tr>
<td>Fever, chills, headache, myalgia following antibiotic treatment for syphilis</td>
<td>Jarisch-Herxheimer reaction (rapid lysis of spirochetes results in endotoxin release)</td>
</tr>
<tr>
<td>Fever, cough, conjunctivitis, coryza, diffuse rash</td>
<td>Measles</td>
</tr>
<tr>
<td>Fever, night sweats, weight loss</td>
<td>B symptoms (staging) of lymphoma</td>
</tr>
<tr>
<td>Fibrous plaques in soft tissue of penis with abnormal curvature</td>
<td>Peyronie disease (connective tissue disorder)</td>
</tr>
<tr>
<td>Golden brown rings around peripheral cornea</td>
<td>Wilson disease (Kayser-Fleischer rings due to copper accumulation)</td>
</tr>
<tr>
<td>Gout, intellectual disability, self-mutilating behavior in a boy</td>
<td>Lesch-Nyhan syndrome (HGPRT deficiency, X-linked recessive)</td>
</tr>
<tr>
<td>Hamartomatous GI polyps, hyperpigmentation of mouth/feet/hands/genitalia</td>
<td>Peutz-Jeghers syndrome (inherited, benign polyposis can cause bowel obstruction; ↑ cancer risk, mainly GI)</td>
</tr>
<tr>
<td>Hepatosplenomegaly, pancytopenia, osteoporosis, aseptic necrosis of femoral head, bone crises</td>
<td>Gaucher disease (glucocerebrosidase deficiency)</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Diagnosis/Disease</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hereditary nephritis, sensorineural hearing loss, cataracts</td>
<td>Alport syndrome (mutation in collagen IV)</td>
</tr>
<tr>
<td>Hyperphagia, hypersexuality, hyperorality, hyperdocility</td>
<td>Klüver-Bucy syndrome (bilateral amygdala lesion)</td>
</tr>
<tr>
<td>Hypertension, Babinski sign present</td>
<td>UMN damage</td>
</tr>
<tr>
<td>Hyporeflexia, hypotonia, atrophy, fasciculations</td>
<td>LMN damage</td>
</tr>
<tr>
<td>Hypoxemia, polycythemia, hypercapnia</td>
<td>Chronic bronchitis (hyperplasia of mucous cells, “blue bloater”)</td>
</tr>
<tr>
<td>Indurated, ulcerated genital lesion</td>
<td>Nonpainful: chancre (1° syphilis, <em>Treponema pallidum</em>)</td>
</tr>
<tr>
<td></td>
<td>Painful, with exudate: chancroid (<em>Haemophilus ducreyi</em>)</td>
</tr>
<tr>
<td>Infant with cleft lip/palate, microcephaly or holoprosencephaly, polydactyly, cutis aplasia</td>
<td>Patau syndrome (trisomy 13)</td>
</tr>
<tr>
<td>Infant with hypoglycemia, hepatomegaly</td>
<td>Cori disease (debranching enzyme deficiency) or Von Gierke disease (glucose-6-phosphatase deficiency, more severe)</td>
</tr>
<tr>
<td>Infant with microcephaly, rocker-bottom feet, clenched hands, and structural heart defect</td>
<td>Edwards syndrome (trisomy 18)</td>
</tr>
<tr>
<td>Jaundice, palpable distended non-tender gallbladder</td>
<td>Courvoisier sign (distal malignant obstruction of biliary tree)</td>
</tr>
<tr>
<td>Large rash with bull’s-eye appearance</td>
<td>Erythema chronicum migrans from <em>Ixodes</em> tick bite (Lyme disease: <em>Borrelia</em>)</td>
</tr>
<tr>
<td>Lucid interval after traumatic brain injury</td>
<td>Epidural hematoma (middle meningeal artery rupture)</td>
</tr>
<tr>
<td>Male child, recurrent infections, no mature B cells</td>
<td>Bruton disease (X-linked agammaglobulinemia)</td>
</tr>
<tr>
<td>Mucosal bleeding and prolonged bleeding time</td>
<td>Glanzmann thrombasthenia (defect in platelet aggregation due to lack of GpIIb/IIIa)</td>
</tr>
<tr>
<td>Muffled heart sounds, distended neck veins, hypotension</td>
<td>Beck triad of cardiac tamponade</td>
</tr>
<tr>
<td>Multiple colon polyps, osteomas/soft tissue tumors, impacted/supernumerary teeth</td>
<td>Gardner syndrome (subtype of FAP)</td>
</tr>
<tr>
<td>Myopathy (infantile hypertrophic cardiomyopathy), exercise intolerance</td>
<td>Pompe disease (lysosomal α-1,4-glucosidase deficiency)</td>
</tr>
<tr>
<td>Neonate with arm paralysis following difficult birth</td>
<td>Erb-Duchenne palsy (superior trunk [C5–C6] brachial plexus injury: “waiter’s tip”)</td>
</tr>
<tr>
<td>No lactation postpartum, absent menstruation, cold intolerance</td>
<td>Sheehan syndrome (pituitary infarction)</td>
</tr>
<tr>
<td>Nystagmus, intention tremor, scanning speech, bilateral internuclear ophthalmonplegia</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Painful blue fingers/toes, hemolytic anemia</td>
<td>Cold agglutinin disease (autoimmune hemolytic anemia caused by <em>Mycoplasma pneumoniae</em>, infectious mononucleosis, CLL)</td>
</tr>
<tr>
<td>Painful fingers/toes changing color from blue to white to red with cold or stress</td>
<td>Raynaud phenomenon (vasospasm in extremities)</td>
</tr>
<tr>
<td>Painful, raised red lesions on pads of fingers/toes</td>
<td>Osler nodes (infective endocarditis, immune complex deposition)</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Diagnosis/Disease</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Painless erythematous lesions on palms and soles</td>
<td>Janeway lesions (infective endocarditis, septic emboli/microabscesses)</td>
</tr>
<tr>
<td>Painless jaundice</td>
<td>Cancer of the pancreatic head obstructing bile duct</td>
</tr>
<tr>
<td>Palpable purpura on buttocks/legs, joint pain, abdominal pain (child), hematuria</td>
<td>Henoch-Schönlein purpura (IgA vasculitis affecting skin and kidneys)</td>
</tr>
<tr>
<td>Pancreatic, pituitary, parathyroid tumors</td>
<td>MEN 1 (autosomal dominant)</td>
</tr>
<tr>
<td>Periorbital and/or peripheral edema, proteinuria (&gt; 3.5g/day), hypoalbuminemia, hypercholesterolemia</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Pink complexion, dyspnea, hyperventilation</td>
<td>Emphysema (&quot;pink puffer,&quot; centriacinar [smoking] or panacinar [α1-antitrypsin deficiency])</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Pruritic, purple, polygonal planar papules and plaques (6 P's)</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>Ptosis, miosis, anhidrosis</td>
<td>Horner syndrome (sympathetic chain lesion)</td>
</tr>
<tr>
<td>Pupil accommodates but doesn’t react</td>
<td>Neurosyphilis (Argyll Robertson pupil)</td>
</tr>
<tr>
<td>Rapidly progressive limb weakness that ascends following GI/upper respiratory infection</td>
<td>Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculopathy subtype)</td>
</tr>
<tr>
<td>Rash on palms and soles</td>
<td>Coxsackie A, 2° syphilis, Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Recurrent cold (noninflamed) abscesses, unusual eczema, high serum IgE</td>
<td>Hyper-IgE syndrome (Job syndrome: neutrophil chemotaxis abnormality)</td>
</tr>
<tr>
<td>Red “currant jelly” sputum in alcoholic or diabetic patients</td>
<td>Klebsiella pneumoniae pneumonia</td>
</tr>
<tr>
<td>Red “currant jelly” stools</td>
<td>Acute mesenteric ischemia (adults), intussusception (children)</td>
</tr>
<tr>
<td>Red, itchy, swollen rash of nipple/areola</td>
<td>Paget disease of the breast (sign of underlying neoplasm)</td>
</tr>
<tr>
<td>Red urine in the morning, fragile RBCs</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Renal cell carcinoma (bilateral), hemangioblastomas, angiomatosis, pheochromocytoma</td>
<td>von Hippel-Lindau disease (dominant tumor suppressor gene mutation)</td>
</tr>
<tr>
<td>Resting tremor, rigidity, akinesia, postural instability, shuffling gait</td>
<td>Parkinson disease (loss of dopaminergic neurons in substantia nigra pars compacta)</td>
</tr>
<tr>
<td>Retinal hemorrhages with pale centers</td>
<td>Roth spots (bacterial endocarditis)</td>
</tr>
<tr>
<td>Severe jaundice in neonate</td>
<td>Crigler-Najjar syndrome (congenital unconjugated hyperbilirubinemia)</td>
</tr>
<tr>
<td>Severe RLQ pain with palpation of LLQ</td>
<td>Rovsing sign (acute appendicitis)</td>
</tr>
<tr>
<td>Severe RLQ pain with deep tenderness</td>
<td>McBurney sign (acute appendicitis)</td>
</tr>
<tr>
<td>Short stature, café au lait spots, thumb/radial defects, ↑ incidence of tumors/leukemia, aplastic anemia</td>
<td>Fanconi anemia (genetic loss of DNA crosslink repair; often progresses to AML)</td>
</tr>
<tr>
<td>Single palmar crease</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>Situs inversus, chronic sinusitis, bronchiectasis, infertility</td>
<td>Kartagener syndrome (dynein arm defect affecting cilia)</td>
</tr>
<tr>
<td>Skin hyperpigmentation, hypotension, fatigue</td>
<td>1° adrenocortical insufficiency (eg, Addison disease) causes ↑ ACTH and ↑ α-MSH production</td>
</tr>
<tr>
<td>Slow, progressive muscle weakness in boys</td>
<td>Becker muscular dystrophy (X-linked missense mutation in dystrophin; less severe than Duchenne)</td>
</tr>
</tbody>
</table>
### CLASSIC LABS/FINDINGS

<table>
<thead>
<tr>
<th>Lab/Diagnostic Finding</th>
<th>Diagnosis/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ AFP in amniotic fluid/maternal serum</td>
<td>Dating error, anencephaly, spina bifida (neural tube defects)</td>
</tr>
<tr>
<td>Anticentromere antibodies</td>
<td>Scleroderma (CREST)</td>
</tr>
<tr>
<td>Anti-desmoglein (anti-desmosome) antibodies</td>
<td>Pemphigus vulgaris (blistering)</td>
</tr>
<tr>
<td>Anti–glomerular basement membrane antibodies</td>
<td>Goodpasture syndrome (glomerulonephritis and hemoptysis)</td>
</tr>
<tr>
<td>Antihistone antibodies</td>
<td>Drug-induced SLE (eg, hydralazine, isoniazid, phenytoin, procainamide)</td>
</tr>
<tr>
<td>Anti-IgG antibodies</td>
<td>Rheumatoid arthritis (systemic inflammation, joint pannus, boutonnière deformity)</td>
</tr>
<tr>
<td>Antimitochondrial antibodies (AMAs)</td>
<td>1° biliary cirrhosis (female, cholestasis, portal hypertension)</td>
</tr>
<tr>
<td>LAB/DIAGNOSTIC FINDING</td>
<td>DIAGNOSIS/DISEASE</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Antineutrophil cytoplasmic antibodies (ANCAs)</td>
<td>Microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (MPO-ANCA/ p-ANCA); granulomatosis with polyangiitis (Wegener; PR3-ANCA/c-ANCA)</td>
</tr>
<tr>
<td>Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA)</td>
<td>SLE (type III hypersensitivity)</td>
</tr>
<tr>
<td>Antiplatelet antibodies</td>
<td>Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Anti-topoisomerase antibodies</td>
<td>Diffuse systemic sclerosis</td>
</tr>
<tr>
<td>Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies</td>
<td>Celiac disease (diarrhea, weight loss)</td>
</tr>
<tr>
<td>“Apple core” lesion on barium enema x-ray</td>
<td>Colorectal cancer (usually left-sided)</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>EBV</td>
</tr>
<tr>
<td>Azurophilic peroxidase ⊕ granular inclusions in granulocytes and myeloblasts</td>
<td>Auer rods (AML, especially the promyelocytic [M3] type)</td>
</tr>
<tr>
<td>Bacitracin response</td>
<td>Sensitive: S pyogenes (group A); resistant: S agalactiae (group B)</td>
</tr>
<tr>
<td>“Bamboo spine” on x-ray</td>
<td>Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27)</td>
</tr>
<tr>
<td>Basophilic nuclear remnants in RBCs</td>
<td>Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)</td>
</tr>
<tr>
<td>Basophilic stippling of RBCs</td>
<td>Lead poisoning or sideroblastic anemia</td>
</tr>
<tr>
<td>Bloody or yellow tap on lumbar puncture</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>“Boot-shaped” heart on x-ray</td>
<td>Tetralogy of Fallot (due to RVH)</td>
</tr>
<tr>
<td>Branching gram ⊕ rods with sulfur granules</td>
<td>Actinomyces israelii</td>
</tr>
<tr>
<td>Bronchogenic apical lung tumor on imaging</td>
<td>Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome)</td>
</tr>
<tr>
<td>“Brown” tumor of bone</td>
<td>Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color)</td>
</tr>
<tr>
<td>Cardiomegaly with apical atrophy</td>
<td>Chagas disease (Trypanosoma cruzi)</td>
</tr>
<tr>
<td>Cellular crescents in Bowman capsule</td>
<td>Rapidly progressive crescentic glomerulonephritis</td>
</tr>
<tr>
<td>“Chocolate cyst” of ovary</td>
<td>Endometriosis (frequently involves both ovaries)</td>
</tr>
<tr>
<td>Circular grouping of dark tumor cells surrounding pale neurofibrils</td>
<td>Homer-Wright rosettes (neuroblastoma, medulloblastoma)</td>
</tr>
<tr>
<td>Colonies of mucoid Pseudomonas in lungs</td>
<td>Cystic fibrosis (autosomal recessive mutation in CFTR gene → fat-soluble vitamin deficiency and mucous plugs)</td>
</tr>
<tr>
<td>↓ AFP in amniotic fluid/maternal serum</td>
<td>Down syndrome or other chromosomal abnormalities</td>
</tr>
<tr>
<td>Degeneration of dorsal column fibers</td>
<td>Tabes dorsalis (3° syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spinocerebellar tracts affected)</td>
</tr>
<tr>
<td>“Delta wave” on EKG, short PR interval, supraventricular tachycardia</td>
<td>Wolff-Parkinson-White syndrome (Bundle of Kent bypasses AV node)</td>
</tr>
<tr>
<td>Depigmentation of neurons in substantia nigra</td>
<td>Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia)</td>
</tr>
<tr>
<td>Desquamated epithelium casts in sputum</td>
<td>Curschmann spirals (bronchial asthma; can result in whorled mucous plugs)</td>
</tr>
<tr>
<td>LAB/DIAGNOSTIC FINDING</td>
<td>DIAGNOSIS/DISEASE</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Disarrayed granulosa cells arranged around collections of</td>
<td>Call-Exner bodies (granulosa cell tumor of the ovary)</td>
</tr>
<tr>
<td>eosinophilic fluid</td>
<td></td>
</tr>
<tr>
<td>Dysplastic squamous cervical cells with “raisinoid” nuclei and</td>
<td>Koilocytes (HPV: predisposes to cervical cancer)</td>
</tr>
<tr>
<td>hyperchromasia</td>
<td></td>
</tr>
<tr>
<td>Electrical alternans (alternating amplitude on EKG)</td>
<td>Pericardial tamponade</td>
</tr>
<tr>
<td>Enlarged cells with intranuclear inclusion bodies</td>
<td>“Owl eye” appearance of CMV</td>
</tr>
<tr>
<td>Enlarged thyroid cells with ground-glass nuclei with central</td>
<td>“Orphan Annie” eyes nuclei (papillary carcinoma of the thyroid)</td>
</tr>
<tr>
<td>clearing</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic cytoplasmic inclusion in liver cell</td>
<td>Mallory body (alcoholic liver disease)</td>
</tr>
<tr>
<td>Eosinophilic cytoplasmic inclusion in neuron</td>
<td>Lewy body (Parkinson disease and Lewy body dementia)</td>
</tr>
<tr>
<td>Eosinophilic globule in liver</td>
<td>Councilman body (viral hepatitis, yellow fever), represents hepatocyte undergoing</td>
</tr>
<tr>
<td></td>
<td>apoptosis</td>
</tr>
<tr>
<td>Eosinophilic inclusion bodies in cytoplasm of hippocampal</td>
<td>Negri bodies of rabies</td>
</tr>
<tr>
<td>and cerebellar neurons</td>
<td></td>
</tr>
<tr>
<td>Extracellular amyloid deposition in gray matter of brain</td>
<td>Senile plaques (Alzheimer disease)</td>
</tr>
<tr>
<td>Giant B cells with bilobed nuclei with prominent inclusions</td>
<td>Reed-Sternberg cells (Hodgkin lymphoma)</td>
</tr>
<tr>
<td>(“owl’s eye”)</td>
<td></td>
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<tr>
<td>Glomerulus-like structure surrounding vessel in germ cells</td>
<td>Schiller-Duval bodies (yolk sac tumor)</td>
</tr>
<tr>
<td>“Hair on end” (“Crew-cut”) appearance on x-ray</td>
<td>β-thalasemia, sickle cell disease (marrow expansion)</td>
</tr>
<tr>
<td>hCG elevated</td>
<td>Choriocarcinoma, hydatidiform mole (occurs with and without embryo, and multiple</td>
</tr>
<tr>
<td></td>
<td>pregnancy)</td>
</tr>
<tr>
<td>Heart nodules (granulomatous)</td>
<td>Aschoff bodies (rheumatic fever)</td>
</tr>
<tr>
<td>Heterophile antibodies</td>
<td>Infectious mononucleosis (EBV)</td>
</tr>
<tr>
<td>Hexagonal, double-pointed, needle-like crystals in bronchial</td>
<td>Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules)</td>
</tr>
<tr>
<td>secretions</td>
<td></td>
</tr>
<tr>
<td>High level of d-dimers</td>
<td>DVT, PE, DIC</td>
</tr>
<tr>
<td>Hilar lymphadenopathy, peripheral granulomatous lesion in</td>
<td>Ghon complex (1° TB: Mycobacterium bacilli)</td>
</tr>
<tr>
<td>middle or lower lung lobes (can calcify)</td>
<td></td>
</tr>
<tr>
<td>“Honeycomb lung” on x-ray or CT</td>
<td>Interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>Hypercoagulability (leading to migrating DVTs and vasculitis)</td>
<td>Trousseau syndrome (adenocarcinoma of pancreas or lung)</td>
</tr>
<tr>
<td>Hypersegmented neutrophils</td>
<td>Megaloblastic anemia (B12 deficiency: neurologic symptoms; folate deficiency: no</td>
</tr>
<tr>
<td></td>
<td>neurologic symptoms)</td>
</tr>
<tr>
<td>Hypertension, hypokalemia, metabolic alkalosis</td>
<td>1° hyperaldosteronism (Conn syndrome)</td>
</tr>
<tr>
<td>Hypochromic, microcytic anemia</td>
<td>Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes</td>
</tr>
<tr>
<td></td>
<td>present)</td>
</tr>
<tr>
<td>Intranuclear eosinophilic droplet-like bodies</td>
<td>Cowdry type A bodies (HSV or VZV)</td>
</tr>
<tr>
<td>Iron-containing nodules in alveolar septum</td>
<td>Ferruginous bodies (asbestosis: ↑ chance of mesothelioma)</td>
</tr>
<tr>
<td>Keratin pearls on a skin biopsy</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Large granules in phagocytes, immunodeficiency</td>
<td>Chédiak-Higashi disease (congenital failure of phagolysosome formation)</td>
</tr>
<tr>
<td>“Lead pipe” appearance of colon on abdominal imaging</td>
<td>Ulcerative colitis (loss of haustra)</td>
</tr>
<tr>
<td>Linear appearance of IgG deposition on glomerular and</td>
<td>Goodpasture syndrome</td>
</tr>
<tr>
<td>alveolar basement membranes</td>
<td></td>
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<tr>
<td>LAB/DIAGNOSTIC FINDING</td>
<td>DIAGNOSIS/DISEASE</td>
</tr>
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<tr>
<td>Low serum ceruloplasmin</td>
<td>Wilson disease (hepatolenticular degeneration)</td>
</tr>
<tr>
<td>“Lumpy bumpy” appearance of glomeruli on immunofluorescence</td>
<td>Poststreptococcal glomerulonephritis (due to deposition of IgG, IgM, and C3)</td>
</tr>
<tr>
<td>Lytic (“punched-out”) bone lesions on x-ray</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Mammary gland (“blue domed”) cyst</td>
<td>Fibrocystic change of the breast</td>
</tr>
</tbody>
</table>
| 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 |
<p>| Mucin-filled cell with peripheral nucleus | “Signet ring” (gastric carcinoma) |
| Narrowing of bowel lumen on barium x-ray | “String sign” (Crohn disease) |
| Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis | Granulomatosis with polyangiitis (Wegener; PR3-ANCA/c-ANCA) and Goodpasture syndrome (anti–basement membrane antibodies) |
| Needle-shaped, ☠ birefringent crystals | Gout (monosodium urate crystals) |
| Nodular hyaline deposits in glomeruli | Kimmelstiel-Wilson nodules (diabetic nephropathy) |
| Novobiocin response | Sensitive: <em>S. epidermidis</em>; resistant: <em>S. saprophyticus</em> |
| “Onion skin” periosteal reaction | Ewing sarcoma (malignant small blue cell tumor) |
| Optochin response | Sensitive: <em>S. pneumoniae</em>; resistant: viridans streptococci (<em>S. mutans, S. sanguis</em>) |
| Podocyte fusion or “effacement” on electron microscopy | Minimal change disease (child with nephrotic syndrome) |
| Polished, “ivory-like” appearance of bone at cartilage erosion | Eburnation (osteoarthritis resulting in bony sclerosis) |
| Protein aggregates in neurons from hyperphosphorylation of tau protein | Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease) |
| Psammoma bodies | Meningiomas, papillary thyroid carcinoma, mesothelioma, papillary serous carcinoma of the endometrium and ovary |
| Pseudopalisading tumor cells on brain biopsy | Glioblastoma multiforme |
| Raised peristeum (creating a “Codman triangle”) | Aggressive bone lesion (eg, osteosarcoma, Ewing sarcoma, osteomyelitis) |
| RBC casts in urine | Glomerulonephritis |
| Rectangular, crystal-like, cytoplasmic inclusions in Leydig cells | Reinke crystals (Leydig cell tumor) |
| Recurrent infections, eczema, thrombocytopenia | Wiskott-Aldrich syndrome |
| Renal epithelial casts in urine | Intrinsic renal failure (eg, ischemia or toxic injury) |
| Rhomboid crystals, ☠ birefringent | Pseudogout (calcium pyrophosphate dihydrate crystals) |
| Rib notching (inferior surface, on x-ray) | Coarctation of the aorta |
| Ring-enhancing brain lesion on CT/MRI in AIDS | <em>Toxoplasma gondii</em>, CNS lymphoma |
| Sheets of medium-sized lymphoid cells with scattered pale, tingible body–laden macrophages (“starry sky” histology) | Burkitt lymphoma ([t(8;14) c-myc activation, associated with EBV; “starry sky” made up of malignant cells]) |
| Silver-staining spherical aggregation of tau proteins in neurons | Pick bodies (Pick disease: progressive dementia, changes in personality) |</p>
<table>
<thead>
<tr>
<th>LAB/DIAGNOSTIC FINDING</th>
<th>DIAGNOSIS/DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Soap bubble” in femur or tibia on x-ray</td>
<td>Giant cell tumor of bone (generally benign)</td>
</tr>
<tr>
<td>“Spikes” on basement membrane, “dome-like” subepithelial</td>
<td>Membranous nephropathy (nephrotic syndrome)</td>
</tr>
<tr>
<td>deposits</td>
<td></td>
</tr>
<tr>
<td>Stacks of RBCs</td>
<td>Rouleaux formation (high ESR, multiple myeloma)</td>
</tr>
<tr>
<td>“Steeple” sign on frontal CXR</td>
<td>Group (parainfluenza virus)</td>
</tr>
<tr>
<td>Stippled vaginal epithelial cells</td>
<td>“Clue cells” (Gardnerella vaginalis)</td>
</tr>
<tr>
<td>Streptococcus bovis bacteremia</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>“Tennis racket”-shaped cytoplasmic organelles (EM) in</td>
<td>Birbeck granules (Langerhans cell histiocytosis)</td>
</tr>
<tr>
<td>Langerhans cells</td>
<td></td>
</tr>
<tr>
<td>Thousands of polyps on colonoscopy</td>
<td>Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)</td>
</tr>
<tr>
<td>Thrombi made of white/red layers</td>
<td>Lines of Zahn (arterial thrombus, layers of platelets/RBCs)</td>
</tr>
<tr>
<td>“Thumb sign” on lateral neck x-ray</td>
<td>Epiglottitis (Haemophilus influenzae)</td>
</tr>
<tr>
<td>Thyroid-like appearance of kidney</td>
<td>Chronic pyelonephritis (usually due to recurrent infections)</td>
</tr>
<tr>
<td>“Tram-track” appearance of capillary loops of glomerular</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>basement membranes on light microscopy</td>
<td></td>
</tr>
<tr>
<td>Triglyceride accumulation in liver cell vacuoles</td>
<td>Fatty liver disease (alcoholic or metabolic syndrome)</td>
</tr>
<tr>
<td>↑ uric acid levels</td>
<td>Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics</td>
</tr>
<tr>
<td>“Waxy” casts with very low urine flow</td>
<td>Chronic end-stage renal disease</td>
</tr>
<tr>
<td>WBC casts in urine</td>
<td>Acute pyelonephritis</td>
</tr>
<tr>
<td>WBCs that look “smudged”</td>
<td>CLL (almost always B cell)</td>
</tr>
<tr>
<td>“Wire loop” glomerular capillary appearance on light</td>
<td>Diffuse proliferative glomerulonephritis (usually seen with lupus)</td>
</tr>
<tr>
<td>microscopy</td>
<td></td>
</tr>
<tr>
<td>Yellowish CSF</td>
<td>Xanthochromia (eg, due to subarachnoid hemorrhage)</td>
</tr>
</tbody>
</table>

**CLASSIC/RELEVANT TREATMENTS**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>COMMON TREATMENT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence seizures</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Acute gout attack</td>
<td>NSAIDs, colchicine, glucocorticoids</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia (M3)</td>
<td>All-trans retinoic acid</td>
</tr>
<tr>
<td>ADHD</td>
<td>Methylphenidate, CBT, atomoxetine, guanfacine, clonidine</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Disulfiram, acamprosate, naltrexone, supportive care</td>
</tr>
<tr>
<td>Alcohol withdrawal</td>
<td>Long-acting benzodiazepines</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Nutrition, psychotherapy, mirtazapine</td>
</tr>
<tr>
<td>Arrhythmia in damaged cardiac tissue</td>
<td>Class IB antiarrhythmic (lidocaine, mexiletine)</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>α1-antagonists, 5α-reductase inhibitors, PDE-5 inhibitors</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics</td>
</tr>
<tr>
<td>Condition</td>
<td>Common Treatment(s)</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Breast cancer in postmenopausal woman</td>
<td>Aromatase inhibitor (anastrozole)</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>SSRI</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Topical azoles (vaginitis); nystatin, fluconazole, caspofungin (oral/esophageal); fluconazole, caspofungin, amphotericin B (systemic)</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Octreotide</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>Doxycycline (+ ceftriaxone for gonorrhea coinfection), erythromycin eye drops (prophylaxis in infants)</td>
</tr>
<tr>
<td>Chronic gout</td>
<td>Xanthine oxidase inhibitors (eg, allopurinol, febuxostat); pegloticase; probenecid</td>
</tr>
<tr>
<td>Chronic hepatitis B or C</td>
<td>IFN-α (HBV and HCV); ribavirin, simeprevir, sofosbuvir (HCV)</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>Imatinib</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Antitoxin</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Oral metronidazole; if refractory, oral vancomycin</td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td>Antitoxin</td>
</tr>
<tr>
<td>CMV</td>
<td>Ganciclovir, foscarin, cidofovir</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Corticosteroids, infliximab, azathioprine</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Fluconazole (in AIDS patients)</td>
</tr>
<tr>
<td>Cyclophosphamide-induced hemorrhagic cystitis</td>
<td>Mesna</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRIs (first-line)</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic)</td>
</tr>
<tr>
<td>Diabetes mellitus type 1</td>
<td>Dietary intervention (low carbohydrate) + insulin replacement</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>Dietary intervention, oral hypoglycemics, and insulin (if refractory)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Fluids, insulin, K+</td>
</tr>
<tr>
<td>Drug of choice for anticoagulation during pregnancy</td>
<td>Heparin</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Vancomycin, aminopenicillins/cephalosporins</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Sildenafil, tadalafl, vardenafil</td>
</tr>
<tr>
<td>ER+ breast cancer</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Ethylene glycol/methanol intoxication</td>
<td>Fomepizole (alcohol dehydrogenase inhibitor)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> (B)</td>
<td>Rifampin (prophylaxis)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>SSRIs, SNRIs (first line); buspirone (second line)</td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (Wegener)</td>
<td>Cyclophosphamide, corticosteroids</td>
</tr>
<tr>
<td>Heparin reversal</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>HER2/neu+ breast cancer</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>CONDITION</td>
<td>COMMON TREATMENT(S)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Statin (first-line)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Fibrate</td>
</tr>
<tr>
<td>Immediate anticoagulation</td>
<td>Heparin</td>
</tr>
<tr>
<td>Infertility</td>
<td>Leuprolide, GnRH (pulsatile), clomiphene</td>
</tr>
<tr>
<td>Influenza</td>
<td>Oseltamivir, zanamivir</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>IVIG, high-dose aspirin</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>Macrolides (eg, azithromycin)</td>
</tr>
<tr>
<td>Long-term anticoagulation</td>
<td>Warfarin, dabigatran, rivaroxaban and apixaban</td>
</tr>
<tr>
<td>Malaria</td>
<td>Chloroquine, mefloquine, atovaquone/proguanil (for blood schizont), primaquine (for liver hypnozoite)</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Dantrolene</td>
</tr>
<tr>
<td>Medical abortion</td>
<td>Mifepristone</td>
</tr>
<tr>
<td>Migraine</td>
<td>Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis (eg, propranolol, topiramate, CCBs, amitriptyline)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Disease-modifying therapies (eg, β-interferon, natalizumab); for acute flares, use IV steroids</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>RIPE (rifampin, isoniazid, pyrazinamide, ethambutol)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Ceftriaxone (add doxycycline to cover likely concurrent Chlamydia trachomatis)</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Penicillin/ceftriaxone, rifampin (prophylaxis)</td>
</tr>
<tr>
<td>Neural tube defect prevention</td>
<td>Prenatal folic acid</td>
</tr>
<tr>
<td>Osteomalacia/rickets</td>
<td>Vitamin D supplementation</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>Close with indomethacin; keep open with PGE analogs</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>α-antagonists (eg, phenoxybenzamine)</td>
</tr>
<tr>
<td>Pneumocystis jirovecii</td>
<td>TMP-SMX (prophylaxis and treatment in immunosuppressed patients)</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>Cabergoline/bromocriptine (dopamine agonists)</td>
</tr>
<tr>
<td>Prostate adenocarcinoma/uterine fibroids</td>
<td>Leuprolide, GnRH (continuous)</td>
</tr>
<tr>
<td>Prostate adenocarcinoma</td>
<td>Flutamide</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Antipseudomonal penicillins, aminoglycosides, carbapenems</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension (idiopathic)</td>
<td>Sildenafil, bosentan, epoprostenol</td>
</tr>
<tr>
<td>Rickettsia rickettsii</td>
<td>Doxycycline, chloramphenicol</td>
</tr>
<tr>
<td>Schizophrenia (negative symptoms)</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Schizophrenia (positive symptoms)</td>
<td>Typical and atypical antipsychotics</td>
</tr>
<tr>
<td>SIADH</td>
<td>Fluid restriction, IV hypertonic saline, conivaptan/tolvaptan, demeclocycline</td>
</tr>
<tr>
<td>Condition</td>
<td>Common Treatment(s)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Hydroxyurea (↑ fetal hemoglobin)</td>
</tr>
<tr>
<td><em>Sporothrix schenckii</em></td>
<td>Itraconazole, oral potassium iodide</td>
</tr>
<tr>
<td>Stable angina</td>
<td>Sublingual nitroglycerin</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>MSSA: nafcillin, oxacillin, dicloxacillin (antistaphylococcal penicillins); MRSA: vancomycin, daptomycin, linezolid, ceftaroline</td>
</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
<td>Penicillin prophylaxis; evaluation for colon cancer if linked to endocarditis</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Penicillin/cephalosporin (systemic infection, pneumonia), vancomycin (meningitis)</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Penicillin prophylaxis</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>High-dose steroids</td>
</tr>
<tr>
<td>Tonic-clonic seizures</td>
<td>Levetiracetam, phenytoin, valproate, carbamazepine</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Sulfadiazine + pyrimethamine</td>
</tr>
<tr>
<td><em>Treponema pallidum</em></td>
<td>Penicillin</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>Metronidazole (patient and partner)</td>
</tr>
<tr>
<td>Trigeminal neuralgia (tic douloureux)</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>5-ASA preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy</td>
</tr>
<tr>
<td>UTI prophylaxis</td>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Warfarin reversal</td>
<td>Fresh frozen plasma (acute), vitamin K (non-acute)</td>
</tr>
</tbody>
</table>

### Key Associations

<table>
<thead>
<tr>
<th>Disease/Finding</th>
<th>Most Common/Important Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic (solar) keratosis</td>
<td>Precursor to squamous cell carcinoma</td>
</tr>
<tr>
<td>Acute gastric ulcer associated with CNS injury</td>
<td>Cushing ulcer (↑ intracranial pressure stimulates vagal gastric H+ secretion)</td>
</tr>
<tr>
<td>Acute gastric ulcer associated with severe burns</td>
<td>Curling ulcer (greatly reduced plasma volume results in sloughing of gastric mucosa)</td>
</tr>
<tr>
<td>Alternating areas of transmural inflammation and normal colon</td>
<td>Skip lesions (Crohn disease)</td>
</tr>
<tr>
<td>Aortic aneurysm, abdominal</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Aortic aneurysm, ascending or arch</td>
<td>3rd syphilis (syphilitic aortitis), vasa vasorum destruction</td>
</tr>
<tr>
<td>Aortic aneurysm, thoracic</td>
<td>Marfan syndrome (idiopathic cystic medial degeneration)</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Atrophy of the mammillary bodies</td>
<td>Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion)</td>
</tr>
<tr>
<td>DISEASE/FINDING</td>
<td>MOST COMMON/IMPORTANT ASSOCIATIONS</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Autosplenectomy (fibrosis and shrinkage)</td>
<td>Sickle cell disease (hemoglobin S)</td>
</tr>
<tr>
<td>Bacteria associated with gastritis, peptic ulcer disease, and gastric malignancies (eg, adenocarcinoma, MALtoma)</td>
<td><em>H pylori</em></td>
</tr>
<tr>
<td>Bacterial meningitis (adults and elderly)</td>
<td><em>S pneumoniae</em></td>
</tr>
<tr>
<td>Bacterial meningitis (newborns and kids)</td>
<td>Group B streptococcus/<em>E coli</em> (newborns), <em>S pneumoniae/N meningitidis</em> (kids/teens)</td>
</tr>
<tr>
<td>Bilateral ovarian metastases from gastric carcinoma</td>
<td>Krukenberg tumor (mucin-secreting signet ring cells)</td>
</tr>
<tr>
<td>Bleeding disorder with GpIb deficiency</td>
<td>Bernard-Soulier syndrome (defect in platelet adhesion to von Willebrand factor)</td>
</tr>
<tr>
<td>Brain tumor (adults)</td>
<td>Supratentorial: metastasis, astrocytoma (including glioblastoma multiforme), meningioma, schwannoma</td>
</tr>
<tr>
<td>Brain tumor (kids)</td>
<td>Infratentorial: medulloblastoma (cerebellum) or supratentorial: craniopharyngioma</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Invasive ductal carcinoma</td>
</tr>
<tr>
<td>Breast mass</td>
<td>Fibrocystic change, carcinoma (in postmenopausal women)</td>
</tr>
<tr>
<td>Breast tumor (benign, young woman)</td>
<td>Fibroadenoma</td>
</tr>
<tr>
<td>Cardiac 1° tumor (kids)</td>
<td>Rhabdomyoma, often seen in tuberous sclerosis</td>
</tr>
<tr>
<td>Cardiac manifestation of lupus</td>
<td>Marantic/thrombotic endocarditis (nonbacterial)</td>
</tr>
<tr>
<td>Cardiac tumor (adults)</td>
<td>Metastasis, myxoma (90% in left atrium; “ball and valve”)</td>
</tr>
<tr>
<td>Cerebellar tonsillar herniation</td>
<td>Chiari II malformation</td>
</tr>
<tr>
<td>Chronic arrhythmia</td>
<td>Atrial fibrillation (associated with high risk of emboli)</td>
</tr>
<tr>
<td>Chronic atrophic gastritis (autoimmune)</td>
<td>Predisposition to gastric carcinoma (can also cause pernicious anemia)</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma of the vagina</td>
<td>DES exposure in utero</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia, hypotension</td>
<td>21-hydroxylase deficiency</td>
</tr>
<tr>
<td>Congenital cardiac anomaly</td>
<td>VSD</td>
</tr>
<tr>
<td>Congenital conjugated hyperbilirubinemia (black liver)</td>
<td>Dubin-Johnson syndrome (inability of hepatocytes to secrete conjugated bilirubin into bile)</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
<td>TB (developing world); idiopathic, viral illness (developed world)</td>
</tr>
<tr>
<td>Coronary artery involved in thrombosis</td>
<td>LAD &gt; RCA &gt; circumflex</td>
</tr>
<tr>
<td>Cretinism</td>
<td>Iodine deficit/congenital hypothyroidism</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Latrogenic (from corticosteroid therapy)</td>
</tr>
<tr>
<td></td>
<td>Adrenocortical adenoma (secretes excess cortisol)</td>
</tr>
<tr>
<td></td>
<td>ACTH-secreting pituitary adenoma (Cushing disease)</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic (due to ACTH secretion by tumors)</td>
</tr>
<tr>
<td>Cyanosis (early; less common)</td>
<td>Tetralogy of Fallot, transposition of great vessels, truncus arteriosus</td>
</tr>
<tr>
<td>Death in CML</td>
<td>Blast crisis</td>
</tr>
<tr>
<td>Death in SLE</td>
<td>Lupus nephropathy</td>
</tr>
<tr>
<td>Disease/Finding</td>
<td>Most Common/Important Associations</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dementia</td>
<td>Alzheimer disease, multiple infarcts (vascular dementia)</td>
</tr>
<tr>
<td>Demyelinating disease in young women</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>DIA</td>
<td>Severe sepsis, obstetric complications, cancer, burns, trauma, major surgery, acute pancreatitis, APL</td>
</tr>
<tr>
<td>Diverticulum in pharynx</td>
<td>Zenker diverticulum (diagnosed by barium swallow)</td>
</tr>
<tr>
<td>Ejection click</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Squamous cell carcinoma (worldwide); adenocarcinoma (US)</td>
</tr>
<tr>
<td>Food poisoning (exotoxin mediated)</td>
<td>S. aureus, B. cereus</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Glomerulonephritis (adults)</td>
<td>Berger disease (IgA nephropathy)</td>
</tr>
<tr>
<td>Gynecologic malignancy</td>
<td>Endometrial carcinoma (most common in US); cervical carcinoma (most common worldwide)</td>
</tr>
<tr>
<td>Heart murmur, congenital</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Heart valve in bacterial endocarditis</td>
<td>Mitral &gt; aortic (rheumatic fever), tricuspid (IV drug abuse)</td>
</tr>
<tr>
<td>Helminth infection (US)</td>
<td>Enterobius vermicularis, Ascaris lumbricoides</td>
</tr>
<tr>
<td>Hematoma—epidural</td>
<td>Rupture of middle meningeal artery (trauma; lentiform shaped)</td>
</tr>
<tr>
<td>Hematoma—subdural</td>
<td>Rupture of bridging veins (crescent shaped)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Multiple blood transfusions or hereditary HFE mutation (can result in heart failure, “bronze diabetes,” and ↑ risk of hepatocellular carcinoma)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Cirrhotic liver (associated with hepatitis B and C and with alcoholism)</td>
</tr>
<tr>
<td>Hereditary bleeding disorder</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>Hereditary harmless jaundice</td>
<td>Gilbert syndrome (benign congenital unconjugated hyperbilirubinemia)</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>Psoriatic arthritis, ankylosing spondylitis, IBD-associated arthritis, reactive arthritis (formerly Reiter syndrome)</td>
</tr>
<tr>
<td>HLA-DR3</td>
<td>Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease</td>
</tr>
<tr>
<td>HLA-DR4</td>
<td>Diabetes mellitus type 1, rheumatoid arthritis, Addison disease</td>
</tr>
<tr>
<td>Holosystolic murmur</td>
<td>VSD, tricuspid regurgitation, mitral regurgitation</td>
</tr>
<tr>
<td>Hypercoagulability, endothelial damage, blood stasis</td>
<td>Virchow triad (↑ risk of thrombosis)</td>
</tr>
<tr>
<td>Hypertension, 2°</td>
<td>Renal artery stenosis, chronic kidney disease (eg, polycystic kidney disease, diabetic nephropathy), hyperaldosteronism</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Accidental excision during thyroidectomy</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Pituitary adenoma (usually benign tumor)</td>
</tr>
<tr>
<td>Infection 2° to blood transfusion</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Infections in chronic granulomatous disease</td>
<td>S. aureus, E. coli, Aspergillus (catalase ⊕)</td>
</tr>
<tr>
<td>Disease/Finding</td>
<td>Most Common/Important Associations</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>Down syndrome, fragile X syndrome</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>- Calcium = radiopaque&lt;br&gt;- Struvite (ammonium) = radiopaque (formed by urease&lt;br&gt;⊕ organisms such as Klebsiella, Proteus species, and S saprophyticus)&lt;br&gt;- Uric acid = radiolucent&lt;br&gt;- Cystine = radiolucent</td>
</tr>
<tr>
<td>Late cyanotic shunt (uncorrected left to right becomes right to left)</td>
<td>Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Alcoholic cirrhosis</td>
</tr>
<tr>
<td>Lysosomal storage disease</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Male cancer</td>
<td>Prostatic carcinoma</td>
</tr>
<tr>
<td>Malignancy associated with noninfectious fever</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Malignancy (kids)</td>
<td>ALL, medulloblastoma (cerebellum)</td>
</tr>
<tr>
<td>Metastases to bone</td>
<td>Prostate, breast &gt; lung &gt; thyroid</td>
</tr>
<tr>
<td>Metastases to brain</td>
<td>Lung &gt; breast &gt; genitourinary &gt; melanoma &gt; GI</td>
</tr>
<tr>
<td>Metastases to liver</td>
<td>Colon &gt;&gt; stomach, pancreas</td>
</tr>
<tr>
<td>Microcytic anemia</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Mitochondrial inheritance</td>
<td>Disease occurs in both males and females, inherited through females only</td>
</tr>
<tr>
<td>Mitral valve stenosis</td>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>Mixed (UMN and LMN) motor neuron disease</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Coxsackie B</td>
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<tr>
<td>Nephrotic syndrome (adults)</td>
<td>Focal segmental glomerulosclerosis</td>
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<tr>
<td>Nephrotic syndrome (kids)</td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>Neuron migration failure</td>
<td>Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)</td>
</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td>S aureus, Pseudomonas, other enteric gram ⊕ rods</td>
</tr>
<tr>
<td>Obstruction of male urinary tract</td>
<td>BPH</td>
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<tr>
<td>Opening snap</td>
<td>Mitral stenosis</td>
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<td>Opportunistic infection in AIDS</td>
<td>Pneumocystis jirovecii pneumonia</td>
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<tr>
<td>Osteomyelitis</td>
<td>S aureus (most common overall)</td>
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<td>Osteomyelitis in sickle cell disease</td>
<td>Salmonella</td>
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<tr>
<td>Osteomyelitis with IV drug use</td>
<td>Pseudomonas, Candida, S aureus</td>
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<td>Ovarian tumor (benign, bilateral)</td>
<td>Serous cystadenoma</td>
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<tr>
<td>Ovarian tumor (malignant)</td>
<td>Serous cystadenocarcinoma</td>
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<td>Pancreatitis (acute)</td>
<td>Gallstones, alcohol</td>
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<tr>
<td>Pancreatitis (chronic)</td>
<td>Alcohol (adults), cystic fibrosis (kids)</td>
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<tr>
<td>Pelvic inflammatory disease</td>
<td>C trachomatis, N gonorrhoeae</td>
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<tr>
<td>Philadelphia chromosome t(9;22) (BCR-ABL)</td>
<td>CML (may sometimes be associated with ALL/AML)</td>
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<tr>
<td>Pituitary tumor</td>
<td>Prolactinoma, somatotropin adenoma</td>
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<tr>
<td>Disease/Finding</td>
<td>Most Common/Important Associations</td>
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<td>----------------------------------------------------------------------------------------------------</td>
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<tr>
<td>1° amenorrhea</td>
<td>Turner syndrome (45, XO or 45,XO/46, XX mosaic)</td>
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<tr>
<td>1° bone tumor (adults)</td>
<td>Multiple myeloma</td>
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<tr>
<td>1° hyperaldosteronism</td>
<td>Adenoma of adrenal cortex</td>
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<tr>
<td>1° hyperparathyroidism</td>
<td>Adenomas, hyperplasia, carcinoma</td>
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<tr>
<td>1° liver cancer</td>
<td>Hepatocellular carcinoma (chronic hepatitis, cirrhosis, hemochromatosis, α1-antitrypsin deficiency, Wilson disease)</td>
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<tr>
<td>Pulmonary hypertension</td>
<td>Idiopathic, heritable, left heart disease (eg, HF), lung disease (eg, COPD), hypoxemic vasoconstriction (eg, OSA), thromboembolic (eg, PE)</td>
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<tr>
<td>Recurrent inflammation/thrombosis of small/medium vessels in extremities</td>
<td>Buerger disease (strongly associated with tobacco)</td>
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<tr>
<td>Refractory peptic ulcers and high gastrin levels</td>
<td>Zollinger-Ellison syndrome (gastrinoma of duodenum or pancreas), associated with MEN1</td>
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<tr>
<td>Renal tumor</td>
<td>Renal cell carcinoma: associated with von Hippel-Lindau and cigarette smoking; paraneoplastic syndromes (EPO, renin, PTHrP, ACTH)</td>
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<tr>
<td>Right heart failure due to a pulmonary cause</td>
<td>Cor pulmonale</td>
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<tr>
<td>S3 heart sound</td>
<td>† ventricular filling pressure (eg, mitral regurgitation, HF), common in dilated ventricles</td>
</tr>
<tr>
<td>S4 heart sound</td>
<td>Stiff/hypertrophic ventricle (aortic stenosis, restrictive cardiomyopathy)</td>
</tr>
<tr>
<td>2° hyperparathyroidism</td>
<td>Hypocalcemia of chronic kidney disease</td>
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<tr>
<td>Sexually transmitted disease</td>
<td>C trachomatis (usually coinfected with N gonorrhoeae)</td>
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<tr>
<td>SIADH</td>
<td>Small cell carcinoma of the lung</td>
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<tr>
<td>Site of diverticula</td>
<td>Sigmoid colon</td>
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<tr>
<td>Sites of atherosclerosis</td>
<td>Abdominal aorta &gt; coronary artery &gt; poplite artery &gt; carotid artery</td>
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<tr>
<td>t(14;18)</td>
<td>Follicular lymphomas (BCL-2 activation, anti-apoptotic oncogene)</td>
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<tr>
<td>t(8;14)</td>
<td>Burkitt lymphoma (c-myc fusion, transcription factor oncogene)</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>Philadelphia chromosome, CML (BCR-ABL activation, tyrosine kinase oncogene)</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>Risk of ipsilateral blindness due to occlusion of ophthalmic artery; polymyalgia rheumatica</td>
</tr>
<tr>
<td>Testicular tumor</td>
<td>Seminoma (malignant, radiosensitive), † placental ALP</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Papillary carcinoma (childhood irradiation)</td>
</tr>
<tr>
<td>Tumor in women</td>
<td>Leiomyoma (estrogen dependent, not precancerous)</td>
</tr>
<tr>
<td>Tumor of infancy</td>
<td>Strawberry hemangioma (grows rapidly and regresses spontaneously by childhood)</td>
</tr>
<tr>
<td>Tumor of the adrenal medulla (adults)</td>
<td>Pheochromocytoma (usually benign)</td>
</tr>
<tr>
<td>Tumor of the adrenal medulla (kids)</td>
<td>Neuroblastoma (malignant)</td>
</tr>
<tr>
<td>Type of Hodgkin lymphoma</td>
<td>Nodular sclerosing (vs mixed cellularity, lymphocytic predominance, lymphocytic depletion)</td>
</tr>
</tbody>
</table>
### Disease/Finding

<table>
<thead>
<tr>
<th>Disease/Finding</th>
<th>Most Common/Important Associations</th>
</tr>
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<tbody>
<tr>
<td>Type of non-Hodgkin lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>UTI</td>
<td><em>E. coli</em>, <em>Staphylococcus saprophyticus</em> (young women)</td>
</tr>
<tr>
<td>Vertebral compression fracture</td>
<td>Osteoporosis (type I: postmenopausal woman; type II: elderly man or woman)</td>
</tr>
<tr>
<td>Viral encephalitis affecting temporal lobe</td>
<td>HSV-1</td>
</tr>
<tr>
<td>Vitamin deficiency (US)</td>
<td>Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects)</td>
</tr>
</tbody>
</table>

### Equation Review

<table>
<thead>
<tr>
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<th>Equation</th>
<th>Page</th>
</tr>
</thead>
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<td>Sensitivity</td>
<td>Sensitivity = TP / (TP + FN)</td>
<td>33</td>
</tr>
<tr>
<td>Specificity</td>
<td>Specificity = TN / (TN + FP)</td>
<td>33</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>PPV = TP / (TP + FP)</td>
<td>33</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>NPV = TN / (FN + TN)</td>
<td>33</td>
</tr>
<tr>
<td>Odds ratio (for case-control studies)</td>
<td>OR = (\frac{a/c}{b/d}) (\frac{ad}{bc})</td>
<td>34</td>
</tr>
<tr>
<td>Relative risk</td>
<td>RR = (\frac{a(a + b)}{c(c + d)})</td>
<td>34</td>
</tr>
<tr>
<td>Attributable risk</td>
<td>AR = (\frac{a}{a + b} - \frac{c}{c + d})</td>
<td>34</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>RRR = 1 - RR</td>
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<tr>
<td>Absolute risk reduction</td>
<td>ARR = (\frac{c}{c + d} - \frac{a}{a + b})</td>
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</tr>
<tr>
<td>Number needed to treat</td>
<td>NNT = 1/ARR</td>
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</tr>
<tr>
<td>Number needed to harm</td>
<td>NNH = 1/AR</td>
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<tr>
<td>Hardy-Weinberg equilibrium</td>
<td>(p^2 + 2pq + q^2 = 1)\  (p + q = 1)</td>
<td>69</td>
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<tr>
<td>Volume of distribution</td>
<td>(V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}})</td>
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<tr>
<td>Half-life</td>
<td>(t_{1/2} = \frac{0.693 \times V_d}{CL})</td>
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<tr>
<td>Drug clearance</td>
<td>(CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e) (elimination constant)</td>
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<tr>
<td>Loading dose</td>
<td>(LD = \frac{C_p \times V_d}{F})</td>
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<tr>
<td>Maintenance dose</td>
<td>(D = \frac{C_p \times CL \times \tau}{F})</td>
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<td>--------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>( \text{CO} = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}} )</td>
<td>266</td>
</tr>
<tr>
<td></td>
<td>( \text{CO} = \text{stroke volume} \times \text{heart rate} )</td>
<td></td>
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<tr>
<td>Mean arterial pressure</td>
<td>( \text{MAP} = \text{cardiac output} \times \text{total peripheral resistance} )</td>
<td>266</td>
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<tr>
<td></td>
<td>( \text{MAP} = \frac{2}{3} \text{diastolic} + \frac{1}{3} \text{systolic} )</td>
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<tr>
<td>Stroke volume</td>
<td>( \text{SV} = \text{EDV} - \text{ESV} )</td>
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<td>Ejection fraction</td>
<td>( \text{EF} = \frac{\text{SV}}{\text{EDV}} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} )</td>
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<tr>
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<td>268</td>
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<tr>
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<tr>
<td>Renal clearance</td>
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<td>Glomerular filtration rate</td>
<td>( \text{GFR} = U_{\text{ulin}} \times \frac{V}{P_{\text{ulin}}} = C_{\text{ulin}} )</td>
<td>534</td>
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<tr>
<td></td>
<td>( \text{GFR} = K_f[(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})] )</td>
<td></td>
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<tr>
<td>Effective renal plasma flow</td>
<td>( \text{cRPF} = U_{\text{PAH}} \times \frac{V}{P_{\text{PAH}}} = C_{\text{PAH}} )</td>
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<tr>
<td>Renal blood flow</td>
<td>( \text{RBF} = \frac{\text{RPF}}{1 - \text{Hct}} )</td>
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<td>( \text{FF} = \frac{\text{GFR}}{\text{RPF}} )</td>
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<td>Henderson-Hasselbalch equation for extracellular pH</td>
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<td>( \text{PCO}_2 = 1.5 [\text{HCO}_3^-] + 8 \pm 2 )</td>
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<td>( \text{V}_D = V_T \times \frac{\text{PaCO}_2 - \text{PECO}_2}{\text{PaCO}_2} )</td>
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<tr>
<td>Pulmonary vascular resistance</td>
<td>( \text{PVR} = \frac{P_{\text{pulmonary}} - P_{\text{Lumen}}}{\text{cardiac output}} )</td>
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</table>
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

“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

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Microbiology and Immunology 655
Pathology 656
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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.

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- The cost
- The readability of the text
- 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)
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<td>A*</td>
<td>USMLEWorld Qbank</td>
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## Anatomy, Embryology, and Neuroscience

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### Pharmacology

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### Physiology

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<td>Endoscopic retrograde cholangiopancreatography</td>
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<tr>
<td>ERP</td>
<td>Effective refractory period</td>
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<tr>
<td>eRPF</td>
<td>Effective renal plasma flow</td>
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<td>ERT</td>
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<tr>
<td>ERV</td>
<td>Expiratory reserve volume</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<td>ESRD</td>
<td>End-stage renal disease</td>
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<td>ESV</td>
<td>End-systolic volume</td>
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<td>Bioavailability</td>
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<td>FA</td>
<td>Fatty acid</td>
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<tr>
<td>Fab</td>
<td>Fragment, antigen-binding</td>
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<tr>
<td>FAD</td>
<td>Flavin adenine dinucleotide</td>
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<tr>
<td>FAD&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Oxidized flavin adenine dinucleotide</td>
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<tr>
<td>FADH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Reduced flavin adenine dinucleotide</td>
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<td>FAP</td>
<td>Familial adenomatous polyposis</td>
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<td>F&lt;sub&gt;1&lt;/sub&gt;6BP</td>
<td>Fructose-1,6-bisphosphate</td>
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<tr>
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<td>Fructose-2,6-bisphosphate</td>
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<td>FBPase</td>
<td>Fructose bisphosphatase</td>
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<td>Ferritin</td>
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<td>FeR</td>
<td>Ferric receptor</td>
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<td>5-FdUMP</td>
<td>5-Fluorodeoxyuridine monophosphate</td>
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<tr>
<td>Fe&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Ferrous ion</td>
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<tr>
<td>Fe&lt;sup&gt;3+&lt;/sup&gt;</td>
<td>Ferric ion</td>
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<tr>
<td>FE Na</td>
<td>Excreted fraction of filtered sodium</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in 1 second</td>
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<td>FF</td>
<td>Filtration fraction</td>
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<td>Free fatty acid</td>
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<td>Fibroblast growth factor receptor</td>
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<td>Fluid-attenuated inversion recovery</td>
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<td>False positive</td>
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<td>FSH</td>
<td>Follicle-stimulating hormone</td>
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<td>FSMB</td>
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<tr>
<td>FTA-ABS</td>
<td>Fluorescent treponemal antibody—absorbed</td>
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<td>Forced vital capacity</td>
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<td>Galactose</td>
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<td>Glomerular basement membrane</td>
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<td>GC</td>
<td>Glomerular capillary</td>
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<tr>
<td>G-CSF</td>
<td>Granulocyte colony-stimulating factor</td>
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<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
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<td>GFAP</td>
<td>Glial fibrillary acidic protein</td>
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<td>GFR</td>
<td>Glomerular filtration rate</td>
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<td>Gamma-hydroxybutyrate</td>
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<td>Growth hormone–releasing hormone</td>
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<td>GI</td>
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<td>Gastrointestinal</td>
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<td>GIP</td>
<td>Gastric inhibitory peptide</td>
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<td>Granulocyte macrophage</td>
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<td>GM-CSF</td>
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<tr>
<td>GMP</td>
<td>Guanosine monophosphate</td>
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<td>Glycoprotein</td>
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<td>Glucose-6-phosphate dehydrogenase</td>
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<td>Globus pallidus interna</td>
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<td>Gastrin-releasing peptide</td>
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<td>G&lt;sub&gt;S&lt;/sub&gt;</td>
<td>G protein, S polypeptide</td>
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<td>Glycogen synthase</td>
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<td>GU</td>
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</tr>
<tr>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
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<td>Abbreviation</td>
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<td>HAVAb</td>
<td>hepatitis A antibody</td>
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<tr>
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<td>hemoglobin</td>
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<td>oxidized hemoglobin</td>
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<td>HBeAg</td>
<td>hepatitis B core antigen</td>
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<td>hepatitis B early antibody</td>
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<td>hepatitis B early antigen</td>
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<td>hepatitis B surface antibody</td>
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<td>HbsAg</td>
<td>hepatitis B surface antigen</td>
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<td>HDL</td>
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<td>HDV</td>
<td>hepatitis D virus</td>
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<td>H&amp;E</td>
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<td>HEV</td>
<td>hepatitis E virus</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<td>Hfr</td>
<td>high-frequency recombination [cell]</td>
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<td>HGPRT</td>
<td>hypoxanthine-guanine phosphoribosyltransferase</td>
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<td>human hemoglobin</td>
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<td>HHV</td>
<td>human herpesvirus</td>
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<tr>
<td>5-HIAA</td>
<td>5-hydroxyindoleacetic acid</td>
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<td>hypoxic ischemic encephalopathy</td>
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<td>Histo</td>
<td>histidine</td>
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<td>hepatin-induced thrombocytopenia</td>
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<tr>
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<td>human immunodeficiency virus</td>
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<td>HL</td>
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<td>HLA</td>
<td>human leukocyte antigen</td>
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<td>HMG-CoA</td>
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<td>hexose monophosphate</td>
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<td>HSV</td>
<td>herpes simplex virus</td>
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<td>5-HT</td>
<td>5-hydroxytryptamine (serotonin)</td>
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<td>hypertension</td>
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<td>hemolytic transfusion reaction</td>
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<tr>
<td>HUS</td>
<td>hemolytic-uremic syndrome</td>
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<tr>
<td>HVA</td>
<td>homovanillic acid</td>
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<td>HZV</td>
<td>herpes zoster virus</td>
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<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>IBS</td>
<td>irritable bowel syndrome</td>
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<tr>
<td>IC</td>
<td>inspiratory capacity, immune complex</td>
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<tr>
<td>ICa</td>
<td>calcium current [heart]</td>
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<td>ICf</td>
<td>funny current [heart]</td>
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<td>ICA</td>
<td>internal carotid artery</td>
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<tr>
<td>ICAM</td>
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<td>ICD</td>
<td>implantable cardioverter defibrillator</td>
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<tr>
<td>ICE</td>
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<tr>
<td>ICG</td>
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<td>ICPR</td>
<td>intracranial pressure</td>
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<td>ID</td>
<td>identification</td>
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<tr>
<td>ID50</td>
<td>median infective dose</td>
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<tr>
<td>IDDM</td>
<td>insulin-dependent diabetes mellitus</td>
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<td>IDL</td>
<td>intermediate-density lipoprotein</td>
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<td>inspiratory/expiratory [ratio]</td>
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<td>interferon</td>
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<td>immunoglobulin</td>
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<td>IGF</td>
<td>insulin-like growth factor</td>
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<td>interleukin</td>
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<td>IMA</td>
<td>inferior mesenteric artery</td>
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<td>international medical graduate</td>
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<td>imidazole monophosphate</td>
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<td>inferior mesenteric vein</td>
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<td>International Normalized Ratio</td>
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<td>inferior oblique [muscle]</td>
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<td>intraocular pressure</td>
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<td>inositol triphosphate</td>
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<td>IPV</td>
<td>inactivated polio vaccine</td>
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<td>IR</td>
<td>current x resistance [Ohm’s law], inferior rectus [muscle]</td>
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<td>IRV</td>
<td>inspiratory reserve volume</td>
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<td>idiopathic thrombocytopenic purpura</td>
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<td>IUD</td>
<td>intrauterine device</td>
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<td>inferior vena cava</td>
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<td>intravenous drug use</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>JVP</td>
<td>jugular venous pulse</td>
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<tr>
<td>K+</td>
<td>potassium ion</td>
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<td>KatG</td>
<td>catalase-peroxidase produced by M tuberculosis</td>
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<td>ABBREVIATION</td>
<td>MEANING</td>
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<tr>
<td>--------------</td>
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<tr>
<td>K&lt;sub&gt;e&lt;/sub&gt;</td>
<td>elimination constant</td>
</tr>
<tr>
<td>K&lt;sub&gt;f&lt;/sub&gt;</td>
<td>filtration constant</td>
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<td>KG</td>
<td>potassium glutarate</td>
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<td>K&lt;sub&gt;m&lt;/sub&gt;</td>
<td>Michaelis-Menten constant</td>
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<td>potassium hydroxide</td>
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<td>L</td>
<td>left</td>
</tr>
<tr>
<td>LA</td>
<td>left atrial, left atrium</td>
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<tr>
<td>LAD</td>
<td>left anterior descending [artery]</td>
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<td>LAF</td>
<td>left anterior fascicle</td>
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<td>left coronary artery</td>
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<td>LCAT</td>
<td>lecithin-cholesterol acyltransferase</td>
</tr>
<tr>
<td>LCFA</td>
<td>long-chain fatty acid</td>
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<tr>
<td>LCL</td>
<td>lateral collateral ligament</td>
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<td>LGME</td>
<td>Liaison Committee on Medical Education</td>
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<td>loading dose</td>
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<td>median lethal dose</td>
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<td>lower esophageal sphincter</td>
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<td>leukocyte function–associated antigen</td>
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<td>lipopolysaccharide</td>
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<td>LR</td>
<td>lateral rectus [muscle]</td>
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<td>LT</td>
<td>labile toxin leukotriene</td>
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<td>left ventricle, left ventricular</td>
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<td>Lys</td>
<td>lysine</td>
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<td>M&lt;sub&gt;1&lt;/sub&gt;-M&lt;sub&gt;5&lt;/sub&gt;</td>
<td>muscarinic (parasympathetic) ACh receptors</td>
</tr>
<tr>
<td>MAC</td>
<td>membrane attack complex, minimal alveolar concentration</td>
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<td>transforming growth factor</td>
</tr>
<tr>
<td>TGN</td>
<td>trans-Golgi network</td>
</tr>
<tr>
<td>Th cell</td>
<td>helper T cell</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofolic acid</td>
</tr>
<tr>
<td>TI</td>
<td>therapeutic index</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>TIBC</td>
<td>total iron-binding capacity</td>
</tr>
<tr>
<td>TIPS</td>
<td>transjugular intrahepatic portosystemic shunt</td>
</tr>
<tr>
<td>TLC</td>
<td>total lung capacity</td>
</tr>
<tr>
<td>Tm</td>
<td>maximum rate of transport</td>
</tr>
<tr>
<td>TMP</td>
<td>trimethoprim</td>
</tr>
<tr>
<td>TN</td>
<td>true negative</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TNM</td>
<td>tumor, node, metastases [staging]</td>
</tr>
<tr>
<td>TOEFL</td>
<td>Test of English as a Foreign Language</td>
</tr>
<tr>
<td>ToRChE/S</td>
<td>Toxoplasma gondii, rubella, CMV, HIV, HSV-2, syphilis</td>
</tr>
<tr>
<td>TP</td>
<td>true positive</td>
</tr>
<tr>
<td>tPA</td>
<td>tissue plasminogen activator</td>
</tr>
<tr>
<td>TPP</td>
<td>thiamine pyrophosphate</td>
</tr>
<tr>
<td>TPR</td>
<td>total peripheral resistance</td>
</tr>
<tr>
<td>TR</td>
<td>tricuspid regurgitation</td>
</tr>
<tr>
<td>TRAP</td>
<td>tetratrate-resistant acid phosphatase</td>
</tr>
<tr>
<td>TRH</td>
<td>thyrotropin-releasing hormone</td>
</tr>
<tr>
<td>ABBREVIATION</td>
<td>MEANING</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>tRNA</td>
<td>transfer ribonucleic acid</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid-stimulating hormone</td>
</tr>
<tr>
<td>TSI</td>
<td>triple sugar iron</td>
</tr>
<tr>
<td>TSS</td>
<td>toxic shock syndrome</td>
</tr>
<tr>
<td>TSST</td>
<td>toxic shock syndrome toxin</td>
</tr>
<tr>
<td>TTP</td>
<td>thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>TTR</td>
<td>transthyretin</td>
</tr>
<tr>
<td>TV</td>
<td>tidal volume</td>
</tr>
<tr>
<td>Tx</td>
<td>translation [factor]</td>
</tr>
<tr>
<td>TXA₂</td>
<td>thromboxane A₂</td>
</tr>
<tr>
<td>UGV</td>
<td>Underground Clinical Vignettes</td>
</tr>
<tr>
<td>UDP</td>
<td>uridine diphosphosphate</td>
</tr>
<tr>
<td>UMN</td>
<td>upper motor neuron</td>
</tr>
<tr>
<td>UMP</td>
<td>uridine monophosphosphate</td>
</tr>
<tr>
<td>UPD</td>
<td>uniparental disomy</td>
</tr>
<tr>
<td>URI</td>
<td>upper respiratory infection</td>
</tr>
<tr>
<td>USMLE</td>
<td>United States Medical Licensing Examination</td>
</tr>
<tr>
<td>UTE</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>UTP</td>
<td>uridine triphosphate</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>V₁, V₂</td>
<td>Vasopressin receptors</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affairs</td>
</tr>
<tr>
<td>VC</td>
<td>vital capacity</td>
</tr>
<tr>
<td>V₄</td>
<td>volume of distribution</td>
</tr>
<tr>
<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>
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<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>MEANING</th>
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<tbody>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>V₄H</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>VJ</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>V̇max</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, nystatin [media]</td>
</tr>
<tr>
<td>V/Q</td>
<td>ventilation/perfusion [ratio]</td>
</tr>
<tr>
<td>VRE</td>
<td>vancomycin-resistant enterococcus</td>
</tr>
<tr>
<td>VSD</td>
<td>ventricular septal defect</td>
</tr>
<tr>
<td>V₁</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>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>VMAT</td>
<td>vesicular monoamine transporter</td>
</tr>
<tr>
<td>XR</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>XX</td>
<td>normal complement of sex chromosomes for female</td>
</tr>
<tr>
<td>XY</td>
<td>normal complement of sex chromosomes for male</td>
</tr>
<tr>
<td>ZDV</td>
<td>zidovudine [formerly AZT]</td>
</tr>
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Biochemistry

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110 **Stains:** Image D. *Cryptococcus neoformans* on India ink stain. Courtesy of the US Department of Health and Human Services.

110 **Stains:** Image E. *Coccioides immitis* on silver stain. Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

122 **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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120 **Streptococcus pneumoniae.** Courtesy of the US Department of Health and Human Services and Dr. Mike Miller.

120 **Streptococcus pyogenes** (group A streptococci). Gram stain. This image is a derivative work, adapted from the following source, available under [GFDL] at https://en.wikipedia.org/wiki/Streptococcus_pyogenes. Courtesy of Y. Yambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [GFDL].

121 **Bacillus anthracis.** Ulcer with black eschar. Courtesy of the US Department of Health and Human Services and James H. Steele.

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149 Herpesviruses: Image B. Herpes labialis. [source] Courtesy of the US Department of Health and Human Services and Dr. Herrmann.

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Immunology

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217  Necrosis: Image A. Coagulative necrosis. Courtesy of the US Department of Health and Human Services and Dr. Steven Rosenberg.


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233 **Common metastases: Image B.** Thyroid cancer metastasis to brain. Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.

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**Cardiovascular**

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Hematology and Oncology


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**SECTION IV**

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Renal

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