

# FIRST AID FOR THE<sup>®</sup> INTERNAL MEDICINE BOARDS



FOURTH EDITION

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**Hundreds of full-color clinical images and tables**

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Education

Tao Le • Thomas E. Baudendistel  
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# FIRST AID FOR THE®

# Internal Medicine Boards

## Fourth Edition

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ISBN: 978-1-25-983504-9

MHID: 1-25-983504-9.

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-983503-2,  
MHID: 1-25-983503-0.

eBook conversion by codeMantra

Version 1.0

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## **DEDICATION**

To the contributors to this and future editions, who took time to share their knowledge, insight, and humor for the benefit of residents and clinicians.

*and*

To our families, friends, and loved ones, who endured  
and assisted in the task of assembling this guide.

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# Preface

With this revised and expanded edition of *First Aid for the Internal Medicine Boards*, we hope to provide residents and clinicians with the most useful and up-to-date preparation guide for the American Board of Internal Medicine (ABIM) certification and recertification exams. This edition represents an outstanding effort by a talented group of authors and includes the following:

- Concise summaries of high-yield board-testable topics
- Hundreds of clinical images, tables, diagrams, and illustrations
- Short case-based questions to test your clinical knowledge
- Mnemonics throughout, making learning memorable and fun

We invite you to share your thoughts and ideas to help us improve *First Aid for the Internal Medicine Boards*. See How to Contribute, p. xiii.

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# Acknowledgments

This has been a collaborative project from the start. We gratefully acknowledge the thoughtful comments, corrections, and advice of the residents, international medical graduates, and faculty who have supported the authors in the development of *First Aid for the Internal Medicine Boards*.

For support and encouragement throughout the process, we are grateful to Thao Pham.

Thanks to our publisher, McGraw-Hill, for the valuable assistance of their staff. For enthusiasm, support, and commitment to this challenging project, thanks to Bob Boehringer. For outstanding editorial support, we thank Linda Geisler, Emma Underdown, Catherine Johnson, and Louise Petersen. We also want to thank Artemisa Gogollari, Susan Mazik, Virginia Abbott, Marvin Bundo, and Hans Neuhart for superb illustration work. A special thanks to Rainbow Graphics, especially David Hommel, for remarkable editorial and production work.

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# How to Contribute

To continue to produce a high-yield review source for the ABIM exam, you are invited to submit any suggestions or corrections. We also offer **paid internships** in medical education and publishing ranging from 3 months to 1 year (see below for details). Please send us your suggestions for

- Study and test-taking strategies for the ABIM
- New facts, mnemonics, diagrams, and illustrations
- Low-yield topics to remove

For each entry incorporated into the next edition, you will receive a gift card worth up to \$10, as well as personal acknowledgment in the next edition. Diagrams, tables, partial entries, updates, corrections, and study hints are also appreciated, and 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.

The preferred way to submit entries, suggestions, or corrections is via our blog at [www.firstaidteam.com](http://www.firstaidteam.com) or e-mail at [firstaidteam@yahoo.com](mailto:firstaidteam@yahoo.com). Please include your name, address, institutional affiliation, phone number, and e-mail address (if different from the address of origin).

## NOTE TO CONTRIBUTORS

All entries become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. In the event that similar or duplicate entries are received, only the first entry received will be used. Include a reference to a standard textbook to facilitate verification of the fact. Please follow the style, punctuation, and format of this edition if possible.

## INTERNSHIP OPPORTUNITIES

The author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated physicians. Internships may range from 3 months (eg, 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. Writing/editing experience, familiarity with Microsoft Word, and Internet access are desired. For more information, e-mail a résumé or a short description of your experience along with a cover letter to [firstaidteam@yahoo.com](mailto:firstaidteam@yahoo.com).

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## Introduction

For house officers, the American Board of Internal Medicine (ABIM) certification exam represents the culmination of 3 years of diligence and hard work. For practicing physicians, it is part of the maintenance-of-certification (MOC) process. However, the certification and recertification process represents far more than just another set of exams in a series of costly tests. To your patients, it means that you have attained the level of clinical knowledge and competency necessary for the provision of good clinical care. In fact, a poll conducted for the ABIM showed that about 72% of adult patients are aware of their physicians' board-certification status.

### KEY FACT

The majority of your patients will be aware of your certification status.

## ABIM—The Basics

### HOW DO I REGISTER TO TAKE THE EXAM?

The ABIM exam is usually held in August and registration starts 6 months prior, from December to February. You can register for the ABIM exam online by going to [www.abim.org](http://www.abim.org) and following the instructions to sign in. The current registration fee for the exam, as of 2017, is \$1365. If you miss the application deadline, a \$400 nonrefundable late fee is tacked on. There is also an international test-center fee of \$500. Please visit the ABIM Web site for the most up-to-date fees and policies.

### KEY FACT

Register early to avoid an extra \$400 late fee.

### WHAT IF I NEED TO CANCEL THE EXAM OR CHANGE TEST CENTERS?

ABIM currently provides partial refunds if a written cancellation is received before certain deadlines. You can also change your test center by providing a written request before a specific deadline. Be sure to check the ABIM Web site for the latest information on its refund and cancellation policies and for the most recent list of testing centers near you.

### HOW IS THE ABIM EXAM STRUCTURED?

The ABIM exam has been a 1-day computer-based test (CBT). The exam is divided into four 2-hour sections. You have 100 minutes of optional break time that can be taken in between the sections. Each section has a maximum of 60 questions, for a total of 240 questions. Images (blood smears, radiographs, ECGs, patient photos), videos, and audio examples are embedded in certain questions. Headphones are provided. During the time allotted for each block, examinees can answer test questions in any order as well as review responses and change answers. However, examinees **cannot go back and change answers from previous blocks**. The CBT format allows you to make your own notes, highlights, or strikethroughs on each question using a pop-up box, and it also permits you to click a box to designate which questions you might wish to review before the end of the session (time permitting). You will be given a 5-minute on-screen warning before the end of each block. An electronic calculator with commonly used internal medicine formulas and a lab value reference chart are provided. Please check the ABIM Web site for Web demos, updates, and details about the CBT format.

## WHAT TYPES OF QUESTIONS ARE ASKED?

All questions on the ABIM exam are **single-best-answer** types only. You will be presented with a scenario and a question followed by four to six options. Virtually all questions on the exam are vignette based. A substantial amount of extraneous information may be given, or a clinical scenario may be followed by a question that you might be able to answer without actually reading the case. Some questions require interpretation of photomicrographs, radiology studies, photographs of physical findings, and the like. It is your job to determine which information is superfluous and which is pertinent to the case at hand.

Question content is based on a content “blueprint” developed by ABIM (Table 1). This blueprint may change from year to year, so check the ABIM Web site for the latest information. About 75% of the **primary content** focuses on traditional subspecialties such as cardiology and gastroenterology. The remaining 25% pertains to certain outpatient or related specialties and to subspecialties such as allergy/immunology, dermatology, and psychiatry. There are also **cross-content** questions that may integrate information from multiple primary content areas.



### KEY FACT

Virtually all questions are case based.

TABLE 1. ABIM Certification Blueprint

PRIMARY CONTENT AREAS	RELATIVE PROPORTIONS
Cardiovascular disease	14%
Endocrinology, diabetes, and metabolism	9%
Gastroenterology	9%
Infectious disease	9%
Pulmonary disease	9%
Rheumatology and orthopedics	9%
Hematology	6%
Nephrology and urology	6%
Oncology	6%
Neurology	4%
Psychiatry	4%
Dermatology	3%
Geriatric syndromes	3%
Obstetrics and gynecology	3%
Allergy and immunology	2%
Miscellaneous	2%
Ophthalmology	1%
Otolaryngology	1%
<b>Total</b>	100%

(continues)

**TABLE 1. ABIM Certification Blueprint (*continued*)**

CROSS-CONTENT AREAS	RELATIVE PROPORTIONS
Critical care medicine	10%
Geriatric medicine	10%
Prevention	6%
Women's health	6%
Clinical epidemiology	3%
Ethics	3%
Nutrition	3%
Palliative/end-of-life care	3%
Adolescent medicine	2%
Occupational medicine	2%
Patient safety	2%
Substance abuse	2%

Data from [www.abim.org](http://www.abim.org), 2017.

### HOW ARE THE SCORES REPORTED?

Passing scores are established before the administration of the ABIM exam, so your status will not be influenced by the relative performance of others taking the test with you. The scoring and reporting of test results may take up to **3 months**. Once your score has been determined, however, your pass/fail status will be posted on the ABIM Web site and accessible to registered users, and it will be e-mailed to you.

Your score report will give you a “pass/fail” decision; the overall number of questions you answered correctly with a corresponding percentile; and the number of questions you answered correctly with a corresponding percentile for the primary and cross-content subject areas noted in the blueprint. Each year, between **20 and 40 questions** on the exam do not count toward your final score. Again, these may be “experimental” questions or questions that are subsequently disqualified. Historically, between **85% and 94%** of first-time examinees pass on their first attempt (Table 2). About 90% of examinees who are recertifying pass on their first attempt, and some 97% are ultimately successful with multiple attempts. There is no limit on the number of times you can retake the exam if you fail.

**TABLE 2. Performance of First-Time Test Takers of Certification Examination in Internal Medicine**

YEAR	NUMBER TAKING	PERCENTAGE PASSED
2016	7853	90%
2015	7839	89%
2014	7601	87%
2013	7482	86%
2012	7303	85%

Data from [www.abim.org](http://www.abim.org), 2017.

## THE MAINTENANCE-OF-CERTIFICATION (MOC) EXAM

Physicians who have previously passed the ABIM exam are required to recertify every 10 years. The MOC exam is given twice per year, typically in April and October. It is a 1-day exam that consists of three modules lasting 2 hours each. Each module has a maximum of 60 multiple-choice questions for a total of 180 questions. The MOC exam is currently administered as a CBT at a Pearson VUE testing site. Performance on the MOC exam is similar to that of the certification exam. Since 2008, 85% of MOC test takers have passed on their first attempt, and 96% have ultimately passed (Table 3).

## TEST PREPARATION ADVICE

The good news about the ABIM exam is that it tends to focus on the diagnosis and management of diseases and on conditions that you have likely seen as a resident and should expect to see as an internal medicine specialist. Assuming that you have performed well as a resident, *First Aid* and a good source of practice questions may be all that you need to pass. However, you might consider using *First Aid* as a guide along with multiple supplementary resources, such as a standard textbook, journal review articles, MKSAP, UWorld QBank, and electronic texts (eg, *UpToDate*) as part of your studies. Original research articles are low yield, and very new research (ie, research done less than 1-2 years before the exam) will not be tested. In addition, a number of high-quality board review courses are offered throughout the country. Such review courses are costly but can be of benefit to those who need some focus and discipline.

Ideally, you should begin your preparation early in your **last year of residency**, especially if you are starting a demanding job or fellowship right after residency. Cramming in the period between the end of residency and the exam is **not advisable**.

It's helpful to take a practice/diagnostic exam or use the results of the medicine in-service exam that residents take to guide studying and to figure out which areas you need to focus on. As you study, concentrate on the **nuances of management**, especially for difficult or complicated cases. For **common diseases**, learn both common and **uncommon presentations**; for **uncommon diseases**, focus on **classic presentations** and manifestations. Draw on the experiences of your residency training to anchor some of your learning. When you take the exam, you will realize that you've seen most of the clinical scenarios in your 3 years of wards, clinics, morning report, case conferences, and grand rounds.

## OTHER HIGH-YIELD AREAS

Focus on topic areas that are typically not emphasized during residency training but are board favorites. These include the following:

- Topics in outpatient specialties (eg, allergy, dermatology, ENT, ophthalmology)
- Formulas that are needed for quick recall (eg, alveolar gas, anion gap, creatinine clearance)
- Basic biostatistics (eg, sensitivity, specificity, positive predictive value, negative predictive value)
- Adverse effects of drugs



### KEY FACT

Check the ABIM Web site for the latest passing requirements.

**TABLE 3. MOC Internal Medicine Exam Performance**

YEAR	PERCENT PASSED
2016	91%
2015	88%
2014	80%
2013	78%
2012	84%

Data from [www.abim.org](http://www.abim.org), 2017.



### KEY FACT

Use a combination of *First Aid*, question banks, textbooks, and journal reviews.



### KEY FACT

The ABIM exam tends to focus on the horses, not the zebras.

**TEST-TAKING ADVICE**

By this point in your life, you have probably gained more test-taking expertise than you care to admit. Nevertheless, here are a few tips to keep in mind when taking the exam:

- For long vignette questions, read the question stem and scan the options; **then** go back and read the case. You may get your answer without having to read through the whole case.
- There's no penalty for guessing, so you should **never** leave a question blank.
- Good pacing is key. You need to leave adequate time to get to all the questions. Even though you are allotted an average of 2 minutes per question, you should aim for a pace of 90 to 100 seconds per question. If you don't know the answer within a short period, make an educated guess and move on.
- It's okay to **second-guess** yourself. Research shows that our "second hunches" tend to be better than our first guesses.
- Don't panic when you confront "impossible" questions. These may be **experimental questions** that won't count toward your score. So again, take your best guess and move on.
- Note the age and race of the patient in each clinical scenario. When ethnicity is given, it is often relevant. Know these well, especially for more common diagnoses.
- Remember that questions often describe clinical findings rather than naming eponyms (eg, they cite "tender, erythematous bumps in the pads of the finger" instead of "Osler's nodes").
- Manage your break time. On exam day, it's important to return to the test area at least 10 to 15 minutes before your break ends to make sure the testing center official has time to check in all test takers.

**KEY FACT**

Never leave a question blank! Remember that there is no penalty for guessing.

## Testing and Licensing Agencies

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# CHAPTER 1

# Allergy and Immunology

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## MNEMONIC

**Gell-Coombs classification system—**

### ACID

Anaphylactic: type I

Cytotoxic: type II

Immune complex: type III

Delayed hypersensitivity: type IV

## Gell and Coombs Classification of Immunologic Reactions

The Gell and Coombs Classification is the traditional framework that is used to describe immune-mediated reactions. It is not inclusive of all complex immune processes.

### TYPE I: IMMEDIATE REACTIONS (IGE MEDIATED)

In type I (immediate) reactions, specific antigen exposure causes **cross-linking of IgE on mast cell/basophil surfaces**, leading to the release of histamine, leukotrienes, prostaglandins, and **tryptase**:

- Mediator release leads to symptoms of **urticaria, angioedema, rhinitis, wheezing, diarrhea, vomiting, hypotension**, and may result in **anaphylaxis**, usually within minutes of antigen exposure.
- Late-phase type I reactions may cause **recurrence in symptoms 4 to 8 hours** after exposure.
- Clinical examples: urticaria, allergic rhinitis, insect venom allergy, many drug/food reactions.

### TYPE II: CYTOTOXIC REACTIONS

Type II (cytotoxic) reactions are mediated by **antibodies**, primarily IgG and IgM, directed at **cell surface or tissue antigens**. Antigens may be native, foreign, or haptens (small foreign particles attached to larger native molecules):

- Antibodies **destroy cells** by opsonization (coating for phagocytosis), complement-mediated lysis, or antibody-dependent cellular cytotoxicity.
- Clinical examples: penicillin-induced autoimmune **hemolytic anemia** (directed at cell surface), Goodpasture disease (directed at tissue antigen—basement membrane), myasthenia gravis (directed at tissue antigen—acetylcholine [ACh] receptor on muscle cells).

### TYPE III: IMMUNE COMPLEX REACTIONS

In type III (immune complex) reactions, exposure to antigen in genetically predisposed individuals causes **antigen-antibody complex formation**:

- Antigen-antibody complexes **activate complement and neutrophil infiltration**, leading to tissue inflammation that most commonly affects the **skin, kidneys, joints, and lymphoreticular system**.
- Clinically presents with symptoms of “**serum sickness**” **10 to 14 days** after exposure; most frequently caused by **β-lactam antibiotics** or nonhuman antiserum (antithymocyte globulin, antivenoms).
- Clinical examples: serum sickness, immune complex mediated vasculitis.

### TYPE IV: DELAYED HYPERSENSITIVITY REACTIONS (T-CELL MEDIATED)

In type IV (delayed hypersensitivity) reactions, exposure to antigen causes direct activation of **sensitized T cells**, usually CD4+ cells:

- T-cell activation causes tissue **inflammation 48 to 96 hours** after exposure.
- Clinical examples: allergic contact dermatitis (eg, from poison ivy), tuberculin sensitivity.

## Diagnostic Testing in Allergy

### ALLERGY SKIN TESTING

- Allergy skin testing is a confirmatory test for the presence of **allergen-specific IgE antibody**. Types include:
  - **Prick-puncture skin testing:** Adequate for most purposes. A drop of allergen extract is placed on the skin surface, and epidermal puncture is performed with a specialized needle.
  - **Intradermal skin testing:** Used for venom and penicillin testing; allergen is injected intracutaneously.
- All skin testing should use  $\oplus$  (histamine) and  $\ominus$  (saline) controls. Skin testing **wheal-and-flare reactions** are measured 15 to 20 minutes after placement.

### LABORATORY ALLERGY TESTING

- Radioallergosorbent serologic testing (**RAST**) is performed to confirm the presence of **allergen-specific IgE antibody**:
  - Results are generally comparable to skin testing for pollen- and food-specific IgE.
  - Recommended when the subject has **anaphylactic sensitivity** to the antigen; useful when skin testing is either not available or not possible because of skin conditions or interfering medications (eg, diffuse eczema or antihistamine use).
  - RAST testing alone is generally **not** adequate for **venom or drug allergy testing**.



### KEY FACT

Consider lab testing instead of skin testing in patients with severe anaphylactic reaction, interfering dermatologic disease, or history of ongoing antihistamine use (can cause false negatives for skin test).

### DELAYED-TYPE HYPERSENSITIVITY SKIN TESTING

- Delayed-type hypersensitivity skin testing is an effective screening test for functional **cell-mediated immunity** (type IV hypersensitivity reaction):
  - Involves **intradermal injection** of 0.1 mL of **purified antigen**. The standard panel includes *Candida*, mumps, tetanus toxoid, and PPD.
  - The injection site is examined for **induration 48 hours** after injection.
  - Approximately 95% of normal subjects will respond to one of the above-mentioned antigens.
  - The absence of a response suggests deficient cell-mediated immunity or anergy.

### ALLERGEN PATCH TESTING

Allergen patch testing is the appropriate diagnostic tool for **allergic contact dermatitis**:

- Suspected substances are applied to the skin with adhesive test strips for 48 hours.
- The skin site is examined 48 and 72 hours after application for evidence of erythema, edema, and vesiculation (reproduction of contact dermatitis).

## Diagnostic Testing in Immunology

### COMPLEMENT DEFICIENCY TESTING

- The complement pathway is important in various aspects of host defense, including inducing the humoral immune response, improving phagocytosis, and clearing of immune complexes and apoptotic cells.
- The complement pathway consists of the **classic** (immune complex mediated), **alternative** (induced by microbial surfaces), and **lectin** (induced by mannose-binding lectin on microbial surfaces) pathways (Figure 1.1).
- CH50** is a screening test for the **classic complement pathway**.
  - All nine elements of C1 to C9 are required to produce a normal CH50.
  - A normal CH50 does not exclude the possibility of low C3 or C4.
- Deficiencies that lead to disease include:
  - C1-inhibitor (C1-INH):** Hereditary angioedema.
  - C2, C3, C4:** Recurrent sinopulmonary infections (encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*).
  - C1, C2, C4: SLE.**
  - C1, C3, C4: Pyogenic bacterial infections.**
  - C5 to C9: *Neisseria* infections.**



### KEY FACT

Think of **terminal complement deficiency (C5-C9)** in an otherwise healthy patient presenting with **recurrent neisserial meningitis**. Test for total hemolytic complement (CH50) assay, and if low, check individual complement levels.

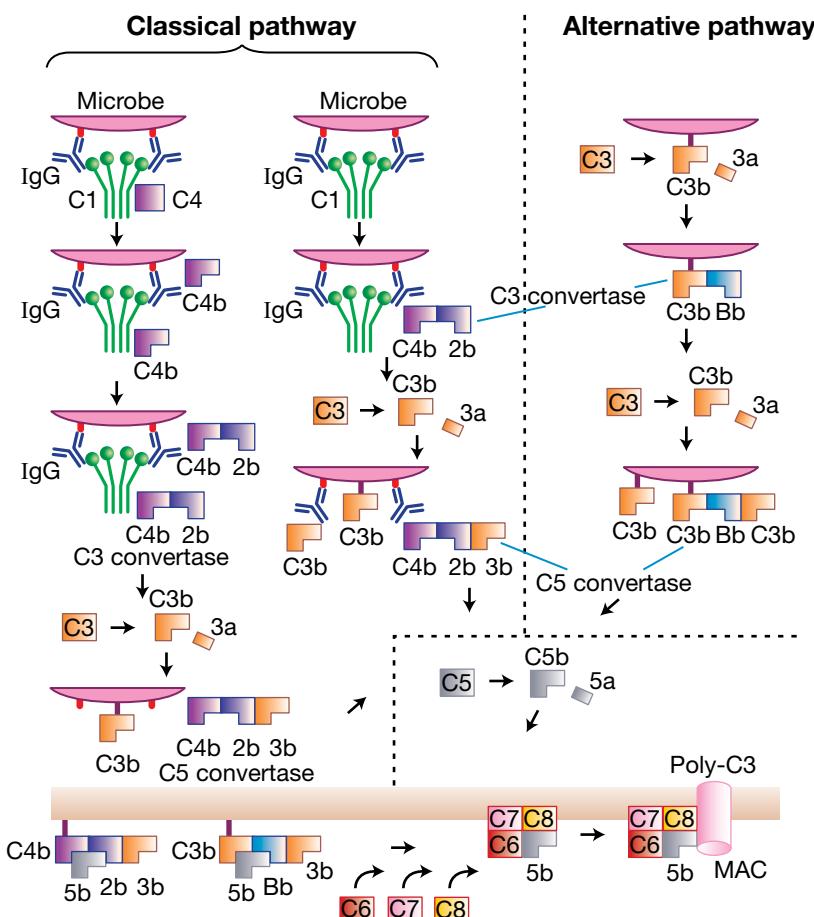


FIGURE 1.1. Complement cascade. (Reproduced with permission from USMLE-Rx.com.)

## HUMORAL (B-CELL) AND CELLULAR (T-CELL) DEFICIENCY TESTING

Testing for B- and T-cell deficiency is as follows:

- CD19: For B-cell immunity.
- IgG, IgM, IgA, IgE: For antibody.
- CD3, CD4, CD8: For T-cell immunity.
- CD16, CD56: For natural killer cell immunity.

## 1° Immunodeficiency in Adults

Adult 1° immunodeficiencies (non-HIV) generally present in the second or third decade of life with **recurrent respiratory infections** due to antibody deficiency (hypogammaglobulinemia). Conditions include **common variable immunodeficiency** (CVID), **selective IgA deficiency** (most common, with an incidence of 1:500), IgG subclass deficiency, and selective antibody deficiency with normal immunoglobulins (SADNI).

### Symptoms

- Presents with frequent **respiratory tract infections** (sinusitis, otitis, pneumonia); a need for IV or prolonged oral antibiotic courses to clear infections; and **chronic GI symptoms** such as diarrhea, cramping abdominal pain, and malabsorption.
- Selective IgA deficiency is often asymptomatic.

### Exam

Nasal congestion and discharge; respiratory wheezing or rales; digital clubbing secondary to chronic lung disease; lymphadenopathy; splenomegaly, dysmorphic facies if there is an associated syndrome (eg, DiGeorge).

### Differential

- Hypogammaglobulinemia due to loss (GI, renal).
- Hypogammaglobulinemia due to medications (immunosuppressants, anticonvulsants).
- HIV, CF, allergic respiratory disease.

### Diagnosis

Suspect in patients with a **history** of recurrent infection. Identify **antibody deficiency by laboratory testing**:

- Order quantitative immunoglobulins: Initially (IgG, IgA, IgM, IgE), after which IgG subclasses may be obtained.
- **CVID: Low IgG (<500 mg/dL)**, usually with low IgA and/or IgM. Also with poor antibody response to vaccines.
- **Selective IgA deficiency: Absence of IgA (<7 mg/dL) with normal IgG and IgM** (the most common 1° immunodeficiency).
- **IgG subclass deficiency:** Low levels of one or more IgG subclasses (IgG1, IgG2, IgG3, IgG4). Clinical significance is unclear unless vaccine response impaired.
- **SADNI:** Normal immunoglobulin levels with failure to produce protective antibody levels against specific immunizations (most commonly pneumococcus; rarely tetanus).
- **Exclude other causes of hypogammaglobulinemia:** Antibody loss due to protein-losing enteropathy or nephropathy, medication (especially steroids), and lymphopenia.

### KEY FACT

Suspect **IgA deficiency** in a patient with an anaphylactic reaction that occurs seconds to minutes after a blood transfusion. Treat by immediately administering epinephrine and discontinuing the transfusion.



### QUESTION

A 32-year-old man presents for cough and fever. CXR reveals right middle lobe pneumonia. This is the fourth time in the last 18 months that he has had pneumonia requiring antibiotics; he has also been treated for several sinus infections over this time. Laboratory evaluation shows normal IgG levels and undetectable IgA level. What is the appropriate treatment for this patient?

## Management

- **CVID:**
  - **IVIG** 400 to 500 mg/kg monthly.
  - Aggressive treatment of infections.
  - Monitor lung function; pulmonary hygiene for bronchiectasis. Also monitor for malignancies and autoimmune disease.
- **Selective IgA deficiency:**
  - Antibiotic therapy and/or prophylaxis as necessary.
  - **IVIG** is contraindicated owing to possible anti-IgA, IgG, or IgE antibody.
  - Patients should receive only washed blood products due to the risk of anaphylaxis with exposure to IgA.
- **IgG subclass deficiency and SADNI:**
  - Antibiotic therapy as needed.
  - IVIG is reserved for rare patients with significant infection despite preventive antibiotics.

## Complications

- **CVID:** Variable T-cell deficiency, ↑ risk of **GI malignancy** (gastric cancer, small bowel lymphoma), **bronchiectasis**, **lymphoproliferative disease**, noncaseating granulomas of internal organs, **autoimmune disease**.
- **Selective IgA deficiency:** Celiac disease, lymphoproliferative disease, **GI malignancy** (gastric cancer, small bowel lymphoma), **autoimmune disease**.

## Anaphylaxis

A systemic type I (IgE-mediated) hypersensitivity reaction that is often life-threatening. Requires **previous exposure** (known or unknown) for sensitization. Risk factors include parenteral antigen exposure and repeated interrupted antigen exposure. Common causes are **foods** (especially peanuts and shellfish), **drugs** (especially penicillin), **latex**, and **stinging insects**.

### Symptoms/Exam

- Skin erythema, pruritus, urticaria, angioedema, laryngeal edema, wheezing, chest tightness, cramping abdominal pain, nausea, vomiting, diarrhea, diaphoresis, dizziness, a sense of “impending doom,” hypotension, syncope, and shock.
- Symptoms most frequently appear **seconds to minutes after exposure** but may be delayed up to 2 hours for ingested agents.
- Exam findings: Urticaria, angioedema, flushing, wheezing, stridor, diaphoresis, hypotension, tachycardia.

### Diagnosis

- **Diagnosis is clinical.** Usually requires two or more of the following symptoms: respiratory compromise (eg, dyspnea, wheeze), hypotension, urticaria, and/or persistent GI symptoms in the context of an allergen exposure are key.
- ↑ **serum tryptase** drawn 30 minutes to three hours after onset can help confirm mast cell release (but is also elevated in anaphylactoid reactions).
- **Presence of allergen-specific IgE antibody** by skin or RAST testing (best performed one month after event). This is negative in anaphylactoid reactions.

## Management

- **Epinephrine 1:1000 0.3 mL IM:** Repeat every 15 minutes as needed. Give IV epinephrine 1:10,000 0.3 mL only if anaphylactic shock.
- **H<sub>1</sub> antagonist (diphenhydramine 50 mg IV/IM/PO).**
- **Corticosteroids** (prednisone 60 mg or equivalent) IV/IM/PO: Reduce late-phase recurrence of symptoms 4 to 8 hours later.



### KEY FACT

Anaphylaxis is a highly likely diagnosis in the following clinical scenarios:

- Acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both PLUS respiratory compromise or reduced BP (or associated symptoms of end-organ dysfunction).
- Acute illness (minutes to hours) after exposure to a likely allergen for that patient that manifests with two or more of the following: skin/mucosal involvement, respiratory compromise, reduced BP or associated symptoms, GI symptoms.
- Reduced BP (minutes to hours) after exposure to known allergen for that patient; typically ↓ systolic BP (age specific) or >30% ↓ in systolic BP.

(Data from Bjornsson HM, et al. Improving diagnostic accuracy of anaphylaxis in the acute care setting. West J Emerg Med. 2010;11(5):456-461.)



### ANSWER

Vaccination and antibiotics as needed for **selective IgA deficiency**. There is **no role for IVIG** given its unclear benefit and potential adverse reactions in this condition. Monitor patients for potential complications such as autoimmune and lymphoproliferative diseases and celiac disease. Patients with evidence of celiac disease by history will have ⊖ serologies (which are IgA antibodies) and will require endoscopy for diagnosis.

- **Maintain airway:** O<sub>2</sub>, inhaled bronchodilators (eg, albuterol) for wheezing; intubation if necessary.
- Rapid IV fluids if the patient is hypotensive.
- Vasopressor medications in the presence of persistent hypotension.
- Consider **glucagon** for patients on  $\beta$ -blockers whose symptoms are refractory to therapy.
- Monitor patients for 8 to 12 hours after the reaction.
- Ensure that patients have access to injectable epinephrine and antihistamines on discharge.

**KEY FACT**

Treat anaphylaxis with prompt administration of **epinephrine**. Mortality is strongly associated with delays in epinephrine administration.

**Complications**

Respiratory obstruction, cardiovascular collapse, death.

## Anaphylactoid Reactions

Clinically indistinguishable from anaphylactic reactions, but caused by **nonspecific mast cell activation (not IgE mediated)**. May occur with initial exposure to medication. Common causes include **radiocontrast media, vancomycin, amphotericin, opiates, and general anesthetics** (induction agents and muscle relaxants).

- **Diagnosis** may be confirmed with:
  - ↑ serum tryptase drawn 30 minutes to 3 hours after onset helps confirm mast cell release.
  - **Absence of allergen-specific IgE antibody** to suspected antigens by skin or RAST testing (best performed one month after the event).
- **Management:** The same as that for anaphylaxis, although epinephrine reserved only for true anaphylaxis if known.
- Anaphylactoid reactions are **generally preventable with pretreatment** through use of corticosteroids and antihistamines. Pretreatment is recommended for patients with a history of reactions to radiocontrast media. May be avoided if the following is applied:
  - Slow infusion rate for **vancomycin**.
  - Use low-osmolality forms of **radiocontrast media**.

## Mastocytosis

A rare disease characterized by **excessive numbers of mast cells** in the skin, internal organs, and bone marrow. Caused by a somatic **KIT gene mutation**. Has variable severity ranging from the isolated cutaneous form to indolent systemic disease to aggressive lymphoma-like disease or mast cell leukemia. Children tend to have cutaneous forms that improve/resolve; adults tend to present with systemic symptoms that persist.

**Symptoms/Exam**

**Pruritus and flushing are characteristic.** Other symptoms include urticaria, diarrhea, nausea, vomiting, abdominal pain, headache, hypotension, anaphylaxis.

Presents with **urticaria pigmentosa** (a pigmented macular skin rash that urticates with stroking) as well as systemic disease with shock, lymphadenopathy, hepatomegaly, and splenomegaly.

**KEY FACT**

Mastocytosis should be suspected when an **urticular rash** is accompanied by abdominal (eg, diarrhea), lymphadenopathy (eg, splenomegaly), or anaphylactic signs and symptoms.

**Differential**

- **Anaphylaxis:** Drugs, foods, venoms, exercise induced, idiopathic.
- **Flushing syndromes:** Scombroid, carcinoid, VIPoma, pheochromocytoma.
- **Angioedema:** Hereditary or acquired.

### Diagnosis

Diagnosed by the presence of one major plus one minor or three minor criteria.

- **Major criteria:** Characteristic multifocal dense **infiltrates of mast cells on bone marrow biopsy**.
- **Minor criteria:**
  - Spindle-shaped morphology of mast cells on **tissue biopsy**.
  - Detection of the **c-KIT mutation**.
  - **Flow cytometry** of bone marrow mast cells coexpressing CD117, CD2, and CD25.
  - Serum tryptase levels of >20 ng/mL.

### KEY FACT

**Serum tryptase** is a good screening test for mastocytosis versus anaphylaxis. Mastocytosis causes constant elevations in tryptase, whereas anaphylaxis causes episodic elevations.

### Management

- H<sub>1</sub> and H<sub>2</sub> antagonists.
- Epinephrine for episodes of anaphylaxis.
- Topical steroids for skin lesions; oral corticosteroids for advanced disease.
- Hematopoietic stem cell transplantation or chemotherapy for patients with aggressive disease or associated hematologic disorders.

## Food Allergy

True (IgE-mediated) food allergy in adults is most commonly caused by **peanuts, crustaceans, tree nuts, and fish**. Sensitivities to these foods tend to be lifelong. Multiple food allergies are rare in adults. Anaphylactic signs and symptoms occur **minutes to 2 hours after ingestion**.

### Differential

- Nonallergic food intolerance (lactase deficiency, celiac disease, symptoms due to vasoactive amines).
- Food poisoning, including scombroid.
- Eosinophilic gastroenteritis.

### Diagnosis

- Anaphylaxis may be confirmed with ↑ serum tryptase if the test is conducted 30 minutes to 3 hours after the reaction.
- $\oplus$  **allergy skin or RAST tests** to food antigen.
- Conduct a double-blind placebo-controlled food challenge if the diagnosis is unclear.

### Management

- Treat anaphylaxis in an acute setting (see above).
- Eliminate implicated foods from the diet.
- Ensure patient access to injectable epinephrine.

## Stinging Insect Allergy

Allergic reactions occur with three major stinging insect families: **vespids** (yellow jackets, hornets, wasps), **apids** (honeybees and bumblebees), and **fire ants**. Reactions are classified as **local** (symptoms at the sting site) or **systemic** (anaphylactic).

## Symptoms/Exam

- **Local reaction:** Swelling and erythema; pain at the sting site lasting several hours.
- **Large local reaction:** Extensive swelling and erythema at the sting site lasting up to 1 week.
- **Systemic reaction:** Anaphylactic symptoms occurring within 15 minutes of sting.

## Differential

**Toxic venom reaction:** Results from large venom burden delivery by **multiple simultaneous stings**. The pharmacologic properties of venom may cause hypotension and shock.

## Diagnosis

- Systemic reactions may be confirmed by an ↑ serum tryptase if drawn 30 minutes to 3 hours after the reaction.
- Any systemic reaction should be confirmed with **venom-specific IgE** by **allergy skin or RAST testing** given the risk of recurrence with repeat stings. Testing should be performed several weeks after the reaction.

## Management

- **Large local:** Antihistamines; analgesics; a short prednisone course for severe or disabling local reactions.
- **Systemic:** Treatment is the same as that for **anaphylaxis**.
- **Venom immunotherapy:** Recommended for patients with a history of systemic reaction and  $\oplus$  venom-specific IgE tests. Immunotherapy is 98% effective in preventing systemic allergic reactions on reexposure.
- Insect avoidance.
- Ensure patient access to antihistamines and injectable epinephrine.

## Drug Allergy

### IMMUNOLOGIC DRUG REACTION

Only a small portion of adverse drug reactions are drug hypersensitivity reactions (immune mediated), of which a smaller subset represents true drug allergy (IgE mediated). The most common is  **$\beta$ -lactam allergy**. Cross-reactivity with cephalosporins is low (1%-3%); cross-reactivity with carbapenems is very low.

Note: there are also more severe drug allergies that are not IgE mediated (eg, Stevens-Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN] and drug reaction with eosinophilia and systemic symptoms [DRESS]). See the Dermatology chapter for additional information.

## Symptoms/Exam

Immunologic drug reactions may present with a wide range of symptoms. Common symptoms include urticaria, angioedema, morbilliform rash, blistering mucocutaneous lesions, cough, dyspnea, wheezing, anaphylaxis, arthralgias, fever, and lymphadenopathy.

- **Dermatologic findings:** Urticaria, angioedema, morbilliform rash, purpura, petechiae, exfoliative dermatitis, bullous skin lesions.
- **Other:** Wheezing, lymphadenopathy, jaundice, fever.

### KEY FACT

Any adult who reacts systemically to an insect sting, regardless of reaction severity, should be evaluated for **venom immunotherapy**.

### KEY FACT

People who have an anaphylactic reaction to insect stings should be educated about their venom sensitivity and provided with self-administered injectable epinephrine.



### QUESTION

A 32-year-old man with HIV is diagnosed with neurosyphilis. He states that he had difficulty breathing when he received penicillin as a child. He is admitted for treatment, and a skin test confirms a positive reaction to penicillin. How would you manage this patient?

**Differential****KEY FACT**

The vast majority of adverse drug reactions are due to predictable drug effects and do not represent true drug allergy.

**KEY FACT**

Drugs can result in various allergic skin reactions. Drug allergy skin testing is a method of diagnosing IgE-mediated reactions to various drugs.

**Diagnosis**

- **Nonimmunologic adverse drug reaction:** Dose-related toxicity, pharmacologic side effects, drug-drug interactions.
  - **Pseudoallergic reaction:** Direct mast cell release ( opiates, vancomycin, radiocontrast media, NSAIDs, aspirin). Not IgE-mediated. No skin testing available. Remember the triad of rhinosinusitis, nasal polyps, and asthma specifically for aspirin-exacerbated respiratory disease.
- Based on clinical judgment using the following **general criteria**:
    - The patient's symptoms are consistent with an immunologic drug reaction.
    - The patient was administered a drug known to cause the symptoms.
    - The temporal sequence of drug administration and the appearance of symptoms is consistent with a drug reaction. Cessation of the drug results in resolution of the symptoms in most cases.
    - Other causes of the symptoms have effectively been excluded.
  - When available, **diagnostic testing** supportive of an immunologic mechanism to explain the drug reaction (Table 1.1). The **drug challenge procedure** is the definitive diagnostic test but should be performed only by an experienced clinician if an **absolute indication** exists for the drug.

**TABLE 1.1. Diagnostic Testing and Therapy for Drug Hypersensitivity**

IMMUNOLOGIC REACTION	CLINICAL MANIFESTATIONS	LABORATORY TESTS	THERAPEUTIC CONSIDERATIONS
Type I	Anaphylaxis, angioedema, urticaria, bronchospasm	Skin testing, RAST testing, serum tryptase	Discontinue drug; epinephrine, antihistamines, systemic corticosteroids, bronchodilators; inpatient monitoring if severe
Type II	Hemolytic anemia, thrombocytopenia, neutropenia	Direct/indirect Coombs test	Discontinue drug; consider systemic corticosteroids; transfusion in severe cases
Type III	Serum sickness, vasculitis, glomerulonephritis	Immune complexes, ESR, complement studies, ANA/ANCA, C-reactive protein, tissue biopsy for immunofluorescence studies	Discontinue drug; NSAIDs, antihistamines; systemic corticosteroids or plasmapheresis if severe
Type IV	Allergic contact dermatitis; maculopapular drug rash <sup>a</sup>	Patch testing; lymphocyte proliferation assay <sup>b</sup>	Discontinue drug; topical corticosteroids, antihistamines; systemic corticosteroids if severe

<sup>a</sup>Suspected type IV reaction; mechanism not fully elucidated.

<sup>b</sup>Investigational test.

**A****ANSWER**

**Desensitization.** Since penicillin is the treatment of choice for neurosyphilis and he has confirmed IgE-mediated allergy to penicillin, the next step would be systematic desensitization. The patient would likely be admitted to the ICU, given incrementally increasing doses of penicillin, and monitored closely.

## Management

- **Discontinuation of the drug:**
  - In most instances, symptoms promptly resolve if the diagnosis is correct.
  - If the drug is absolutely indicated, refer the patient for **graded challenge/desensitization**.
- **Symptomatic treatment for specific symptoms:** Antihistamines, topical corticosteroids, bronchodilators; oral corticosteroids in severe cases.
- **Patient education:** Educate patients with regard to the risk of future reaction, drug avoidance, and cross-reactive medications.
- **Prevention (eg, for contrast allergy):** Premedicate with corticosteroids and antihistamines.
- **Desensitization** (consider for cases where there is no alternative option for effective therapy):
  - Induce tolerance by giving incrementally higher doses of the medication. This only works temporarily and repeat desensitization is necessary for future episodes.
  - Only helpful for IgE-mediated drug allergies and is **contraindicated** for cases of severe non-IgE-mediated reactions (SJS/TEN, DRESS).

## Complications

- **Fatal drug hypersensitivity:** Anaphylaxis, TEN.
- **“Multiple drug allergy syndrome”:** Lack of patient/physician understanding of adverse drug reactions can lead to multiple medication avoidance and restrictive, ineffective medical therapy.

## TRANSFUSION REACTIONS

Types of transfusion reactions are shown in Table 1.2.

- **Management:** For all types of transfusion reactions, **stop transfusion and notify blood bank**. Supportive care targeted to specific type of reaction.

**TABLE 1.2. Transfusion Reactions**

	PREVALENCE	CLINICAL MANIFESTATIONS	LABORATORY TESTS	THERAPEUTIC CONSIDERATIONS
Acute hemolytic	<1:250,000	Fever, hypotension, flank pain, renal failure <24 h after transfusion	ABO incompatibility (Ab positive against donor RBC)	Aggressive IVF, vasopressors
Delayed hemolytic	<1:100,000	Fever, flank pain, renal failure 5-7 days after transfusion	Allo-Abs against minor antigens (tested by blood bank)	Supportive. Important to know for future transfusions and special minor antigen matching
Febrile nonhemolytic	1:100	Fevers <6 h after transfusion	Abs against donor WBCs and cytokines	Acetaminophen
Transfusion-related acute lung injury	1:5000	Respiratory distress typically during transfusion, often with low-normal BP	Low B-natriuretic peptide (BNP) Pulmonary edema on CXR (noncardiogenic) Normal cardiac ejection fraction	Diuretics (inconsistent response)
Transfusion-associated circulatory overload	1:5000	Respiratory distress typically <6 h after transfusion, with normal-high BP	High BNP Pulmonary edema on CXR Low cardiac ejection fraction	Diuretics
Transfusion-related urticaria and anaphylaxis	1:100	Anaphylaxis, angioedema, urticaria, bronchospasm	Low IgA levels + anti-IgA	Diphenhydramine If anaphylaxis: epinephrine, ± corticosteroids

## Skin Allergy

### URTICARIA AND ANGIOEDEMA

Angioedema and urticaria are characterized by localized edema in the skin or mucous membranes. Distinguished as follows:

- Angioedema occurs deeper in the dermal or submucosal tissue, with severe soft tissue swelling due to inflammation-induced vascular permeability (Figure 1.2). Can be **histamine** (pruritus) or **bradykinin mediated** (no pruritus). Patients may have abdominal pain (bowel wall edema), scrotal edema. Common causes include food and medication allergies, bee stings.
- Urticaria (hives) are more superficial and typically last <24 hours. May be acute (<6 weeks of symptoms) or chronic (>6 weeks). Generally, **histamine mediated** (pruritus).
- **Hereditary angioedema** presents with **recurrent** episodes of angioedema without pruritus or urticaria.

#### KEY FACT

A patient with angioedema and well-controlled hypertension? Think ACEIs.

#### KEY FACT

Think of hereditary angioedema in a patient presenting with recurrent episodes of **angioedema without pruritus** or urticaria.

#### KEY FACT

It is important to distinguish urticarial vasculitis: Think hives lasting >24 hours in a fixed location. Diagnose by skin biopsy.

### Symptoms/Exam

Exam findings may include erythematous blanching skin wheals; soft tissue swelling as described above. No scarring or pigmentary changes can be seen at previously affected sites. Exam may be normal between symptomatic flares.

### Differential

- **IgE-mediated allergic reaction:** Food, medication, insect stings.
- **Non-IgE reactions:** ASA, narcotics, radiocontrast media.
- **Physical urticaria:** Pressure, vibratory, solar, cholinergic, local heat and cold.
- **Autoimmunity:** Vasculitis, associated thyroiditis, autoantibody for IgE receptor on mast cells.
- **Infections:** Mononucleosis, viral hepatitis, fungal and parasitic disease.
- **Idiopathic:** Accounts for most cases of chronic urticaria.
- **Isolated angioedema:** Consider hereditary angioedema or acquired angioedema (associated with vasculitis and neoplasms).
- **Other:** Dermatographism; cutaneous mastocytosis.



**FIGURE 1.2. Angioedema.** (A) Angioedema leading to closure of both eyes. (B) Sublingual angioedema. (Image A courtesy of Dr. James Heilman; image B reproduced from Marques A, et al. Postanesthetic severe oral angioedema in patient's taking angiotensin-converting enzyme inhibitor. *Case Rep Anesthesiol*. 2014;2014:693191.)

## Diagnosis

- The clinical history suggests diagnostic testing.
- Provocative testing for physical urticarias (ie, **ice cube test**, which induces urticaria by placing ice cube on skin for several minutes in cases of cold urticaria).
- Labs include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), skin biopsy (to exclude vasculitis or malignancy), and Fc epsilon receptor antibody or antithyroid antibodies if autoimmunity is suspected.
- Order a CBC with differential (look for eosinophils), a viral hepatitis panel, and a stool ova and parasites test if the history is suggestive of infection.
- In the setting of angioedema alone, obtain a **C1 esterase inhibitor (C1-INH) assay** to exclude hereditary angioedema; determine the C1q level to exclude acquired angioedema.

## Management

- For urticaria unless specified:
  - Avoid inciting exposure (eg, remove culprit medication) or treat the underlying condition if it is identified.
  - Antihistamines: Regular use of nonsedating H<sub>1</sub> antagonists is preferred. Sedating H<sub>1</sub> antagonists may also be used every night at bedtime.
  - H<sub>2</sub>-receptor blockers may be helpful adjunctive medication for moderate-to-severe symptoms.
- Other:
  - Oral corticosteroids for severe, refractory cases.
  - Epinephrine for life-threatening laryngeal edema (angioedema).
  - Danazol, stanozolol, C1-INH concentrate, recombinant C1-INHs, bradykinin B<sub>2</sub>-receptor antagonists, and kallikrein inhibitors (hereditary angioedema only).

## Complications

Laryngeal edema.

### ATOPIC DERMATITIS

A chronic inflammatory skin disease that is often associated with a personal or family history of atopy. Usually begins in childhood.

## Symptoms/Exam

- Characterized by intense **pruritus** and an erythematous papular rash typically occurring in the flexural areas of the elbows, knees, ankles, and neck (Figure 1.3). Pruritus precedes the rash (“**an itch that rashes**”).
- Presents with an erythematous papular rash in **flexural areas** as well as with excoriations, serous exudate, lichenification (if chronic). Other findings of atopic disease (boggy nasal mucosa, conjunctival erythema, expiratory wheezing).

## Differential

- Other dermatitis:** Seborrheic, irritant, contact, psoriasis.
- Neoplasia:** Cutaneous T-cell lymphoma.
- Infectious:** Scabies, candidiasis, tinea versicolor.
- Hyper-IgE syndrome:** Usually diagnosed in childhood.

## Diagnosis

- Readily made through the history and physical.
- Consider skin biopsy to rule out cutaneous T-cell lymphoma in new-onset eczema in an adult.

### KEY FACT

C1-INH deficiency is associated with angioedema but not urticaria.

### KEY FACT

When used regularly at adequate doses, antihistamines successfully treat most cases of urticaria.

### KEY FACT

In contrast to angioedema associated with anaphylaxis, hereditary angioedema does not respond to epinephrine. Treat with C1-INH concentrate acutely.

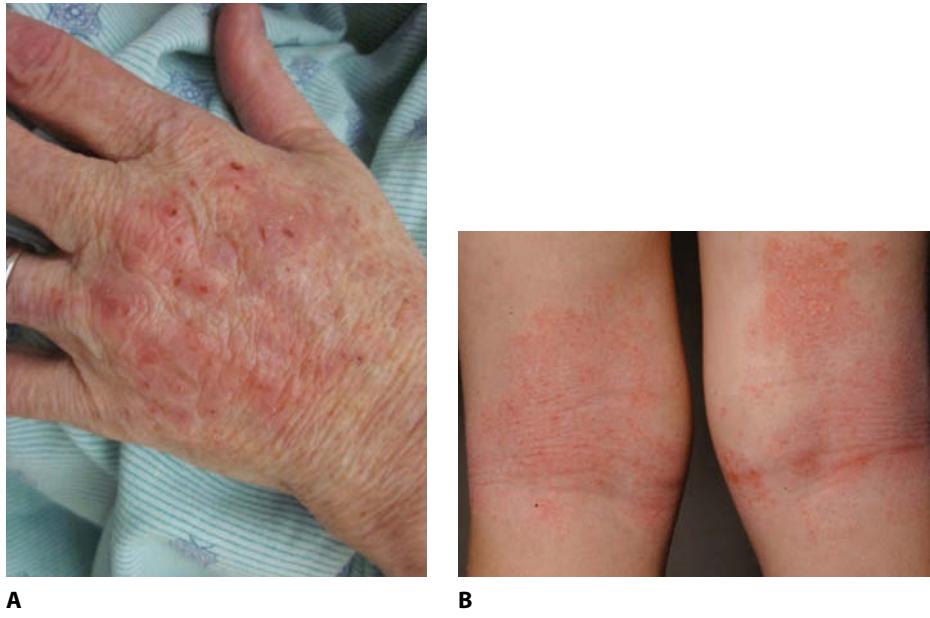
### KEY FACT

Angioedema can be life-threatening if it involves the airway. Treat with systemic epinephrine and glucocorticoids. Patient should carry injectable epinephrine at all times.



### QUESTION

A 35-year-old woman presents with persistent symptoms of allergic rhinitis. She has previously tried antihistamines, pseudoephedrine, and nasal corticosteroids, with only modest benefit. She returns for further evaluation. What is the best course of therapy for this patient?



**FIGURE 1.3. Atopic dermatitis.** (A) Eczema of the hand. (B) Typical lichenified atopic dermatitis in the knee folds. (Image A reproduced with permission from USMLE-Rx.com; image B reproduced from Salava A, et al. Role of the skin microbiome in atopic dermatitis. *Clin Transl Allergy*. 2014;4:33.)

### Management

- **Skin hydration:** Emollients are better than lotions.
- **Topical corticosteroids:** Medium-high potency for body, low potency for face (risk atrophy and steroid-induced acne).
- **Antihistamines** to reduce pruritus.
- Avoid skin irritants (eg, abrasive clothing, temperature extremes, harsh soaps).
- Avoid allergic triggers if identified (food [uncommon], aeroallergens).
- Treat bacterial, fungal, and viral **superinfection** as necessary.
- Topical **tacrolimus/pimecrolimus** and oral corticosteroids for severe disease.

### Complications

- **Chronic skin changes:** Scarring, hyperpigmentation.
- **Cutaneous infection:** Bacterial (primarily *S aureus*), viral (primarily HSV); risk of eczema vaccinatum with smallpox vaccine.

### ALLERGIC CONTACT DERMATITIS

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### ANSWER

Diagnostic allergy testing and/or immunotherapy. Empiric therapy is often an effective means of controlling allergy symptoms, and antihistamines and nasal corticosteroids have generally shown the most benefit for such symptoms. Evaluation by allergy testing can help in planning allergen avoidance or determine the need for immunotherapy.

A lymphocyte-mediated **delayed hypersensitivity reaction** causing a skin rash on an antigen-exposed area. Requires **sensitization** to antigen from repeat exposure. Common allergens include nickel, neomycin, poison ivy.

This is **different from irritant dermatitis**, which can affect anybody with enough exposure. **Sensitization is not required.** Common irritants include soapy water, rubbing alcohol, household cleaner.

### Symptoms/Exam

Characterized by a **pruritic** rash that typically appears 5 to 21 days after the initial exposure or 12 to 96 hours after reexposure in sensitized individuals.

The typical pattern is **erythema** leading to **papules** and then **vesicles**. The rash precedes pruritus and appears in the distribution of antigen exposure (Figure 1.4).

- **Acute stage:** Skin erythema, papules, vesicles.
- **Subacute or chronic stage:** Crusting, scaling, lichenification, and thickening of the skin.

### Differential

Atopic dermatitis, seborrheic dermatitis, irritant dermatitis (antigen-nonspecific irritation, usually due to chemicals or detergents), psoriasis.

### Diagnosis

- **Location of the rash:** Suggests the cause—eg, feet (shoes), neck/ears (jewelry), face (cosmetics/hair products).
- **Allergy patch testing:** Apply common test allergens to skin and observe for reaction after 2 or 3 days.

### Management

Antigen avoidance, topical corticosteroids, antihistamines for pruritus; oral prednisone in severe or extensive cases.

### Complications

2° infection from scratching affected skin.

## ALLERGIC CONJUNCTIVITIS

There are three major types of allergic conjunctivitis: acute, seasonal, and perennial. This is from environmental allergens contacting the surface of the eye and is a type I IgE-mediated hypersensitivity.

### Symptoms/Exam

- Red eyes (usually bilateral) and characteristically **itching/burning** (Figure 1.5). If itching is not described, consider alternative causes of conjunctivitis.
- Crusting around eyes upon waking.
- Watery and nonpurulent discharge.
- **NO eye pain.**

### Differential

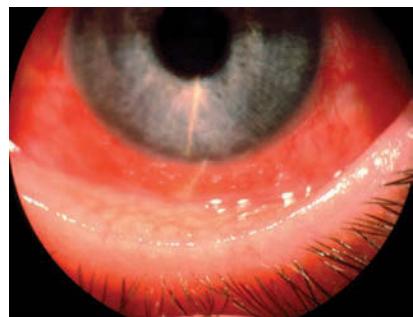
- Viral conjunctivitis (usually unilateral but can be bilateral).
- Bacterial conjunctivitis (usually painful and purulent).
- Dry eye (corneal involvement instead of conjunctiva involvement; characterized by vital dye uptake).
- Blepharitis (involves eyelids).
- Toxic conjunctivitis (irritant reaction, eg, to contact lens solution; conjunctival injection and itching are common).

### Diagnosis

- Clinical: Laboratory testing is not needed, but allergen testing can be done to determine which allergens to avoid.
- **Acute allergic conjunctivitis:** Sudden-onset (eg, within 30 minutes) hypersensitivity reaction caused by environmental exposure (eg, cat dander).
- **Seasonal allergic conjunctivitis:** Caused by seasonal outdoor airborne pollens (eg, tree pollens in the spring, grass pollens in the summer, weed pollens in the fall) and can have associated rhinitis; onset is over days to weeks.
- **Perennial allergic conjunctivitis:** Mild, chronic, waxing and waning form when exposed to year-round allergen (eg, dust mites, animal dander, mold).



**FIGURE 1.4. Contact dermatitis.** Erythematous papules, vesicles, and serous weeping localized to areas of contact with the offending agent are characteristic. (Reproduced with permission from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*. Stamford, CT: Appleton & Lange, 1991, 3.)



**FIGURE 1.5. Allergic conjunctivitis.** Slit-lamp photograph of the left eye demonstrating conjunctival injection and a papillary reaction of the conjunctiva seen in the inferior fornix. 40-year-old male presenting with a 2-month history of red eyes and itchiness. (Reproduced with permission from USMLE-Rx.com.)



### QUESTION

An 18-year-old man presents to the ED with recurrent abdominal pain. He has had similar episodes over the past several years, with each episode resolving slowly over time and associated with swelling of his arms bilaterally. His episode today is worse, and he again has arm swelling bilaterally. Which tests would be useful in determining the cause of his recurrent symptoms?

### Management

- **Supportive:** Discontinue contact lens use while symptomatic, avoid rubbing eyes, apply cool compresses, use artificial tears, avoid allergens.
- Can use OTC **topical antihistamines, steroid eye drops, or vasoconstrictors** (eg, naphazoline HCl/pheniramine maleate) up to four times a day for symptomatic relief.
- If severe or recurrent, consider **allergen immunotherapy**.

## Rhinitis

Allergic factors are the **most common cause** of chronic rhinitis—present in 75% of rhinitis cases. May be **seasonal or perennial**; incidence is greatest in adolescence and ↓ with advancing age. Usually persistent, with occasional spontaneous remission.

### Symptoms/Exam

- Sneezing, nasal itching, rhinorrhea, nasal congestion, sore throat, throat clearing, itching of the throat and palate.
- Sleep disturbance; association with obstructive sleep apnea.
- Concomitant conjunctivitis with ocular itching, lacrimation, and puffiness.

Patients present with swollen nasal turbinates with pale or bluish mucosa, clear nasal discharge, clear to white secretions along the posterior wall of the oropharynx, cobblestoning of posterior pharynx, infraorbital darkening, conjunctival erythema, and lacrimation.

### Differential

- **Nonallergic rhinitis:** Vasomotor or gustatory rhinitis. ⊖ skin test.
- **Rhinitis medicamentosa:** Overuse of vasoconstricting nasal sprays, leading to rebound nasal congestion and associated symptoms.
- **Hormonal rhinitis:** Associated with pregnancy, use of OCPs, and hypothyroidism.
- **Drug-induced rhinitis:** Common causes include β-blockers, α-blockers, and cocaine.
- **Atrophic rhinitis:** Develops in elderly patients with atrophy of the nasal mucosa. Treat with nasal saline.
- **Infectious rhinosinusitis:** Acute viral syndromes lasting 7 to 10 days; bacterial sinusitis.
- **Nasal obstruction due to a structural abnormality:** Septal deviation, nasal polyps, nasal tumor, foreign body.
- **Granulomatosis with polyangiitis:** Nasal ulcerations with systemic signs and symptoms. ANCA vasculitis.

### Diagnosis

Based on the history and ⊕ **skin testing** to common aeroallergens (eg, grass/tree/weed pollen, house dust mites, cockroaches, dog and cat dander, mold).



### KEY FACT

First, remove environmental triggers. Following that, intranasal corticosteroids are the most effective treatment for allergic rhinitis. Both interventions may take up to 6 to 8 weeks to take effect.



### ANSWER

C1-INH assay and C1q level. This patient has symptoms consistent with recurrent angioedema, which can be acquired or hereditary. Angioedema often presents with abdominal pain, as gut edema is common. Treatment involves replacement of inhibitor, often via C1-INH concentrate, kallikrein inhibitor, or bradykinin receptor antagonist.

### Management

- **Allergen avoidance measures:** Most effective for house dust mites (involves the use of allergen-impermeable bed and pillow casings and washing of bedding in hot water). Indoor pollen exposure can be ↓ by keeping windows closed and using air conditioners.
- **Intranasal corticosteroids:** The most effective medication for allergic and nonallergic rhinitis. Have no significant systemic side effects; most beneficial when used regularly.

- **Antihistamines:** ↓ sneezing, rhinorrhea, and pruritus. Less effective for nasal congestion; best if used regularly. Not effective for nonallergic rhinitis. Nonsedating antihistamines are preferable.
- **Oral decongestants:** Effectively ↓ nasal congestion in allergic and nonallergic rhinitis. May cause insomnia and exacerbate hypertension or arrhythmia.
- **Allergen immunotherapy:** Indicated as an alternative or adjunct to medications. **The only effective therapy that has been demonstrated to modify the long-term course of the disease.**



### KEY FACT

Sedating antihistamines (diphenhydramine, hydroxyzine) cross the blood-brain barrier and can lead to anticholinergic side effects. Avoid use in the elderly.

## Complications

Chronic sinusitis and otitis; exacerbation of asthma.

## Sinusitis

### ACUTE AND CHRONIC SINUSITIS

Sinusitis is mucosal inflammation of the paranasal sinuses. Acute sinusitis is defined as <4 weeks, chronic sinusitis is defined as persistent symptoms lasting >8 weeks. Recurrent acute sinusitis is defined as ≥4 episodes of acute sinusitis per year, with complete resolution between episodes.

#### Symptoms/Exam

- Purulent nasal discharge, congestion, ↓ olfaction, and facial pain or pressure are primary symptoms. Can also have headaches, fever, dental pain, ear pain.
- **Alarm features:** Proptosis, diplopia, ↓ extraocular movements, severe headaches, high fevers, eye pain, altered mental status. **Urgent evaluation warranted for deep infection.**

#### Differential

- **Viral:** Typically also have upper respiratory tract infection (URTI) symptoms.
- **Bacterial:** *S pneumoniae*, *H influenzae* > *Moraxella catarrhalis* > *S aureus* and anaerobes.
- **Fungal:** See the Infectious Diseases chapter. Invasive fungal sinusitis (eg, in immunocompromised patients) is a **medical emergency!**
- **Structural abnormality** (eg, nasal polyps): This is strongly associated with asthma and aspirin-exacerbated respiratory disease.
- **Allergic:** From chronic allergic inflammation against colonizing fungi (see next section, Allergic Fungal Sinusitis).
- **Rheumatologic:** See the Rheumatology chapter.

#### Diagnosis

- Viral cause is most likely in context of URTI and symptoms <10 days.
- Consider bacterial if symptoms persist >10 days, or if symptoms improve, then worsen again (“double-sickening”). Also consider this if high fevers, purulent nasal discharge, or severe facial pain at beginning of an illness.
- Consider fungal etiology in immunocompromised hosts. More in Infectious Disease chapter.



### QUESTION

A 19-year-old man with a history of asthma presents with persistent daily wheezing and coughing and nightly symptoms that occur twice per week. He currently takes an inhaled corticosteroid twice daily and albuterol as needed. What would be the next appropriate change in his medications?

### Evaluation

- **Acute sinusitis:** Often no workup is needed. Empiric antibiotics if suspect bacterial sinusitis. If **alarm symptoms**, obtain **CT sinuses** to evaluate for facial/orbital spread.
- **Recurrent or resistant** (not improving after 72 hours of antibiotics): consider non-infectious, structural abnormalities. Consider ENT aspiration for culture. Nasopharyngeal swabs are not helpful.
- **Chronic sinusitis:** Generally, requires **CT sinuses**, **ENT referral** for visualization. Consider **allergy evaluation** as well as rheumatologic or immunologic causes.

### Management

- **Acute:** Usually self-limited. Focus on establishing and promoting sinus drainage:
  - Saline irrigation two to three times a day.
  - Intranasal corticosteroids to reduce inflammation.
  - Empiric antibiotics if bacterial infection is suspected based on above. Augmentin for 5 to 7 days; doxycycline or fluoroquinolone second line.
- **Chronic:** Treatment is based on underlying cause.

### ALLERGIC FUNGAL SINUSITIS

An immunologic reaction to fungal aeroallergens (*Aspergillus*, *Bipolaris*, *Curvularia*, *Alternaria*, *Fusarium*) that causes chronic, refractory sinus disease.

### Symptoms/Exam

- Sinus congestion and obstruction that are refractory to antibiotics; thick mucoid secretions (“peanut butter” appearance); nasal polyposis; proptosis; asthma.
- Presents with thickening of the sinus mucosa, allergic mucin on rhinoscopy, and nasal polyps.

### Differential

- **Chronic rhinosinusitis:** Bacterial, allergic (nonfungal).
- **Invasive fungal disease:** Seen in immunocompromised patients (HIV, diabetes).
- **Other:** Nasal polyposis without allergic fungal sinusitis; mycetoma (fungus ball).

### Diagnosis

**Diagnostic criteria** include the following:

- Chronic sinusitis for >6 months.
- **Allergic mucin** containing many eosinophils and fungal hyphae.
- Sinus CT showing opacification of the sinus (often unilateral) with **hyperattenuated**, expansile material.
- Absence of invasive fungal disease.
- **Other supportive findings** include peripheral blood eosinophilia and immediate skin tests  $\oplus$  to fungus.

### Management

- Surgical removal of allergic mucin.
- **Prednisone** 0.5 to 1.0 mg/kg for weeks with slow tapering.
- Intranasal corticosteroids; nasal irrigation.

### Complications

Bony erosions from expansion of allergic mucin; surgical complications; high recurrence rate despite therapy.

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### ANSWER

$\uparrow$  corticosteroid dose to medium-dose agent and add a long-acting  $\beta_2$ -agonist (salmeterol) to treat moderate persistent symptoms. Although one might also consider adding leukotriene modifiers, such agents should not be used in place of long-acting  $\beta_2$ -agonists or inhaled corticosteroids in a moderate persistent asthmatic.

## Asthma

Asthma is a **chronic inflammatory disorder** of the airway resulting in **airway hyperresponsiveness, airflow limitation, and respiratory symptoms**. Often begins in childhood, but may have adult onset. **Atopy** is a strong identifiable **risk factor** for the development of asthma. Subtypes include exercise-induced, occupational, aspirin-sensitive, and cough-variant asthma.

### Symptoms/Exam

- Symptoms include **dyspnea** (at rest or with exertion), **cough, wheezing, mucus hypersecretion, chest tightness, and nocturnal awakenings** with respiratory symptoms.
- Symptoms may have identifiable **triggers** (eg, exercise, exposure to cat dander, NSAIDs, cold exposure).
- **Acute exacerbations:** **Expiratory wheezing**; a prolonged expiratory phase; ↑ respiratory rate.
- **Severe exacerbations:** **Pulsus paradoxus, cyanosis, lethargy, use of accessory muscles of respiration, silent chest** (absence of wheezing due to lack of air movement).
- **Chronic asthma without exacerbation:** Presents with minimal to no wheezing. Signs of allergic rhinosinusitis (boggy nasal mucosa, posterior oropharynx cobblestoning, suborbital edema) are commonly found. **Exam may be normal** between exacerbations.

### Diagnosis

Diagnosed by the history and objective evidence of **obstructive lung disease**.

- **PFTs:** Show a ↓ **FEV<sub>1</sub>/FVC ratio** with **reversible obstruction** (>12% ↑ in FEV<sub>1</sub> after bronchodilator use) and **normal diffusing capacity**.
- **Methacholine challenge:** Useful if baseline lung function is normal but clinical symptoms are suggestive of asthma. A  $\oplus$  methacholine challenge test is not diagnostic of asthma, but a  $\ominus$  test indicates that asthma is unlikely (**high sensitivity, lower specificity**).

### Management

See the Hospital Medicine chapter for management of acute exacerbations.

**Chronic asthma therapy** (Table 1.3) is based on asthma severity. The treatment regimen should be **reviewed every 1 to 6 months**, with changes made depending on symptom severity and clinical course. Additional treatment considerations for both acute and chronic asthma include the following:

- Recognize the exacerbating effects of **environmental factors** such as allergens, air pollution, smoking, and weather (cold and humidity).
- Use potentially **exacerbating medications** (ASA, NSAIDs,  $\beta$ -blockers) **with caution**.
- Always consider **medication compliance and technique** as possible complicating factors in poorly controlled asthma.
- Treatment of **coexisting conditions** (eg, rhinitis, sinusitis, GERD) may improve asthma.
- Consider the addition of anti-IgE monoclonal antibody (omalizumab) for the treatment of **severe persistent allergic asthma**.
- Consider alternative diagnoses if a patient has adult onset asthma that is difficult to control: upper airway obstruction (upper airway wheezing), other lung disease (emphysema, chronic bronchitis, ABPA, eosinophilic granulomatosis with polyangiitis [formerly Churg-Strauss], chronic eosinophilic pneumonia, obstructive sleep apnea, restrictive lung disease, PE), cardiovascular disease (CHF), respiratory infection (pneumonia).

### KEY FACT

In a patient with asthma, sinusitis, and nasal polyps, and who takes aspirin (Samter's triad), consider **aspirin exacerbated respiratory disease** as the cause of asthma. Treatment would include stopping aspirin, performing aspirin desensitization, and lifelong high-dose aspirin and leukotriene inhibitor use.

### KEY FACT

In a patient with new-onset asthma late in adulthood with no obvious environmental trigger, consider 2° causes such as GERD, heart failure, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss).

### KEY FACT

Monotherapy with long-acting  $\beta_2$ -agonists have been associated with asthma-related deaths. Never use these agents as monotherapy in severe asthma.

### KEY FACT

Asthma symptoms that occur more than twice weekly generally indicate the need for inhaled corticosteroid therapy.

### KEY FACT

Think of reactive airway dysfunction syndrome in a patient with symptoms of asthma following a single, large exposure to an irritant such as chlorine or mustard gas (biological warfare). Treat like asthma.

TABLE 1.3. Guidelines for the Treatment of Chronic Asthma

ASTHMA CLASSIFICATION	SYMPTOMS <sup>a</sup>	PULMONARY FUNCTION	RECOMMENDED TREATMENT
Mild intermittent	≤2 days/week, ≤2 nights/month	Peak expiratory flow (PEF) ≥80%	Bronchodilator two to four puffs every 4 hours as needed No daily medications necessary
Mild persistent	>2 days/week but <1 time/day or >2 nights/month	PEF ≥80%	Add low-dose inhaled corticosteroids Leukotriene modifiers, theophylline, and cromolyn may also be added
Moderate persistent	Daily symptoms or >1 night/week	PEF 60%-80%	↑ to medium-dose inhaled corticosteroids and add a long-acting inhaled $\beta_2$ -agonist Leukotriene modifiers or theophylline may also be added
Severe persistent	Continuous symptoms	PEF <60%	↑ to high-dose inhaled corticosteroids plus long-acting inhaled $\beta_2$ -agonists. Daily oral corticosteroids may be added if necessary (60 mg once per day)

<sup>a</sup>Dyspnea (at rest or with exertion), cough, wheezing, mucus hypersecretion, chest tightness, and nocturnal awakenings with respiratory symptoms.

## CHAPTER 2

# Ambulatory Medicine

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## Screening for Common Diseases

### DIABETES MELLITUS

- Screen individuals for type 2 diabetes mellitus (DM) if they are 40 to 70 years old and overweight ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ) or obese. Screening at least every 3 years is recommended. Other risk factors that can trigger screening for DM: dyslipidemia, hypertension, first-degree relative with DM, high-risk ethnic group (Latinos, Asians, African Americans), history of gestational DM, and sedentary lifestyle.
- Why screen?
  - Treatment of type 2 DM can slow the progress of microvascular disease (retinopathy, nephropathy, neuropathy).
  - Early identification of DM can lead to a lower threshold to start treatment of cardiovascular conditions (hyperlipidemia and hypertension).
- Diagnostic criteria include any of the following:
  - Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level  $\geq 6.5\%$  on two separate occasions.
  - Fasting blood glucose level  $\geq 126 \text{ mg/dL}$  on two separate occasions.
  - Symptoms of DM (polyuria, polydipsia, weight loss) and one random blood glucose level  $\geq 200 \text{ mg/dL}$ .
  - A 2-hour blood glucose level  $\geq 200 \text{ mg/dL}$  during an oral glucose tolerance test.
- “Prediabetes” is diagnosed in individuals with fasting blood glucose level of 100 to 125 mg/dL (impaired fasting glucose), HbA<sub>1c</sub> of 5.7% to 6.4%, or abnormal OGTT (impaired glucose tolerance). Prediabetes is associated with an ↑ risk of developing DM. Recommend lifestyle modification and in select cases metformin to reduce progression to DM.

### KEY FACT

In prediabetes, lifestyle modification (weight loss, exercise) is even better than metformin in delaying onset of type 2 DM. So start walking!

### ABDOMINAL AORTIC ANEURYSM

Conduct one-time abdominal aortic aneurysm (AAA) screening for men 65 to 75 years of age who have ever smoked. The preferred modality is ultrasound. Surgical repair of AAAs  $\geq 5.5 \text{ cm}$  ↓ AAA-specific mortality in this population.

## Obesity

Obesity is defined as a  $\text{BMI} \geq 30 \text{ kg/m}^2$ . Risk factors include female gender, middle age (lower risk in younger and older adults), ethnicity (African Americans, Hispanics, Native Americans). Obesity ↑ morbidity and mortality, particularly from complications of hypertension, type 2 DM, hyperlipidemia, coronary artery disease (CAD), osteoarthritis, sleep apnea, and steatohepatitis.

### Differential

- Hypothyroidism, Cushing syndrome, polycystic ovarian syndrome.
- Medications, such as steroids, insulin, atypical antipsychotics, and antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors [SSRIs], with sertraline being the least obesogenic of the SSRIs).
- Most common cause is excess caloric intake, as <1% of obese patients have another identifiable medical cause.

### Diagnosis

The BMI is calculated by dividing measured body weight (kg) by height (meters squared) and can diagnose excess adipose tissue. BMI ( $\text{kg/m}^2$ ) categories are as follows:

- **Underweight:** <18.5.
- **Normal:** 18.5 to 24.9.
- **Overweight:** 25 to 29.9.
- **Obese:** ≥30 to 39.9.
- **Extreme obesity:** ≥40.

## Management

### Lifestyle modification and diet:

- Weight loss can improve type 2 DM, hypertension, cardiovascular risk, and hyperlipidemia (HDL, TG). See the Cardiovascular Disease chapter for more on hyperlipidemia.
- A multidisciplinary approach combining a ↓ caloric intake, ↑ aerobic exercise, and social support optimizes weight loss and maintenance of weight loss.
- Low-carbohydrate, low-fat, and Mediterranean style (plant-based; healthy carbohydrates and fats with fruits and vegetables) diets have similar outcomes. Although short-term weight loss occurs, the long-term effectiveness of diets is generally poor. Programs that focus on long-term healthy eating habits, rather than short-term solutions, are generally more effective.
- Very low calorie diets (<800 kcal/day) are no longer used, as overrestriction is associated with poorer outcomes.

### Medications:

- Consider pharmacotherapy in patients with a BMI ≥30 kg/m<sup>2</sup> or in those with a BMI ≥27 kg/m<sup>2</sup> with medical complications (hypertension, DM, hyperlipidemia). However, benefits are marginal.
- FDA-approved pharmacotherapies are listed in Table 2.1. Choose therapies based on side effects, with **orlistat** and **lorcaserin** typically being first line.
- A course of medication for 6 to 12 months in conjunction with dietary modifi-



### KEY FACT

Phentermine is approved only for short-term (12 weeks) for obesity treatment.

**TABLE 2.1. FDA-Approved Obesity Medications**

DRUG	MECHANISM OF ACTION	SIDE EFFECTS
Sympathomimetics		
Phentermine	Approved for <b>short-term</b> use (<6 months) only Suppress appetite; act similar to amphetamine	<b>Adrenergic-like symptoms:</b> Hypertension, ↑ heart rate, dry mouth, insomnia, dizziness Have abuse potential
Diethylpropion		
Phendimetrazine		
Benzphetamine		
Orlistat	Inhibits intestinal lipase and thus ↓ fat digestion and absorption; should be on a low-fat diet Approved for use up to 4 years	<b>Malabsorption:</b> Fatty stools, gas, cramping, kidney stones, vitamin deficiencies (A, D, E, K)
Phentermine/ topiramate	Suppresses appetite; sympathomimetic and antiepileptic drug	Similar to sympathomimetics
Liraglutide injection	Glucagon-like peptide-1 (GLP-1) receptor agonist that signals satiety to brain	GI side effects, hypoglycemia (since this class is also used to treat type 2 DM)
Lorcaserin	Suppresses appetite; binds to certain serotonin receptors	Nausea, dizziness, headache, constipation
Bupropion/naltrexone	Combination opioid antagonist and aminoketone antidepressant	Contraindicated in patients using opiates; nausea, constipation, headache, dizziness, insomnia, kidney stones, glaucoma, ↑ BP, uncommonly suicidal ideation and behaviors

**KEY FACT**

In obesity, caloric restriction is necessary for weight loss. Exercise is less effective for weight loss but helps with maintenance of weight loss.

**KEY FACT**

Consider surgery for patients with a BMI  $\geq 40 \text{ kg/m}^2$  or for those with a BMI  $\geq 35 \text{ kg/m}^2$  plus obesity-related comorbidity (eg, DM, sleep apnea, hypertension, hyperlipidemia).

**KEY FACT**

Intensive lifestyle therapy, including weight loss, exercise, and a healthy diet, is key to managing metabolic syndrome and preventing clinical CVD and type 2 DM.

cation leads to modest weight loss when compared to a placebo, but the long-term efficacy of such treatment has not been established.

- **Bariatric surgery:**

- More effective than other options for achieving long-term weight loss. Surgery leads to weight reduction and improvement of comorbidities, such as type 2 DM, hypertension, hyperlipidemia, and sleep apnea.
- Surgical procedures include gastric banding, gastric bypass (Roux-en-Y), sleeve gastrectomy, and duodenal switch.
- Short- and long-term complications of surgery include anastomotic leaks, dumping syndrome, vitamin deficiencies ( $B_1$ ,  $B_{12}$ , iron), cholecystitis, gastritis, weight regain.

## Metabolic Syndrome

Approximately 60% of obese individuals have metabolic syndrome; confers up to 2 times elevated risk of CAD. Also associated with an  $\uparrow$  risk of type 2 DM due to insulin resistance.

### Diagnosis

Requires three or more of the following:

- Central or visceral fat: Elevated abdominal circumference ( $\geq 40$  inches in men,  $\geq 35$  inches in women)  $\uparrow$  cardiovascular risk.
- Elevated BP ( $\geq 130/85 \text{ mm Hg}$ ).
- Elevated TG ( $\geq 150 \text{ mg/dL}$  or on drug treatment to lower TG).
- Elevated fasting blood glucose ( $\geq 100 \text{ mg/dL}$ ).
- Low HDL cholesterol ( $<40 \text{ mg/dL}$  in men;  $<50 \text{ mg/dL}$  in women).

### Management

- The goal is to  $\downarrow$  the risk of clinical atherosclerotic disease and to prevent the onset of type 2 DM. Losing 5% to 10% of body weight significantly reduces morbidity risks.
- Intensive lifestyle therapy is effective at reducing the rates and complications of metabolic syndrome. Metformin may delay or prevent the development of DM but **lifestyle modification is even more effective**.
- Cardiovascular risk factors (lipids, blood glucose, BP) should be closely monitored and well controlled in these patients. Patients with a 10-year cardiovascular disease (CVD) risk  $>10\%$  should take daily aspirin.

## Cigarette Smoking and Smoking Cessation

Smoking is the leading cause of preventable death in the United States. When recommending smoking cessation, apply the “5 A’s” approach advocated by the National Cancer Institute:

- Ask (about smoking).
- Advise (all smokers to quit).
- Assess (readiness to quit).
- Assist (with pharmacologic and nonpharmacologic measures).
- Arrange (follow-up and support).
- Physician intervention, even if as brief as 1 to 2 minutes, can  $\uparrow$  the rate of compliance. Offer all patients **pharmacotherapy** (Table 2.2), which is **twice as effective** in promoting cessation as behavioral counseling (individual, group, telephone hotlines) alone.

**TABLE 2.2. Smoking Cessation Pharmacotherapy**

METHOD	MECHANISM/USE	SIDE EFFECTS	CONTRAINdications
Nicotine replacement (patch, gum, inhaler, nasal spray)	Apply patch daily; chew gum or use nasal spray/inhaler PRN for cravings	Skin irritation (patch); mucosal irritation (nasal spray); cough (inhaler)	<b>Recent MI</b> , unstable angina, life-threatening arrhythmia, pregnancy (although nicotine replacement may be preferable to continued smoking)
Sustained-release bupropion	Atypical antidepressant; begin 1 week prior to quit date; continue 3 or more months after quitting	Restlessness/anxiety, tremor, insomnia, GI upset	<b>Seizures, head trauma, heavy alcohol use, history of eating disorders</b> (lowers seizure threshold)
Varenicline	Nicotine agonist; start one week prior to quit date; continue for 12 weeks	Nausea/vomiting, constipation, <b>altered dreams, suicidal ideation</b> , depression, agitation	Suicidal ideation, unstable psychiatric status, unstable cardiovascular disease (mixed data on CVD risk)

- Bupropion may be used in combination with nicotine replacement with additive benefits. Bupropion alone is more effective than a nicotine patch alone.
- Varenicline may be more efficacious than bupropion or nicotine replacement. However, it can cause GI upset and has been associated with neuropsychiatric symptoms such as suicidal ideation, agitation, and depressive behavior as well as possible ↑ in CVD risk.

## Cancer Screening

Refer to Table 2.3 for an overview of USPSTF cancer screening guidelines.

### BREAST CANCER

Breast cancer is the most common cancer in all major ethnic groups. Caucasians have the highest rates of breast cancer, followed by African Americans, but the highest mortality rates are found among African Americans. The strongest risk factors are age (>50 years) and gender (female). Other risk factors include the following:

- A personal history of invasive or *in situ* breast cancer (associated with an ↑ risk of invasive breast cancer in the contralateral breast).
- A family history, particularly of premenopausal breast cancer, in one or more first-degree relatives.
- ⊕ mutations of BRCA1 or BRCA2.
- Current or prior use of hormone replacement therapy (HRT) for >5 years.
- Early menarche (<12 years); later menopause (>55 years); later pregnancy (age at first birth >30 years). Principle: ↑ estrogen exposure leads to a higher risk of breast cancer.
- A previous breast biopsy with proliferative changes (eg, complex fibroadenoma, intraductal papilloma, moderate hyperplasia), especially with cytologic atypia, on breast biopsy. Nonproliferative changes are not associated with ↑ risk of breast cancer.
- Heavy alcohol use.
- Obesity (for postmenopausal breast cancer).
- OCP use is probably not a risk factor in average-risk women but may be in those with a ⊕ family history.
- Physical activity and breastfeeding are protective.

### KEY FACT

Answer questions about screening and immunization recommendations based on average risk individuals and what you know is currently true on your test day. Don't overthink it and don't pick the controversial answer.

### KEY FACT

Screening for colorectal, breast, and cervical cancer has been proven to reduce mortality. Screening for prostate cancer has not been shown to lower mortality.

### KEY FACT

Lifestyle modifications to ↓ breast cancer risk:

- ↓ the duration of HRT use.
- Have first child at an earlier age.
- Avoid adult weight gain.
- ↓ **alcohol intake**.
- ↑ physical activity.
- Breastfeeding.

TABLE 2.3. USPSTF Cancer Screening Guidelines

	BREAST	COLON	CERVIX	PROSTATE
Target population	All women	All women and men	All women who have ever had sex and who have a cervix	All men
USPSTF Grade <sup>a</sup>	B	A	A	D
Age to start	Age 50; screening between 40 and 49 years should be a shared decision made by patients and their physicians	Age 50	Age 21	The men most likely to benefit are those ≥50 years of age; men with risk factors should consider starting at age 40-45.
Age to stop	Age 74, although women ≥75 years of age may still benefit if they do not have significant comorbid disease	Age 75; consider screening patients between 76 and 85 years of age if there are no significant comorbid conditions; screening is not recommended in patients >85 years of age	Age 65 if a woman has had regular screening with normal results and is not otherwise at high risk	Screening is not recommended for men ≥75 years of age.
Screening modality	Mammography	Fecal occult blood testing (FOBT)/fecal immunochemical test (FIT) annually, flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years—each has different risks and advantages—there is no clear best test; insufficient evidence for CT colonography and fecal DNA testing	Pap smear; HPV co-testing starting at age 30	PSA ± DRE (PSA is more sensitive).
Frequency of screening	Every 2 years	<b>FOBT/FIT:</b> Annual <b>Flexible sigmoidoscopy:</b> Every 5 years <b>Colonoscopy:</b> Every 10 years	At least every 3 years, can be every 5 years with HPV co-testing starting at age 30 if HPV is negative	If screening has benefit, every year.

<sup>a</sup>Strength of USPSTF recommendations: A—strongly recommended; B—recommended; C—no recommendation for or against; D—against recommendation; I—insufficient evidence.

### Screening

- **Mammography: Biennial** (not annual) screening is recommended for average-risk women 50 to 74 years of age. The decision to screen women between 40 and 49 years should be a shared decision between physician and patient, including a discussion of the patient's values regarding relative benefits and harms, since the mortality benefit is small and the risk of false  $\oplus$  is high in younger women. There is insufficient evidence to recommend:
  - Digital mammography or MRI over film mammography.
  - Clinical breast examination during visit. Breast self-examination has not been shown to have benefit and the USPSTF recommends against teaching this to patients.

- Genetic counseling and consideration of BRCA1/BRCA2 mutation testing are recommended for those with the following risk factors:
  - Close relative with known BRCA1/BRCA2 mutation or another known mutation that ↑ breast cancer risk.
  - A family history of breast cancer in ≥2 first-degree relatives (at least one premenopausal) or ≥3 first- or second-degree relatives.
  - Breast *and* ovarian cancer in the same patient or in any first- and second-degree relatives.
  - A family history of male breast cancer or of women with bilateral breast cancer or breast cancer before age 45.
  - Personal history of invasive ovarian cancer or breast cancer plus family history of invasive ovarian cancer.
  - Ashkenazi Jewish heritage plus a first-degree relative (or two second-degree relatives) with breast or ovarian cancer.

### Prevention

- Women with mutations of BRCA1 or BRCA2 should undergo intensive surveillance and may consider prophylactic mastectomy and/or oophorectomy.
- Tamoxifen and raloxifene are selective estrogen receptor modulators (SERMs) that may ↓ the risk of invasive breast cancer in **high-risk** (particularly close family relatives with breast cancer) patients >35 years of age. Adverse effects include ↑ risk of thromboembolism (tamoxifen > raloxifene) and uterine cancer. Use tamoxifen in premenopausal women.
- For postmenopausal women at **high risk** for breast cancer who would rather not take a SERM, aromatase inhibitors such as anastrozole or exemestane are also options.

## CERVICAL CANCER

Cervical cancer is caused by high-risk types of HPV (types 16 and 18). HPV is a sexually transmitted infection (STI), and risk factors include multiple sexual partners, early onset of intercourse, other STIs, smoking, low socioeconomic status, and HIV/immunosuppression.

### Screening

- Screen average risk women with cytology (Pap smear) every 3 years starting at age 21. Those with known risk factors such as immunocompromise or a history of abnormal Pap smears should be screened more frequently.
- Interval can be ↑ to every 5 years if co-testing is used for women between 30 and 65 years of age with both normal cytology and negative high-risk HPV DNA testing.
- Stop screening at age 65 in women who have had adequate prior screening (three consecutive negative cytology results or two consecutive ⊖ HPV results within 10 years before cessation of screening) and who are otherwise at low risk. Older women who have not had a recent Pap test should be screened.
- There is no need to screen those who had a total hysterectomy that was done for benign reasons.
- Abnormalities on Pap smear are followed up with diagnostic colposcopy and biopsy.

### Prevention

- A vaccine against HPV types 6, 11, 16, and 18 has been developed and is recommended for all girls and young women aged 9 to 26, all boys and young men aged 9 to 21, and for men in certain high-risk populations aged 22 to 26 (see the discussion of immunizations below). Pap smear screening recommendations remain the same in vaccinated and unvaccinated patients. Male vaccination also is likely to benefit women by reducing the spread of HPV.

### KEY FACT

Testing for BRCA1 and BRCA2 mutations should not be performed without prior genetic counseling. It should be considered only for women with family histories highly suggestive of a genetic susceptibility to breast and/or ovarian cancer.

### KEY FACT

In high-risk patients, consider tamoxifen and raloxifene (SERMs) to ↓ the risk of invasive breast cancer.

### KEY FACT

Starting at age 30, cervical cancer screening can be done every 5 years if Pap smear is negative and HPV co-testing is negative. Stop screening at age 65 if low risk.

### QUESTION 1

A 40-year-old man presents for a routine checkup. His father was given a diagnosis of colon cancer at age 52. When should he undergo colon cancer screening?

### QUESTION 2

A 59-year-old man with a 40 pack-year history of smoking comes to a primary care appointment. He quit smoking 10 years ago. In addition to testing for lipids, colorectal cancer, and DM, what screening test should be ordered now?

### QUESTION 3

A woman in her first trimester of pregnancy asks about routine vaccinations. Which vaccinations should she receive?

- Safer sexual practices (barrier contraceptives, fewer sexual partners) may help prevent cervical cancer by decreasing risk of acquiring HPV.

### COLORECTAL CANCER

There is no one “best” screening modality for colorectal cancer (“any screening is better than no screening”). Options include stool-based tests (annual FOBT/FIT), flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, or CT colonography every 5 years. Only FOBT/FIT, flexible sigmoidoscopy, and colonoscopy are recommended by USPSTF.

#### Screening

- Colorectal cancer screening should **begin at age 50 and continue until age 75**. High-risk patients should begin colonoscopy screening at age 40, or 10 years before the youngest affected relative was diagnosed.
- Risks for colon cancer include a personal or strong family history of colorectal cancer or adenomatous polyps, and a family history of hereditary colon cancer syndromes (familial adenomatous polyposis, Lynch syndrome [hereditary nonpolyposis colorectal cancer]).

#### Prevention

- Individuals can consider low-dose aspirin for prevention of colorectal cancer. Starting in 2016, the USPSTF began recommending low-dose aspirin for primary prevention of colon cancer and CVD in adults aged 50 to 59 years with  $\geq 10\%$  10-year CVD risk who are not at  $\uparrow$  bleeding risk.
- Patients with extensive family history or inherited colon cancer syndromes should be referred for counseling, frequent screening, and consideration of colectomy.

### PROSTATE CANCER

- Screening with serum PSA testing, with or without digital rectal examination (DRE), is controversial because of the lack of proven effectiveness in improving health outcomes or  $\downarrow$  mortality. There is insufficient evidence to recommend for or against PSA and/or DRE.
- Shared decision making with men **aged  $\geq 50$**  who do not have significant life-limiting comorbidities should be used. This should include discussion of the potential benefits of PSA screening (early detection of possibly harmful cancers), risks (false-positive and false-negative results, overdiagnosis of highly indolent cancers, more biopsies, anxiety, morbidity associated with prostate cancer treatment), and uncertainties (health outcomes and mortality).
- Discuss at a younger age (40-45 years) if at  $\uparrow$  risk (eg, African American or those with a first-degree relative with prostate cancer diagnosed at an early age), although benefits of earlier screening (and any screening at all) are uncertain.
- If decide to screen, check PSA, with or without DRE.

### LUNG CANCER

Screen for lung cancer **annually with low-dose chest CT scan in individuals aged 55 to 80 years with at least a 30 pack-year history who are current smokers or who quit fewer than 15 years ago (USPSTF Grade B recommendation)**. Stop when more than 15 years out from quit date, if life expectancy is limited from other causes, or if patient is unable or unwilling to have curative lung surgery.

#### KEY FACT

Because there is no direct evidence that screening for prostate cancer  $\downarrow$  mortality, expert groups recommend routinely discussing the pros and cons of screening with at-risk men rather than routinely ordering a serum PSA.

#### KEY FACT

Screen for lung cancer in adults aged 55 to 80 years with a  $\geq 30$  pack-year smoking history who are current smokers or who quit  $< 15$  years ago.

A

#### ANSWER 1

Begin colon cancer screening 10 years prior to his father's colon cancer diagnosis.

A

#### ANSWER 2

Low-dose chest CT for lung cancer screening.

A

#### ANSWER 3

This patient should receive inactivated influenza vaccine if her pregnancy will extend during the fall and winter seasons. Pregnant women should receive one dose of tetanus, diphtheria, and pertussis (Tdap) during each pregnancy (preferably during 27-36 weeks' gestation) regardless of interval since prior Td or Tdap immunization.

## Immunizations

Table 2.4 describes the indications for and uses of common vaccines.

TABLE 2.4. Adult Immunization Recommendations<sup>a</sup>

VACCINE	INDICATIONS	SCHEDULE	SPECIAL CONSIDERATIONS
Td/Tdap	All adults	Td booster every 10 years 1° series of three doses for adults with an uncertain history of 1° vaccination A single dose of Tdap should be given once, in place of Td, to adults <65 years	Give Tdap as soon as two years after the last Td for adults in close contact with <b>infants &lt;12 months</b> of age (eg, immediately postpartum) as well as to all health care workers.
HPV	Girls/young women 9–26 years and boys/young men 9–21 years (regardless of risk); men aged 22–26 years if immunocompromised (including HIV), men who have sex with men (MSM), or have never received HPV vaccine	Vaccinate at 11 or 12 years (or as early as 9 years) with catch-up vaccination between 13 and 26 years	Ideally, should be administered before the onset of sexual activity. Not recommended during pregnancy.
Herpes zoster (shingles)	Adults ≥60 years whether or not they have had a prior episode of VZV	One dose	Contraindicated in severely immunocompromised patients (eg, those with advanced HIV, with a hematologic malignancy, or on high-dose chronic steroids).
MMR	Adults born after 1957 without documentation of prior vaccination; particular targets for vaccination include college students, health care workers, international travelers, and women of childbearing age	One or two doses; a second dose is recommended for those at risk for measles or mumps (eg, students, health care workers, travelers)	Contraindicated in pregnancy and in immunodeficiency states.
Varicella	Adults without a clinical history of varicella, $\oplus$ titers, or a history of vaccination  Target close contacts of immunocompromised patients and patients at high risk for exposure/transmission (health care/child care workers, institutional staff and residents, college students, women of childbearing age)	Two doses 1–2 months apart	Contraindicated during pregnancy and in the setting of immunosuppression (including all HIV-infected patients).
Seasonal influenza	Recommended for all adults; particularly important in adults ≥50 years, any adult <50 years with chronic cardiopulmonary disease, health care workers, pregnant women, household contacts, and caregivers of young children	One dose annually	Live-attenuated intranasal vaccine is no longer recommended given lack of proven efficacy; all patients should receive the “flu shot” or the inactivated influenza vaccine.

(continues)

TABLE 2.4. Adult Immunization Recommendations (*continued*)

VACCINE	INDICATIONS	SCHEDULE	SPECIAL CONSIDERATIONS
Pneumococcal (polysaccharide): PPSV23 (older) PCV13 (newer)	All adults ≥65 years  Adults <65 years with chronic pulmonary disorders (excluding asthma), CVD, DM, chronic liver or renal disease, asplenia, or immunosuppression	Unvaccinated adults ≥65 years: PCV13, then PPSV23 12 months later  At-risk patients 19–64 years with comorbid conditions: PPSV23 vaccine only, give second dose ≥5 years later  Asplenic or immunocompromised patients 19–64 years: Both vaccines (PCV13 first, then PPSV23 8 weeks later)	The vaccine should be given at least 2 weeks before elective splenectomy.
Hepatitis A	Chronic liver disease, recipients of clotting factor concentrates, MSM, illicit drug users, health care workers in contact with infected individuals, travelers to endemic areas	Two doses 6–12 months apart or three doses at 0, 1, and 6 months	
Hepatitis B	Renal failure/dialysis, HIV, chronic liver disease, those at risk for STIs (MSM, those not in a long-term, mutually monogamous relationship), health care workers, injection drug users, recipients of factor concentrates, household contacts of HBV-infected individuals	Three doses (0, 1–2 months, 4–6 months)	Should be offered to any adult seeking protection against HBV.
Meningococcal: 4-valent conjugate Meningococcal B	Those with asplenia (anatomic or functional) or terminal complement deficiency, college students living in dorms, military recruits, travelers to endemic areas	1–3 doses depending on type of vaccine and indication; consider a second dose at 5 years for those given polysaccharide vaccine	

<sup>a</sup>Derived from guidelines established by the Centers for Disease Control and Prevention.

### KEY FACT

Live-attenuated vaccines are contraindicated in pregnancy. Do not give MMR, varicella, or oral polio vaccines to women who are pregnant or who may become pregnant within four weeks of vaccination.

#### Pneumococcal vaccines:

- There are two different types of pneumococcal vaccines: **PPSV23 (older)** and **PCV13 (newer)**.
- Vaccinate those at ↑ risk of invasive pneumococcal disease.
- If age ≥65 and unvaccinated, give one dose of PCV13, then 12 months later give one dose of PPSV23.
- Individuals aged 19 to 64 with comorbid conditions (chronic heart or lung disease, DM, alcoholism, cirrhosis, cigarette smoking) should receive PPSV23.
- Individuals aged 19 to 64 who are asplenic, immunocompromised (such as HIV, chronic renal failure, cancer, solid organ transplant, high-dose steroids for at least two weeks) or have a cerebrospinal fluid leak or cochlear implants should receive PCV13 followed by PPSV23 at least 8 weeks later.

### Nutritional and Herbal Supplements

- Vitamin and other nutritional deficiencies are discussed in the Hematology chapter. Table 2.5 lists the potential benefits of some common nutritional supplements.

**TABLE 2.5. Effects of Selected Dietary Supplements**

SUPPLEMENT	CLINICAL USE	EFFICACY
Glucosamine and chondroitin	Osteoarthritis	Unclear; meta-analyses have shown benefit for pain and function, but the largest randomized clinical trials (RCTs) have not shown improvement over placebo.
Vitamin E	Antioxidant; no current evidence for vitamin E in prevention of CVD, cancer, or dementia	Ineffective for vascular disease prevention. High-dose vitamin E may ↑ all-cause mortality.
Omega-3 fatty acids	Cholesterol lowering; prevention of atherosclerotic disease	No clear benefit in the prevention of CVD, cancer, or overall mortality.
Folic acid	Prevention of neural tube defects; prevention of atherosclerotic disease (through lowering of homocysteine levels)	Doses of 0.4 mg/day or higher are clearly effective in preventing neural tube defects and should be recommended to all women who may become pregnant. Doses of 4 mg/day are recommended for women taking antiepileptic medications during pregnancy. Several trials have shown no benefit in reducing the rate of clinical atherosclerotic disease despite lowered homocysteine levels.
Fiber supplements	Possible prevention of diverticulosis and colon cancer; cholesterol and blood sugar lowering	Epidemiologic studies suggest a benefit from high-fiber diets, but RCT data are limited.

- Because herbs and supplements are not regulated in the same way as prescription drugs, their purity and potency are highly variable. The level of evidence to support commonly used herbal treatments is poor to fair, and none is currently recommended over FDA-approved medications. Common herbal supplements include:
  - Ginkgo biloba: Has no clear benefit for the prevention of memory decline or for claudication symptoms. It may have an anticoagulant effect.
  - St. John's wort, which is used for depression, has inconsistent data for its use. It should not be combined with prescription with antidepressants because of the risk of serotonin syndrome. Be careful as it induces cytochrome P-450, thus decreasing some drug levels (eg, warfarin, digoxin, OCPs, antiretrovirals).

## Athletic Screening for Adolescents

Although rare, sudden death may occur in competitive athletes due to **hypertrophic cardiomyopathy**, **coronary anomalies**, left ventricular hypertrophy, a ruptured aorta (Marfan syndrome), familial arrhythmias, and other rare congenital or acquired cardiac diseases. Students should be evaluated before they participate in high school and college athletics and every 2 years during competition.

In addition to a careful cardiac history and exam, evaluation should include an ECG and echocardiogram in the presence of the following:

- Family history of premature sudden death or CVD.
- Symptoms of chest pain, dyspnea with exercise, syncope, or near-syncope.
- An elevated BP or abnormalities on cardiac exam (eg, murmur or a history of murmur).
- Marfan-like appearance (tall stature with long arms/legs/fingers).

### KEY FACT

Hypertrophic cardiomyopathy is the leading cause of sudden cardiac death in young athletes.

### KEY FACT

Commotio cordis, or sudden death due to direct blunt trauma to the chest wall and myocardium, is more common in young men and is caused by precipitation of a premature ventricular contraction initiating a tachyarrhythmia (ventricular fibrillation).

## Health Care Workers and Disease Exposure/Prevention

- TB can be transmitted in health care settings. All health care workers should have annual purified protein derivative (PPD) testing and screening for symptoms of active TB.
- Vaccines routinely recommended for health care workers include HBV, MMR, varicella (if not immune from natural infection), influenza, and Tdap.
- Blood-borne viruses—particularly HBV, HCV, and HIV—are the most common infections acquired by needlestick injuries.
- In the event of a needlestick or other percutaneous exposure, urgent assessment is warranted and includes the following measures:
  - Clean the wound thoroughly with soap and water.
  - Test the exposed worker for HBV (both active infection [HBV surface antigen] and immunity [HBV surface antibody]), HCV viral load, and HIV viral load.
  - Obtain a history that includes exposure type, the infection status of the source patient (by history and/or laboratory testing), and the vaccination history of the exposed worker.
  - Counsel the worker about the risk of infection and about the risks and benefits of postexposure prophylaxis with antiretrovirals to prevent HIV and/or HBV vaccination/HBIG to prevent HBV if not immune. There is no HCV postexposure prophylaxis.

### KEY FACT

Remember the “rule of 3’s” for occupational needlestick exposure—the likelihood of needlestick transmission is about 30% for HBV, 3% for HCV, and 0.3% for HIV.

## Ophthalmology

### RED EYE

Common causes of red eye include the following conditions.

#### Red Eye Without Pain or Change in Vision

**Conjunctivitis:** The most common cause of red eye. Presents with diffuse conjunctival injection without red flag symptoms (see the Key Fact). The three main etiologies are bacterial (Figure 2.1), viral (Figure 2.2), and allergic.

- Bacteria cause unilateral redness with purulent discharge; treat with erythromycin ointment or polymyxin-trimethoprim drops.



**FIGURE 2.1. Bacterial conjunctivitis.** Note the conjunctival injection and purulent discharge. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 2.2.** **Viral conjunctivitis.** Note the conjunctival injection and watery discharge.  
(Reproduced with permission from USMLE-Rx.com.)

- Viruses often cause bilateral redness with watery discharge; treatment is supportive.
- Allergies lead to bilateral redness with itching and tearing; treat with topical mast cell stabilizers or antihistamines.

### Red Eye With Pain and Change in Vision

Unlike conjunctivitis, the following causes of red eye present with **pain and change in vision**; these require **prompt referral to an ophthalmologist**:

- **Uveitis:** Often seen in the presence infectious, oncologic, and autoimmune disease. The presence of eye pain or ↓ visual acuity should raise suspicion for uveitis in patients presenting with red eye. “**Ciliary flush**” or circumcorneal redness on exam distinguishes this condition from conjunctivitis. May also have miosis, irregular pupil, photophobia.
- **Keratitis:** The most commonly tested etiology of red eye is **HSV keratitis**, which is usually unilateral and suggested by ↓ vision. Branching (dendritic) ulcers on fluorescein stain test are diagnostic. Bacterial keratitis presents with purulent discharge and punctate corneal lesions; common pathogens being *S aureus* and, for contact lens wearers, *Pseudomonas aeruginosa*.
- **Scleritis:** Localized or diffuse injection of the sclera (connective tissue just below the conjunctival epithelium; Figure 2.3). Presents with severe pain and vision loss. Associated with various autoimmune, granulomatous, and infectious diseases.



**FIGURE 2.3.** **Scleritis.** Note the injection of scleral vessels and violaceous hue. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

All patients with a red eye and any of the following red flag symptoms should be referred to an ophthalmologist emergently:

- Moderate to severe eye pain
- ↓ visual acuity
- Photophobia
- Pupillary abnormalities
- Ciliary flush (circumcorneal erythema)
- Hypopyon (layer of white cells in the anterior chamber) or hyphema (layer of red cells in anterior chamber)

### KEY FACT

Bacterial keratitis is an important complication of corneal abrasions in contact lens wearers. It is commonly caused by *Pseudomonas* species and has an aggressive course. Contact lens wearers with corneal abrasions should receive prophylactic topical antibiotics and close follow-up.



### QUESTION 1

A 27-year-old resident physician sustained a needlestick injury 2 hours earlier during a central line placement for a patient who is HIV and HBsAg +. The needle penetrated through the resident's latex glove and into his subcutaneous tissue. He rinsed out the wound. What should you advise at this time?



### QUESTION 2

A woman presents with one day of moderate pain and redness in her right eye. She also has blurry vision, tearing, and photophobia. Exam shows conjunctival injection around the cornea and ↓ acuity. The cornea is constricted, intraocular pressure is normal. Slit exam reveals cells and flares in the chamber and deposits on the posterior corneal surface. What is the most likely diagnosis?

**KEY FACT**

Refer a patient to ophthalmology emergently in the setting of red eye with profound eye pain or visual loss; severe nausea, vomiting, and headache (acute-angle glaucoma); or a mid-dilated and fixed pupil.

**MNEMONIC****Causes of red eye—****GO SUCK**

**G**laucoma  
**O**rbal disease  
**S**cleritis  
**U**veitis  
**C**onjunctivitis (viral, bacterial, allergic)  
**K**eratitis (HSV)

**KEY FACT**

Episcleritis typically presents without pain or visual disturbance; however, if unsure, urgent referral to ophthalmology is indicated.

**ANSWER 1**

Check baseline HBV, HCV, and HIV. Assuming prior immunity to HBV (HBV surface antibody  $\oplus$ ), all he needs to receive is HIV postexposure prophylaxis with antiretrovirals. If not immune to HBV, he would need to receive the HBV vaccine and HBIG immediately.

**ANSWER 2**

Anterior uveitis. The presence of eye pain with  $\downarrow$  visual acuity and "ciliary flush" (redness around the cornea) is concerning for uveitis.

- **Acute angle-closure glaucoma:** Acute onset of severe pain and vision loss, often associated with headache, nausea, and vomiting. On exam, the pupil is midsized and does not react to light, intraocular pressure is high, and the cornea is "steamy" (Figure 2.4). An emergency; refer to an ophthalmologist for laser iridectomy, pupillary constriction (topical pilocarpine), or pressure reduction (topical  $\beta$ -blockers, acetazolamide).

Additional etiologies of red eye include:

- **Foreign body:** Characterized by sharp superficial pain. Perform a fluorescein test to rule out corneal abrasion.
- **Episcleritis:** Presents with irritation, redness, watering without significant pain or visual disturbance. Usually mild and self-limited.
- **Gonorrheal conjunctivitis:** Presents with abrupt onset of redness and profuse purulent discharge in sexually active adults.
- **Chlamydial conjunctivitis:** Associated with chronic red eye in sexually active adults.
- **Subconjunctival hemorrhage:** Spares the limbus; common with trauma, prolonged coughing or vomiting, and anticoagulant use. Painless and resolves spontaneously in 2 to 3 weeks.
- **Hordeolum (stye):** Infection of Moll glands along the lash line. Presents with localized erythema, tenderness, and swelling. Treat with warm compresses; can use topical antibiotics although there is little evidence.
- **Chalazion:** Chronic, granulomatous inflammation of the meibomian gland. Presents with hard, nontender swelling on the upper or lower lid. Treatment by an ophthalmologist consists of incision and curettage or corticosteroid injection.

**LOSS OF VISION**

Vision loss is categorized as either acute or chronic. Etiologies of acute loss of vision include the following:

- **Retinal artery occlusion:** An emergency characterized by sudden, painless, unilateral, near-complete blindness and by a "cherry-red spot" in the macula (Figure 2.5). Can be associated with an afferent pupillary defect. Can be transient (amaurosis fugax, see below) or permanent. Commonly due to thrombosis, embolus, or arteritis (eg, giant cell [temporal] arteritis).
- **Amaurosis fugax** (transient vision loss): Most commonly caused by retinal or optic nerve ischemia from carotid thromboembolism. Patients complain that "a curtain came down over my eye," usually for only a few minutes. Evaluate with carotid imaging (ultrasonography or MRA), and rule out giant cell arteritis with ESR/CRP in patients  $\geq 50$  years. Consider an echocardiogram and a brain MRI.
- **Retinal vein occlusion:** Subacute and painless with varying degrees of visual loss and intra-retinal hemorrhage (Figure 2.6). Commonly due to hypertension, hyperviscosity syndromes, hypercoagulable states (eg, from OCP use), or Behcet disease.



**FIGURE 2.4. Acute angle-closure glaucoma.** Note the firm, red right eye, hazy cornea, and dilated pupil. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 2.5. Retinal artery occlusion.** Color fundus photograph of the left eye demonstrates areas of ischemia (“cotton-wool” spots) and a “cherry-red” spot of the fovea—findings strongly suggest ischemia to the inner retina, as would be found in a central retinal artery occlusion.

(Reproduced with permission from USMLE-Rx.com.)

- **Vitreous hemorrhage:** Bleeding into the vitreous humor due to vitreous detachment, proliferative diabetic retinopathy, retinal tears or trauma. Visual acuity may be normal or ↓ depending on the degree of hemorrhage.
- **Retinal detachment:** Painless unilateral blurred vision that progressively worsens (**floaters or lights in peripheral vision**). May be spontaneous or due to trauma (Figures 2.7 and 2.8). Considered an emergency. Can also occur postoperatively, particularly after cataract surgery.



#### KEY FACT

Retinal artery occlusion can be distinguished from retinal vein occlusion by the presence of the cherry red spot, corresponding to the appearance of the fovea.



**FIGURE 2.6. Central retinal vein occlusion.** Color fundus photograph of the right eye demonstrates four quadrants of intraretinal and nerve fiber layer hemorrhages and exudates (giving a “blood and thunder” appearance). There is also edema of the retina throughout. Patient was a 62-year-old woman with hypertension presenting with painless, dramatically ↓ vision for two days. (Reproduced with permission from USMLE-Rx.com.)



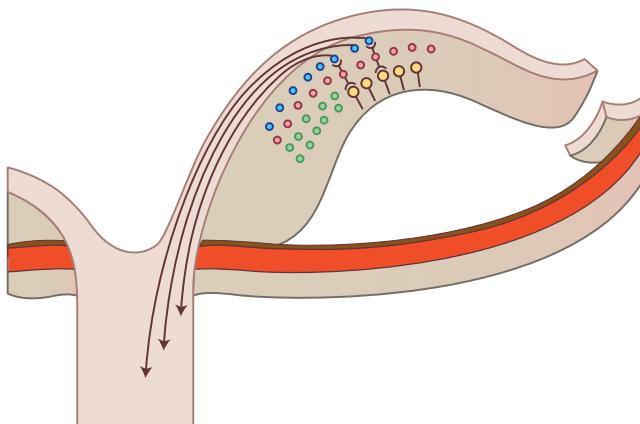
#### QUESTION

A 73-year-old man with hypertension presents with 2 days of painless, sudden vision loss in his right eye. Fundoscopic exam reveals a pale retina and a cherry-red spot in the macula. An afferent pupillary defect is also detected (paradoxical dilation of the pupil when light is moved from the unaffected eye to the affected eye). What is the diagnosis?

**MNEMONIC****Causes of Cataracts—****ABCD**

**A**ging  
**B**ang (trauma)  
**C**ongenital

**D**iabetes and other metabolic diseases  
(long-term corticosteroids)

**FIGURE 2.7. Retinal detachment.** With nerves intact and no afferent pupillary defect.

(Reproduced with permission from USMLE-Rx.com.)

**FIGURE 2.8. Tractional retinal detachment.**

**detachment.** Color fundus photograph of the left eye demonstrates detached retina. Neovascularization of the retinal vasculature and fibrous proliferation along these vessels into the vitreous is also seen, causing retinal traction. Patient was a 60-year-old man with long-standing proliferative diabetic retinopathy and a 3-month history of vision limited to hand movements only. (Reproduced with permission from USMLE-Rx.com.)

Etiologies of chronic loss of vision include the following:

- **Optic neuritis:** Unilateral visual loss that develops over several days, often accompanied by pain with eye movement and afferent pupillary defect that improves within 2 to 3 weeks. Associated with demyelinating diseases, especially multiple sclerosis.
  - **Other:** Uveitis, keratitis, acute angle closure glaucoma. See Red Eye section above.
- Etiologies of chronic loss of vision include the following:
- **Age-related macular degeneration (AMD):** The most common cause of visual loss in older adults in the United States. Irreversible. Risk factors include older age, smoking, HTN, family history of AMD, and white race. Characterized by rapid or gradual loss of central vision, with central scotomas (shadows or distorted vision). “Dry” AMD is characterized by drusen (yellow deposits in the macula; Figure 2.9); “wet” (neovascular) AMD is marked by angiogenesis or choroidal neovascularization. Antioxidants (beta-carotene, vitamins C and E) and zinc supplementation ↓ the

**FIGURE 2.9. Age-related macular degeneration.** Color fundus photograph of the left eye demonstrates many large yellow lesions deep to the retina (behind the retinal blood vessels) consistent with drusen as found in age-related macular degeneration. Patient was a 76-year-old woman with “wavy” vision in her right eye. (Reproduced with permission from USMLE-Rx.com.)**ANSWER**

Retinal artery occlusion. This is suggested by sudden, painless vision loss with cherry red spot in the macula and afferent pupillary defect (APD). The APD is typically due to either severe retinal disease or optic nerve damage; in this case the retinal artery occlusion causes retinal damage.

risk of progression to the wet form. Urgent referral for wet AMD is warranted for possible laser treatment or intravitreal injections of VEGF inhibitors.

- **Open-angle glaucoma:** Loss of peripheral vision (“tunnel vision”) over years. Characterized by ↑ intraocular pressure and an ↑ cup-to-disk ratio (“cupping”). Treatment includes a combination of topical  $\beta$ -blockers,  $\alpha_2$ -agonists, carbonic anhydrase inhibitors, and prostaglandin analogs.
- **Cataracts:** The leading cause of blindness worldwide, yet reversible. Blurred vision occurs over months or years, with visible lens opacities. Treatment consists of surgical lens replacement.
- **Nonproliferative diabetic retinopathy:** The most common cause of legal blindness in adult-onset DM. Characterized by microaneurysms, hard exudates, retinal hemorrhages (Figure 2.10), macular edema (Figure 2.11), ischemia, and cotton-wool spots. Treat with intensive blood glucose control and laser photocoagulation.
- **Proliferative diabetic retinopathy:** Presents with neovascularization (Figure 2.12); vitreous hemorrhage is a common complication. Treat with laser photocoagulation.

### KERATOCONJUNCTIVITIS SICCA (DRY EYE SYNDROME)

A common condition, especially in middle-aged and older women. Hypofunctioning of the lacrimal glands ↓ the aqueous component of tears and leads to dry eyes. Often idiopathic, but may be associated with **Sjögren syndrome** (check ANA, anti-Ro [SSA], and anti-La [SSB]) and with certain drugs (eg, antihistamines, topical  $\beta$ -blockers).

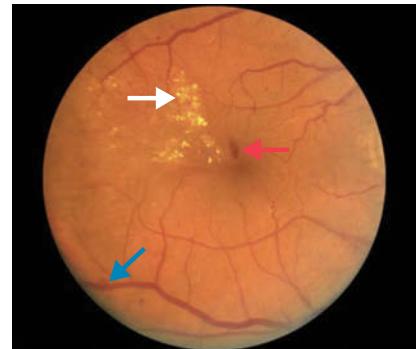
- **Symptoms/Exam:** Presents with dryness, redness, burning, or a “scratchy” feeling in the eyes.
- **Management:** Artificial tears (eg, methylcellulose solution).



**FIGURE 2.11. Clinically significant macular edema.** Color fundus photograph of the left eye demonstrates a ring of exudates from chronic diabetic edema (arrow) that meets the size criteria and proximity to the fovea to be called clinically significant diabetic macular edema. Patient was a 42-year-old man with poorly controlled DM presenting with ↓ visual acuity in the left eye. (Reproduced with permission from USMLE-Rx.com.)


**KEY FACT**

The most common cause of irreversible vision loss in older adults is age-related macular degeneration. Antioxidants and zinc may slow down progression to the “wet” (neovascular) form.



**FIGURE 2.10. Nonproliferative diabetic retinopathy.** Exudates (white arrow), dot-blot hemorrhages (red arrow), and microaneurysms (blue arrow) are seen. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 2.12. Neovascularization (arrow) in proliferative diabetic retinopathy.** (Reproduced with permission from USMLE-Rx.com.)


**KEY FACT**

Consider Sjögren syndrome, an autoimmune disease that attacks the exocrine glands that make tears and saliva, in a middle-aged woman who complains of dry eyes.

## Ear, Nose, and Throat

### KEY FACT

Distinguish bacterial from viral sinusitis with the following characteristics: Severe symptoms, symptoms >10 days without clinical improvement, or "double worsening" with new more severe symptoms after initial improvement.

### KEY FACT

If sinusitis is chronic and resistant to treatment, consider anatomical sinus obstruction, common variable immunodeficiency, a cystic fibrosis variant, or granulomatous polyangiitis.

### KEY FACT

When used for more than a few days, nasal decongestants such as oxymetazoline can cause rebound nasal congestion and discharge (rhinitis medicamentosa).

### KEY FACT

The Boards value antibiotic stewardship. Thus, if it sounds viral in nature, do not give antibiotics.

### BACTERIAL SINUSITIS

The majority of sinusitis cases are viral. Bacterial sinusitis results from impaired mucociliary clearance and obstruction of the osteomeatal complex. Viral and allergic rhinitis predispose to acute bacterial sinusitis. Etiologies are as follows:

- **Most common causative organisms:** *Streptococcus pneumoniae*, other streptococci, *Haemophilus influenzae*.
- **Less common organisms:** *S aureus* and *Moraxella catarrhalis*.
- Chronic sinusitis may also be caused by *P aeruginosa* and anaerobes.

### Symptoms/Exam

- Presents with nasal drainage, fever, unilateral or bilateral pain over the maxillary or frontal sinus, or with a toothache. Acute sinusitis lasts >1 week and up to 4 weeks. Chronic sinusitis lasts >4 weeks.
- Exam reveals purulent nasal discharge and tenderness over the affected sinus.

### Differential

**Mucormycosis** is a rare but invasive fungal disease that spreads through the blood vessels and primarily affects **immunocompromised** patients, including those with DM, end-stage renal disease, bone marrow transplant, lymphoma, and HIV with a low CD4 count. Presents as sinusitis with more extreme facial pain accompanied by a **necrotic eschar** of the nasal mucosa and cranial neuropathies in the later stages. Treat emergently with amphotericin B and ENT surgical debridement.

### Diagnosis

- Generally made through the history and clinical exam; do **not** need a CT scan for uncomplicated sinusitis. If suspect an intracranial or orbital complications, obtain CT (better than x-ray and can detect air-fluid levels or bony abnormalities).
- Symptoms that last  $\geq 10$  days and include any of the following are suggestive of bacterial sinusitis:
  - Purulent nasal discharge (viral has clear discharge).
  - Maxillary **tooth or facial pain**, especially unilateral.
  - Unilateral maxillary sinus tenderness (viral with no tenderness).
  - Symptoms that worsen after initial improvement.
- In cases of chronic or refractory sinusitis, perform a CT scan and consider allergy testing with allergy/immunology, rhinoscopy (nasal endoscopy), and sinus cultures with ENT. Nasal cultures are **not** helpful.
- Abnormal vision, changes in mental status, or periorbital edema may point to intra-cranial or orbital extension of the infection and warrant urgent referral to a specialist.

### Management

- No antibiotics are indicated if suspect viral etiology. Treat symptomatically with intranasal glucocorticoid sprays (eg, fluticasone) and decongestants (oral decongestant or short course of nasal decongestant <3 days).
- **Acute bacterial sinusitis:** Amoxicillin or TMP-SMX; amoxicillin-clavulanate in the presence of risk factors for anaerobes or resistant  $\beta$ -lactamase organisms (some strains of *H influenzae* and *M catarrhalis*). Risk factors include DM, immunocompromised states, and recent antibiotic use.
- **Chronic sinusitis:** Amoxicillin-clavulanate for at least 3 to 4 weeks along with short course of systemic glucocorticoids and nasal rinse or intranasal glucocorticoid sprays.

## ACUTE OTITIS MEDIA

Common causative organisms include *S pneumoniae*, *H influenzae*, *M catarrhalis*, *Streptococcus pyogenes*, and viruses.

### Symptoms/Exam

Presents with ear pain, ear fullness, ↓ hearing, ↓ light reflex, and an erythematous, bulging tympanic membrane (Figure 2.13).

### Differential

Distinguish on exam from serous otitis media, which is characterized by a normal or dull tympanic membrane (TM) that is not red; there should be no purulent fluid behind the TM (do not give antibiotics).

### Management

- Amoxicillin 10 to 14 days.
- For penicillin-allergic patients, give cephalosporin in patients who do not have anaphylaxis to penicillin, or a macrolide (erythromycin, azithromycin, clarithromycin). TMP-SMX can also be used, but check local resistance patterns as there is increasing resistance of *S pneumoniae* to TMP-SMX.

## OTITIS EXTERNA

Predisposing factors include water exposure or mechanical trauma (eg, Q-tips). Often caused by *S aureus*, *S epidermidis*, and gram-negative rods (eg, *Pseudomonas*, *Proteus*). May also be caused by a fungus (eg, *Aspergillus*).

- **Symptoms/Exam:** Characterized by ear pain that is often accompanied by pruritus and a purulent discharge. Pain is elicited on manipulation of the pinna. Erythema and edema of the ear canal with exudate may be seen. A black or white discharge is seen in fungal infections.
- **Management:**
  - Give otic drops combining a corticosteroid with either an antibiotic (eg, neomycin sulfate plus polymyxin B sulfate) or acetic acid.
  - Clear the canal of cerumen and debris with a curette or hydrogen peroxide; use a cotton wick if blockage is severe.

## HEARING LOSS

Hearing loss (HL) is categorized as **conductive** (middle or external ear damage) or **sensorineural** (inner ear—cochlea or auditory nerve).

### Symptoms/Exam

- Differentiate between conductive and sensorineural HL with Weber and Rinne tests (Figure 2.14):
  - **Weber Test:** Tuning fork held on forehead. Sound is equal in both ears in a normal test. If the sound is louder in one ear, it is indicative of either conductive hearing loss in the louder ear or sensorineural hearing loss in softer ear.
  - **Rinne Test:** Tuning fork held against the mastoid process and then moved to outside the external ear canal once the patient can no longer hear the sound conducted by the mastoid process. In a normal test, air conduction > bone conduction and the sound can be heard again. This can be the case in normal patients or with sensorineural hearing loss. If the sound cannot be heard and bone conduction > air conduction, the patient has conductive hearing loss in that ear.
- Conduct an audiology test.



**FIGURE 2.13. Acute otitis media with bulging tympanic membrane.**

(Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

Malignant external otitis is seen in diabetics and other immunocompromised patients. Caused by *P aeruginosa*, the otitis evolves into osteomyelitis and presents with severe ear pain, a foul-smelling discharge, and cranial nerve palsies.

### QUESTION 1

A 54-year-old woman with type 2 DM presents with a cough, nasal congestion, a purulent nasal discharge, and a severe headache for the past month. She looks unwell and has a low-grade fever, right frontal sinus tenderness, and ↓ vision in the right eye. What are the next most appropriate steps in management?

### QUESTION 2

A 40-year-old woman complains of several sporadic and unpredictable "dizzy spells" over the past year, described as an overwhelming spinning sensation accompanied by a sense of ear fullness with ringing and hearing loss. What is the most likely diagnosis and treatment?

**KEY FACT**

In conductive HL, Weber test is positive (louder in AFFECTED ear) and Rinne is abnormal (bone is louder). Common causes are cerumen and otitis media.

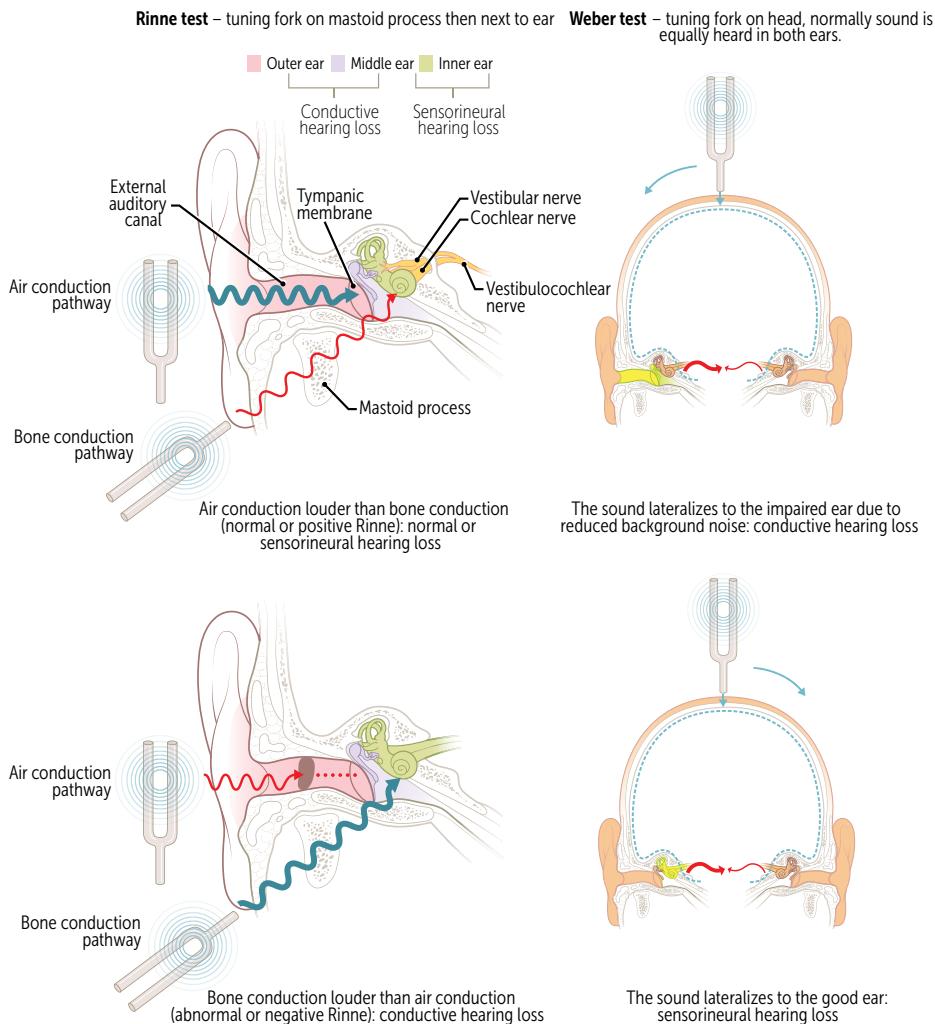


FIGURE 2.14. **Weber and Rinne tests.** (Reproduced with permission from USMLE-Rx.com.)

**A****ANSWER 1**

Urgent CT scan and referral to a specialist to rule out orbital or other intracranial complications associated with chronic sinusitis. With DM, she is also at risk for mucormycosis.

**A****ANSWER 2**

Ménière disease, which is suggested by the episodic vertigo accompanied by hearing loss, ear fullness, and tinnitus. Treat with a low-salt diet and diuretic.

**Differential**

- Sensorineural HL: Problem is in the inner ear (cochlea or cranial nerve VIII). The most common cause is age (presbycusis). Other causes include excessive noise exposure, ototoxic drugs, Ménière disease, acoustic neuroma.
- Conductive HL: Problem is in the outer or middle ears so that the way sound is conducted to inner ear is abnormal. Causes include cerumen, otitis externa, otitis media, otosclerosis, eustachian tube blockage, perforated tympanic membrane.

**Management**

- Prevention is the best treatment. Avoid excessive noise.
- Treat the underlying cause; may necessitate repair of the tympanic membrane or replacement of ossicles (in otosclerosis).
- For persistent sensorineural or conductive HL, consider hearing aids or, in cases of profound HL, cochlear implants.

**TINNITUS**

Tinnitus is the perception of abnormal ear noises, usually due to hearing loss. Although bothersome, it is benign in the absence of other symptoms.

## Differential

- Ménière disease (episodic vertigo, sensorineural HL, tinnitus, and ear pressure).
- Vascular abnormalities, such as carotid stenosis, AVMs, and vascular tumors, cause **pulsatile tinnitus**, which can often be heard by the examiner.
- Thyroid disease, anemia, hyperlipidemia, vitamin B<sub>12</sub> deficiency are treatable causes.

## Management

Avoid exposure to excessive noise and ototoxic drugs (aminoglycosides, salicylates, loop diuretics, cisplatin). No therapy has been shown to be effective. For mild symptoms, a white noise generator or other background noise can help with sleep.

## ORAL LESIONS

Tables 2.6 and 2.7 outline the differential diagnosis of common oral lesions. See Figures 2.15, 2.16, and 2.17 for images of oral thrush, aphthous ulcers, and HSV gingivostomatitis, respectively.

## PHARYNGITIS

Most pharyngitis is due to viruses; however, the main concern lies in identifying group A β-hemolytic streptococcus (GABHS) infection. Antibiotic treatment of GABHS usually **prevents rheumatic fever** and local abscess formation; it does **not** prevent poststreptococcal glomerulonephritis.

## Symptoms/Exam

The four classic features of GABHS infection (Centor criteria) are as follows:

- Fever >38°C (100.4°F).
- Tender anterior cervical lymphadenopathy.
- The absence of cough.
- Pharyngotonsillar exudate.

### KEY FACT

The presence of cough, hoarseness, and rhinorrhea makes GABHS less likely.

**TABLE 2.6. Differential Diagnosis of White Oral Lesions**

	THRUSH	LEUKOPLAKIA	LICHEN PLANUS
Definition/epidemiology	Oral candidiasis, often in immunocompromised patients (AIDS, DM, chemotherapy, local radiation, steroids, antibiotics)	Squamous hyperplasia due to chronic irritation (dentures, tobacco), but ~ 2%-6% represent dysplasia or early invasive squamous cell carcinoma (SCC)	Common; chronic inflammatory autoimmune disease
Symptoms	Pain	None	Discomfort; often confused with candidiasis, leukoplakia, or SCC
Exam	Creamy white patches over red mucosa (see Figure 2.15)	<b>White lesions cannot be rubbed off</b>	Reticular or erosive
Diagnosis	Clinical; can do KOH wet prep (spores)	Biopsy	Biopsy
Treatment	Topical therapy with clotrimazole troches or nystatin; fluconazole × 7-14 days in HIV patient	Treat if cancer	Steroids (oral or topical)



**FIGURE 2.15. Oral candidiasis (thrush).** (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 2.16. Aphthous ulcers.**  
(Source: Hasan A, et al. Remission of severe aphthous stomatitis of celiac disease with etanercept. *Clin Mol Allergy*. 2013;11:6.)



**FIGURE 2.17. Herpes simplex 1° gingivostomatitis.** A 16-year-old girl with mild fever and itchy erosion of the lip with scalloped border and vesicles.  
(Reproduced with permission from USMLE-Rx.com.)

**TABLE 2.7. Differential Diagnosis of Common Mouth Ulcers**

	APHTHOUS ULCER (CANKER SORE)	HERPES STOMATITIS
Cause	Common; unknown cause (possible association with HHV-6)	Common; HSV
Symptoms	Pain up to 1 week; heals within a few weeks	Initial tingling and burning followed by small vesicles and then scabs
Differential	If large or persistent, consider erythema multiforme, HSV, pemphigus, Behcet disease, IBD, or SCC	Aphthous ulcer, erythema multiforme, syphilis, cancer
Treatment	Topical analgesics and steroids	Not needed, but oral acyclovir $\times$ 7-14 days may shorten the course and mitigate postherpetic pain

### Differential

- **Mononucleosis:** Caused by Epstein-Barr virus (EBV), and occurs primarily in young adults, accounting for 5% to 10% of sore throats; characterized by lymphadenopathy, fever, and tonsillar exudates. Symptoms also include severe fatigue, headache, and malaise. Diagnose with a  $\oplus$  heterophile antibody (Monospot) test or a high anti-EBV titer. Complications include hepatitis, a morbilliform rash after ampicillin administration, and splenomegaly occurring within the first 3 weeks. Avoid noncontact sports for 3 to 4 weeks and contact sports for 4 to 6 weeks after symptom onset to  $\downarrow$  the risk of splenic rupture.
- **Diphtheria:** Presents as sore throat, fever, and malaise with gray pseudomembranes on the tonsils. May be complicated by myocarditis and cranial neuropathies.
- **Viruses:** Viral infection is suggested by rhinorrhea and cough, other upper respiratory tract symptoms, and the absence of tonsillar exudate.
- **STIs:** Gonorrheal and chlamydial pharyngitis should be considered in sexually active patients.

### Diagnosis

- Use Centor criteria (see Key Fact).
- **GABHS rapid antigen test:** The test of choice; has  $>90\%$  sensitivity. Routine cultures are not needed.

### Management

- Most pharyngitis is viral, so do not use antibiotics.
- If treating strep, use penicillin or amoxicillin for 10 days. For penicillin-allergic patients, consider clindamycin, cephalexin, cefadroxil, or a macrolide (azithromycin, clarithromycin).
- Antibiotics shorten the symptom course by 1 to 2 days if begun  $<48$  hours after symptom onset and  $\downarrow$  infectivity (consider if the patient lives with small children).

### ACUTE BRONCHITIS

Acute bronchitis is a nonspecific term used to describe patients with normal underlying lungs who develop an acute cough with no clinical evidence of pneumonia. The most common causative organisms are respiratory viruses (coronavirus, rhinovirus, influenza, parainfluenza) and, to a lesser extent, atypical bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*).

## Symptoms/Exam

- Presents with cough (productive or nonproductive) that may persist for 1 to 3 weeks, often with initial upper respiratory tract infection (URTI) symptoms (rhinorrhea, sore throat).
- Exam findings range from clear to wheezes or rhonchi (from bronchospasm).

## Differential

- Community-acquired pneumonia.
- *B pertussis* infection (whooping cough) should be considered if symptoms persist for  $\geq 2$  weeks. Presents as a persistent “barking” or paroxysmal cough following typical URTI symptoms. A high WBC count with striking lymphocytosis is typical. Throat swab for PCR testing or culture are the diagnostic tests of choice to prevent illness among contacts (especially infants), although sensitivity is low at the time of usual presentation. Treat with azithromycin to  $\downarrow$  shedding. Prophylaxis for household and close contacts is azithromycin or erythromycin. Ensure patient and families have received Tdap (see Immunizations above).

## Diagnosis

Made clinically. CXR is not routinely indicated.

## Management

- In patients with no underlying pulmonary disease, antibiotics are not indicated given the common viral etiology.
- Decongestants, expectorants, bronchodilators, and humidified air are used for symptomatic treatment.

## Urology

### URINARY INCONTINENCE

See the Geriatrics chapter for a complete discussion of urinary incontinence, including subtypes, clinical presentation, and treatment.

### BENIGN PROSTATIC HYPERPLASIA

Prevalence of benign prostatic hyperplasia (BPH)  $\uparrow$  with age;  $>90\%$  of men  $>80$  years of age have an enlarged prostate.

## Symptoms/Exam

- Obstructive symptoms include difficulty initiating a stream, terminal dribbling, and a weak stream.
- Irritative symptoms include urgency, frequency, and nocturia.
- DRE may reveal an enlarged, symmetrically firm prostate, but the size of the prostate correlates poorly with symptom severity.

## Differential

Urethral stricture, prostate cancer, bladder cancer, bladder stones, UTI, interstitial cystitis, prostatitis, prostatodynia, neurogenic bladder.

### KEY FACT

Clinical algorithm for GABHS infection: Count the number of Centor criteria present.

- **4 of 4:** Treat empirically without a rapid antigen test
- **2-3 of 4:** Test and treat patients with  $\oplus$  results
- **0-1 of 4:** No test and no antibiotic treatment

### KEY FACT

Treatment of confirmed strep pharyngitis prevents rheumatic fever.

### KEY FACT

If symptoms are refractory to an  $\alpha$ -blocker alone, add a  $5\alpha$ -reductase inhibitor.  $5\alpha$ -reductase inhibitors may be more effective for patients with severe symptoms and larger prostates.



### QUESTION 1

A 78-year-old man presents with one year of progressive nocturia, difficulty initiation stream, urinary urgency and frequency. What is the most appropriate initial treatment for his BPH?



### QUESTION 2

A 50-year-old man with BPH presents to a clinic with fevers, chills, and dysuria for 3 days. He has mild, diffuse tenderness in the lower abdomen without rebound or guarding, and his prostate is very tender. What is the most likely diagnosis and most appropriate management?

**KEY FACT**

Finasteride and dutasteride ( $5\alpha$ -reductase inhibitors) can lower PSA levels by 50%. In men who are being screened for prostate cancer and are taking these drugs, the biopsy threshold should be lowered accordingly.

**Diagnosis**

- Diagnosed mainly by the history and exam.
- Obtain a UA and serum creatinine to diagnose post-obstructive kidney injury.
- PSA may be elevated in BPH but is not needed for diagnosis.

**Management**

Depending on the severity of lower urinary tract symptoms, treatment options include behavioral modifications, pharmacologic therapy, and surgery:

- **Mild:** Behavior modification (avoiding fluids at bedtime, reducing caffeine and alcohol, double voiding to empty bladder more completely).
- **Moderate to severe:** Initiate treatment with  $\alpha$ -blockers for immediate symptomatic relief. If symptoms are severe, combine with a  $5\alpha$ -reductase inhibitor, which blocks conversion of testosterone to dihydrotestosterone. Urology referral and surgery are indicated for severe symptoms or complications of BPH (eg, refractory retention, hydronephrosis, recurrent UTIs, recurrent gross hematuria, renal insufficiency due to BPH, bladder stones, persistent symptoms). Surgical options include transurethral resection of the prostate (TURP) and other minimally invasive procedures. Side effects of TURP include the need for transfusion, retrograde ejaculation, impotence (10%-40%; operator dependent), urethral stricture, and urinary incontinence.

**ERECTILE DYSFUNCTION**

See the Geriatrics chapter for an overview of erectile dysfunction.

**PROSTATITIS**

The differential of prostatitis includes acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, and prostodynia. See Table 2.8 for key features of each.

- **Symptoms/Exam:** Presents with irritative voiding symptoms and perineal or suprapubic pain. Acute bacterial prostatitis is notable for the presence of fever and an exquisitely tender prostate.
- **Management:** Table 2.8 outlines the treatment of acute prostatitis, chronic prostatitis, and chronic pelvic pain syndrome.

**A****ANSWER 1**

Watchful waiting and behavior modification are appropriate for mild symptoms, but the severity of this patient's symptoms warrants treatment with an  $\alpha$ -blocker, such as prazosin, doxazosin, or terazosin.

**Orthopedics****A****ANSWER 2**

Acute bacterial prostatitis. Send UA, urine culture, gonorrhea/chlamydia, and start antibiotics that cover gram-negative rods for 2 to 4 weeks.

**ROTATOR CUFF TENDINITIS OR TEAR**

Spectrum of rotator cuff injuries ranges from subacromial bursitis and tendinopathy to partial or full tear.

**Symptoms/Exam**

- Presents with nonspecific pain in the anterolateral shoulder with occasional radiation down the lateral arm above the elbow that worsens at night or with overhead movement, sleeping, or reaching behind (eg, putting on a jacket).
- **Motor weakness with abduction** suggests the presence of a **tear**.

**TABLE 2.8. Treatment of Prostatitis and Prostodynna**

	ACUTE BACTERIAL PROSTATITIS	CHRONIC BACTERIAL PROSTATITIS	CHRONIC PELVIC PAIN SYNDROME <sup>a</sup>
Fever	+	-	-
UA	+	-	-
Bacterial culture	+	+	-
Prostate exam	Very tender	Normal, boggy, or indurated	Can be normal, boggy, or indurated.
Etiology	Gram-negative rods ( <i>E coli</i> ); less commonly gram-positive organisms ( <i>enterococcus</i> ) or STIs ( <i>Neisseria gonorrhoea</i> or <i>Chlamydia trachomatis</i> )	Gram-negative rods; less commonly enterococcus	Varies; includes voiding dysfunction and pelvic floor musculature dysfunction. Infectious causes have been implicated but largely disproven.
Treatment	Broad coverage of gram-negative rods, initially with a fluoroquinolone or TMP-SMX until cultures return  The duration of treatment is typically 2 weeks and can be extended in severe illness or persistent symptoms  If STI, treatment is the same as urethritis	First line: Fluoroquinolones, or TMP-SMX (diffuse into prostate well)  The duration of treatment is controversial: 4-6 weeks but may be extended  Suppressive therapy may be used in relapses	Trial of one antibiotic course (fluoroquinolone) plus $\alpha$ -blocker.  Continue $\alpha$ -blocker if patient has response.  Second line: 5 $\alpha$ -reductase inhibitors, anti-inflammatories, psychological support.

<sup>a</sup>Formerly known as nonbacterial prostatitis and prostodynna.

(Data from McPhee SJ, et al. *Current Medical Diagnosis & Treatment 2010*. New York, NY: McGraw-Hill, 2010. Table 23-2. Lipsky BA, Byren I, Hoey CT. Treatment of Bacterial Prostatitis. *Clin Infect Dis*. 2010;50(12):1641-1652.)

- Exam reveals pain with abduction between 60 and 120 degrees (“painful arc test”). Tears lead to weakness on abduction (“drop arm test”).
- Pain elicited by 60 to 120 degrees of passive abduction (**impingement sign**) suggests impingement or trapping of an inflamed rotator cuff on the overlying acromion.

### Differential

- Bicipital tendinitis: Due to repetitive overhead motion (eg, throwing, swimming). Exam reveals tenderness along the biceps tendon or muscle and  $\oplus$  Yergason (resisted supination) and Speed (resisted flexion/supination) tests.
- Labral tear.
- Degenerative joint disease.
- Cervical spine disease.
- Systemic arthritis: RA, pseudogout.
- Referred pain: May be derived from a pulmonary process (eg, pulmonary embolism, pleural effusion), a subdiaphragmatic process, cervical spine disease or brachial plexopathy.
- Adhesive capsulitis (frozen shoulder): Presents with progressive loss of range of motion (ROM), usually more from stiffness than from pain. Can follow rotator cuff tendinitis; more common in diabetics and older patients.

### Diagnosis

- Diagnosis is made by the history and exam.
- An MRI can be obtained if a complete tear is suspected or if no improvement is seen despite conservative therapy and the patient is a surgical candidate.



### QUESTION

For 3 days, a 45-year-old man has had right shoulder pain that worsens when he lifts his arms above his head and when he lies on his right side. On exam, he has pain with active and passive abduction, but his strength is intact. What is the likely diagnosis?

### Management

- ↓ exacerbating activities; NSAIDs. Also consider steroid injection.
- Physical therapy in the form of ROM exercises and rotator cuff strengthening can be initiated once acute pain has resolved. Immobilization not advised to avoid developing adhesive capsulitis.
- Refer to orthopedics for possible surgery if there is a complete tear or if no improvement after several months of conservative therapy.

### KNEE PAIN

#### KEY FACT

Knee swelling immediately following trauma suggests a ligamentous tear (with hemarthrosis). Swelling that occurs hours to days after trauma suggests a meniscal injury.

Common etiologies of knee pain include:

- Osteoarthritis (cartilage loss).
- Inflammatory arthritis (eg, gout, pseudogout).
- Septic arthritis.
- Knee injuries (Table 2.9) or referred pain from hip or spine (eg, meniscal or ligamentous injury, bursitis).
- **Diagnosis: Ottawa Knee Rules.** Obtain an x-ray if any of the following risk factors for fracture are present after acute trauma to the knee (nearly 100% sensitivity):
  - Age ≥55 years.

**TABLE 2.9. Common Knee Injuries**

	SYMPOMTS	EXAM/TREATMENT
Iliotibial band syndrome	Lateral knee pain or gradual; tightness after running Often in runners	Tenderness over the lateral femoral epicondyle
Bursitis	Pain with motion and rest; more common in patients with underlying arthritis <b>Prepatellar bursitis:</b> Pain and swelling over the front of the knee <b>Anserine bursitis:</b> Pain medial and inferior to the knee joint	Exquisite tenderness at the bursa For persistent symptoms, corticosteroid injection
Patellofemoral pain syndrome	Anterior knee pain; often exacerbated by walking up and down stairs/hills “Runner’s knee” (from overuse) but also can occur if deconditioned	Pain on patellar compression while the patient contracts the quadriceps; exam is often nonspecific
Medial meniscus tear	A pop or tear at the time of injury; severe pain with “locking,” “catching,” and <b>swelling that peaks the next day</b> Twisting injury while foot is planted on ground (soccer, football) or degenerative tears in older patients	Medial joint line tenderness; pain on hyperflexion and hyperextension; ± knee effusion; $\oplus$ McMurray test (a pop or clicking sensation along the joint line with tibial rotation) Surgery only if symptoms persist
ACL tear	Audible “pop” and giving way; <b>immediate swelling</b> Twisting injury in noncontact sports (eg, skiing)	$\oplus$ anterior drawer sign; $\oplus$ Lachman test ( $\uparrow$ anterior movement of the tibia); knee effusion ACL reconstruction if the patient has a high activity level or significant knee instability

#### A

#### ANSWER

Rotator cuff **tendinitis** caused by repetitive overhead motion.

- Tenderness at the head of the fibula.
- Isolated patellar tenderness.
- Inability to bear weight both immediately after trauma and on exam.
- Inability to flex the knee to 90 degrees.
- **MRI** is most sensitive for soft tissue injuries (eg, meniscal and ligament tears).
- **Management:** Start with conservative therapy for all: RICE (rest, ice, compression, elevation), NSAIDs, and physical therapy as needed. See Table 2.9 for specific treatments.

## FOOT AND ANKLE PAIN

Foot and ankle pain is a common reason for 1° care visits; may be acute or chronic.

- **Differential:** See Table 2.10 for common causes of foot and ankle pain.
- **Diagnosis:** In acute ankle or foot pain after trauma, use the **Ottawa Ankle Rules** to determine the need for x-ray imaging (Figure 2.18).

TABLE 2.10. Common Causes of Foot and Ankle Pain

CAUSE	SYMPOMS	DIAGNOSIS	TREATMENT (CONSIDER NSAIDS FOR PAIN)
Plantar fasciitis	Plantar pain, especially with <b>first steps in morning.</b>	Tenderness over the insertion of the plantar fascia at the medial heel.  <b>X-ray not necessary for diagnosis</b> but may be helpful in ruling out other conditions.  Bone spurs on x-ray are neither sensitive nor specific for plantar fasciitis.	↓ prolonged standing; arch supports; stretches.  In 80% of cases, symptoms resolve within 1 year.
Stress fracture	Foot pain that worsens with weight bearing.  Occurs with increasing intensity of physical activity.	<b>X-ray may miss early fractures.</b>  Obtain a bone scan or an MRI in the setting of high suspicion and when x-ray is ⊖.	Hard-soled shoe or walking cast for 3-4 weeks.  Avoid exacerbating activities until fully healed.  May require unloading or non-weight-bearing.
Morton neuroma	<b>Forefoot pain and paresthesias radiating to the toes</b> due to entrapped nerve; the third web space is classic; patients feel pain while wearing shoes but not when barefoot.	Usually a clinical diagnosis (tenderness in affected web space).  MRI can confirm when surgery is a consideration.	Broad-toed shoes, orthotics, corticosteroid injections.  Surgery should be reserved for refractory cases.
Gout (See "Rheumatology" chapter)	<b>Sudden onset of exquisite pain in the first MTP</b> with redness/swelling.  Can also present as midfoot or Achilles tenosynovitis.	<b>Inflammatory signs</b> at the first MTP.  Other joints or risk factors for gout may be present.	NSAIDs, colchicine, oral or intra-articular corticosteroids.
Achilles tendinitis	Pain with running or jumping that <b>worsens with dorsiflexion</b> of the foot.	Tenderness at the Achilles insertion on the calcaneus.  Calf squeeze ( <b>Thompson test</b> ) diagnostic for complete rupture.  Consider an MRI if Achilles tendon tear is suspected.	Stretches, avoidance of offending activity.  Referral to surgeon if concerned for tear.
Tarsal tunnel syndrome	<b>Heel/plantar foot pain and paresthesias</b> due to entrapped posterior tibial nerve; pain at night and after prolonged weight bearing.	<b>Tinel sign:</b> Reproduction of symptoms by tapping the tibial nerve posterior and inferior to the medial malleolus.  X-ray is indicated to rule out associated bony abnormalities.	NSAIDs, shoe modification or orthotics, corticosteroid injections if not improved with conservative measures.



## QUESTION 1

A 50-year-old obese woman recently began to exercise regularly as part of a weight loss program. For the past month, she has experienced anterior right knee pain with ambulation that worsens when she climbs stairs. What is the most likely diagnosis?



## QUESTION 2

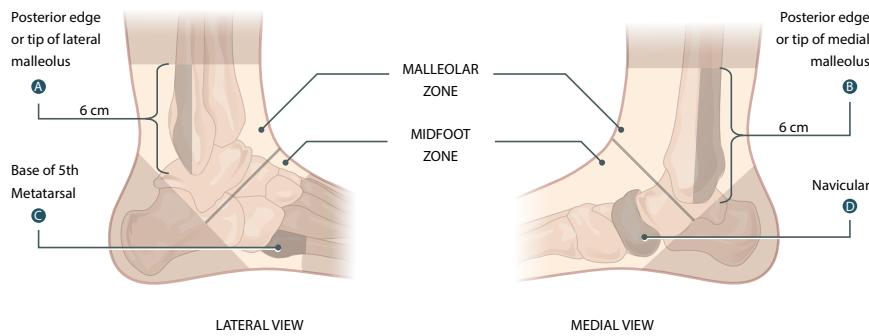
A 65-year-old man presents to your office with 6 months of lower back pain with walking downhill that is alleviated by sitting. Exam, including pulses, is normal. What is the most likely diagnosis?

**A****ANSWER 1**

Patellofemoral pain syndrome. This diagnosis is suggested by anterior knee pain that worsens with going up or down stairs.

**A****ANSWER 2**

Spinal stenosis.



**An ankle x-ray series** is only required if there is any pain in the malleolar zone and any of these findings:

- Bone tenderness at A
- Bone tenderness at B
- Inability to take 4 complete steps both immediately and in ED

**A foot x-ray series** is only required if there is any pain in the midfoot zone and any of these findings:

- Bone tenderness at C
- Bone tenderness at D
- Inability to take 4 complete steps both immediately and in ED

**FIGURE 2.18. Ottawa Ankle Rules for x-rays in ankle/foot trauma.** (Reproduced with permission from USMLE-Rx.com.)

**MNEMONIC****Back pain causes—****DISC MASS**

Degeneration (osteoarthritis, osteoporosis, spondylosis)

**Infection/Injury****Spondylitis**

Compression fracture

**Multiple myeloma/Metastases** (cancer of the breast, kidney, lung, prostate, or thyroid)

**Abdominal pain/Aneurysm**

**Skin** (herpes zoster), **Strain**, **Scoliosis**, and **lordosis**

**Slipped disk/Spondylolisthesis**

**LOWER BACK PAIN**

Lower back pain (LBP) is extremely common, with up to 80% of the population affected at some time. Three-quarters of LBP patients improve within 1 month. Most have self-limited, nonspecific mechanical causes of LBP.

**Symptoms/Exam**

- **Straight-leg raise test:**  $\oplus$  if passive leg flexion up to 60 degrees while supine or seated causes radicular pain. More sensitive (80%) than specific (40%) for lumbar disc herniation.
- A wide-based gait and a  $\oplus$  Romberg sign are specific signs of spinal stenosis.
- Test lower extremity strength, sensation, and reflexes. Exam may also localize the origin of the nerve root syndrome (Table 2.11).

**Differential**

- Serious causes of back pain and their associated risk factors include the following:
  - **Cancer:** Age >50 years, previous cancer history, unexplained weight loss. Most commonly breast, lung, thyroid, prostate, renal cell, and multiple myeloma.
  - **Infection** (epidural abscess, discitis, osteomyelitis, or endocarditis): Fever, recent skin infection or UTI, immunosuppression, injection drug use.

**TABLE 2.11. Nerve Root Syndromes (Sciatica)**

NERVE ROOT	STRENGTH	SENSORY	REFLEXES
S1	Ankle plantar flexion (toe walking)	Lateral foot	Achilles
L5	Great toe dorsiflexion	Medial forefoot	
L4 (less common)	Ankle dorsiflexion (heel walking)	Medial calf	Knee jerk

- **Cauda equina syndrome:** Pain accompanied by bilateral leg weakness, bowel or bladder incontinence, saddle anesthesia. A surgical emergency.
- **Compression fracture:** Age >50, significant trauma, a history of osteoporosis, corticosteroid use.
- **Inflammatory back pain:** Morning stiffness and pain at night, improvement in pain with activity. May have other manifestations of inflammatory or autoimmune conditions.
- Less urgent causes of back pain include herniated disc; spinal stenosis (Table 2.12); sciatica; musculoskeletal strain; and referred pain from a kidney stone, pyelonephritis, an intra-abdominal process, or herpes zoster.

### Diagnosis

- The history and clinical exam are helpful in identifying the cause.
- A plain x-ray is indicated **only if fracture, osteomyelitis, or cancer** is being considered.
- **Urgent MRI or CT** is indicated for **suspected cauda equina syndrome** (Figure 2.19), **cancer, or infection (epidural abscess)**.
- For patients with **suspected disc disease**, imaging is **not indicated unless symptoms persist for >6 weeks with conservative treatment or significant neurologic findings are present**.

### Management

Conservative therapy with NSAIDs and muscle relaxants, education, and **early return to ordinary activity**: Indicated for mechanical causes of acute LBP in the ab-

### KEY FACT

The two most common nerve root impingements are L5 and S1. Test L5 with resisted great toe extension (dorsiflexion). Test S1 by asking the patient to walk on toes (plantar flexion of ankle).

### KEY FACT

"Red flags" in the history of a patient with new-onset back pain:

- Age >50 years
- History of cancer
- Fever
- Weight loss
- Injection drug use
- Osteoporosis
- Lower extremity weakness
- Bowel or bladder dysfunction

**TABLE 2.12. Herniated Disc Versus Spinal Stenosis**

	HERNIATED DISK	SPINAL STENOSIS
Etiology	Degeneration of ligaments results in disc prolapse, leading to compression or inflammation of the nerve root.  Usually caused by disc herniation into L4-L5 or L5-S1 levels.	Narrowing of the spinal canal from osteophytes at facet joints, bulging disks, or a hypertrophied ligamentum flavum.
Symptoms	Sciatica.  <b>Worsens with sitting (lumbar flexion).</b>	Neurogenic claudication/ pseudoclaudication: pain radiating to the buttocks, thighs, or lower legs.  <b>Worsens with prolonged standing or walking (extension of the spine); improves with sitting or walking uphill (flexion of the spine).</b>
Exam/diagnosis	See Table 2.11. A $\oplus$ straight-leg raise (pain at 60 degrees or less) is seen.	May have a $\oplus$ Romberg sign or wide-based gait.  Exam is often unremarkable. MRI confirms the diagnosis.
Treatment	Ordinary activity (no bed rest, limited activity modification); NSAIDs; sometimes muscle relaxants and/or physical therapy to strengthen core.	Exercise to reduce lumbar lordosis, strengthen compensatory core muscles; decompressive laminectomy.



**FIGURE 2.19. Cauda equina syndrome.** Preoperative MRI of the lumbar spine shows a L5/S1 disc prolapse. (Source: Speirs E, et al. Positioning a prone patient with cauda equina syndrome who presents at 15 weeks gestation: a case report. Version 1. F1000Res. 2014;3:117.)

**KEY FACT**

Do **not** order imaging on initial evaluation of acute LBP unless severe/progressive neurologic deficits (incontinence, sensory level) or other red flags (older age, suspicion for underlying malignancy, fever, vertebral tenderness) are present. If fever and concern for cord compression, rule out epidural abscess with CT or MRI.

sence of major neurologic deficits or other alarm symptoms, as most cases of LBP resolve within 1 to 3 months. **Bed rest is ineffective** and can be counterproductive. Strength training at home, physical therapy, chiropractor, and acupuncture referrals are effective adjunctive therapies for mechanical LBP.

**Surgery referral** is indicated in the setting of suspected cauda equina syndrome, progressive motor weakness or refractory radicular symptoms from nerve root compression (eg, disk herniation), or spinal instability due to tumor or infection. For spinal stenosis, decompressive laminectomy may provide at least short-term symptom improvement.

## Common Symptoms

### UNINTENTIONAL WEIGHT LOSS

- Unintentional weight loss is defined as loss of >5% of usual body weight over 6 to 12 months. Associated with excess morbidity and mortality; idiopathic in up to one-third of cases. Other etiologies are as follows:
  - **Cancer, GI disorders** (malabsorption, pancreatic insufficiency), and **psychiatric disorders** (depression, anxiety, dementia, anorexia nervosa) account for up to two-thirds of cases.
  - Other causes include hyperthyroidism, uncontrolled DM, chronic diseases, infections, medications, and substance use. Difficulty with food preparation or intake from any cause (eg, food insecurity, social isolation with inability to shop/cook, ill-fitting dentures, dysphagia) should always be considered.
- **Diagnosis:** History and exam. Initial testing:
  - CBC, TSH, electrolytes, liver function tests, ESR/CRP, glucose, LDH, UA, CXR, and age-appropriate cancer screening. Consider testing for fecal occult blood, HIV, and HCV.
  - If test results are  $\ominus$ , observe the patient over time.
  - If the symptoms/exam are suggestive, pursue further cancer screening or GI evaluation.
- **Management:**
  - Treat the underlying disorder.
  - Set caloric intake goals; give caloric supplementation.
  - Appetite stimulants (megestrol acetate, dronabinol) are sometimes used in the presence of low appetite in patients with conditions such as cancer and HIV.

### FATIGUE

Fatigue is a common symptom and nonspecific complaint with many causes.

**Chronic fatigue syndrome (CFS) (also known as systemic exertion intolerance disease [SEID]):** Consider CFS if a patient has fatigue lasting at least 6 months that is not alleviated by rest and that interferes with daily activities, in combination with four or more of the following: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, polyarthralgias, new headaches, unrefreshing sleep, and post-exertion malaise.

- **Diagnosis:** Clinical—no specific labs are required although many conduct limited laboratory evaluation, including CBC, TSH, metabolic panel. Do **not** routinely send EBV, ANA, RF, or Lyme titers unless there is clinical suspicion.

- Management:** Requires a multidisciplinary approach that includes cognitive-behavioral therapy and graded exercise. **Graded aerobic exercise** improves fatigue and physical functioning. Also consider concomitant antidepressants, which can help with sleep or fibromyalgia-like symptoms.

## CHRONIC COUGH

Cough that lasts >8 weeks is considered chronic cough. The “big three” causes are as follows:

- Postnasal drip or upper airway cough syndrome:** Presents with a boggy nasal mucosa and a “cobblestone” oropharynx.
- Cough-variant asthma:** Cough worsens at night, and wheezes are exacerbated by seasonal allergies, exercise, and cold weather.
- GERD:** May present with heartburn and with cough that worsens at night, but asymptomatic in 75% of cases.

Additional causes include post-URTI cough (may persist for two months), *B pertussis*, chronic bronchitis, and ACEI use (may last for a few weeks after cessation). Also consider non-asthmatic eosinophilic bronchitis, which is a treatable cause of chronic cough.

- Diagnosis:** Based on response to empiric treatment (see below).
- Management:**
  - Empirically treat the “big three” with nasal corticosteroids (postnasal drip), bronchodilators ± inhaled steroids (asthma or non-asthmatic eosinophilic bronchitis), or acid suppressants (GERD).
  - Two to 4 weeks of maximal therapy for the suspected condition is recommended prior to further diagnostic testing.
  - If empiric therapy fails or if there is concern for pulmonary parenchymal disease, consider CXR, PFTs (± methacholine challenge) for suspected asthma, esophageal pH monitoring for GERD, ENT referral, or a sinus CT for postnasal drip.

## INSOMNIA

Insomnia is the most common of all sleep disorders, affecting roughly 15% of patients at some point, with ↑ prevalence associated with lower SES, recent stress, and drug/alcohol abuse. **Chronic insomnia** is defined as >3 weeks of difficulty falling or staying asleep, frequent awakenings during the night, and a feeling of insufficient sleep (daytime fatigue, forgetfulness, irritability). Exacerbating factors include stress, pain, caffeine, daytime napping, early bedtimes, drug withdrawal (alcohol, benzodiazepines, opiates), and alcoholism.

### Differential

See Table 2.13.

### Diagnosis

- Diagnosis is clinical.
- Rule out psychiatric and medical conditions—eg, depression, PTSD, delirium, chronic pain, medication side effects, GERD, and nocturia from BPH or DM.
- Labs for restless leg syndrome (RLS) include CBC, ferritin, and BUN/creatinine.
- Polysomnography may help diagnose periodic limb movement disorder and RLS and may also rule out other sleep-related disorders (eg, sleep apnea).

### KEY FACT

Chronic fatigue syndrome can be mistaken for chronic EBV syndrome. Think of CFS in a patient who presents with 6 months of nonspecific, debilitating symptoms and who becomes very tired after exercising.

### MNEMONIC

**Causes of chronic cough—GASPS AND COugh**

**G**ERD

**A**sthma

**S**moking, chronic bronchitis

**P**ostinfection

**S**inusitis, postnasal drip

**ACEIs**

**N**eoplasm

**D**iverticulum

**CHF**

**O**uter ear disease

**U**pper airway obstruction

### KEY FACT

For chronic cough, empirically treat the “big three”: postnasal drip, asthma, and GERD.

TABLE 2.13. Differential Diagnosis of Insomnia

	RESTLESS LEG SYNDROME	PERIODIC LIMB MOVEMENT DISORDER	INSOMNIA
Symptoms	Unpleasant sensations in leg that are accompanied by an urge to move and emerge during periods of inactivity; temporarily improved with leg movement	Intermittent limb movements during non-REM sleep; seen in >75% of patients with RLS	Difficulty initiating or maintaining sleep with impairment in daytime function
Disease associations	<b>Iron deficiency</b> (even in the absence of anemia), end-stage renal disease, DM; idiopathic in most cases	Uremia, TCAs, MAOIs	Depression, anxiety, stimulants, chronic pain, alcohol
Pathophysiology	Unknown; may involve abnormal dopamine transmission		Unknown or disease specific
Treatment	Correct the underlying disorder (eg, iron supplementation); give dopaminergic agonists (carbidopa/levodopa, pramipexole) or $\alpha_2$ -calcium channel ligand ( gabapentin, pregabalin); benzodiazepines if other treatments fail	Same as RLS	Correct the underlying disorder; CBT, sleep hygiene, medications (short-term use)

### Management

- Treat the underlying disorder.
- Sleep hygiene and relaxation techniques are effective treatments for chronic insomnia.
- **Cognitive behavior therapy** is an evidence-based treatment for insomnia.
- Benzodiazepines and benzodiazepine receptor agonists (zolpidem, zaleplon) are FDA approved for the treatment of short-term insomnia (7–10 days). Only eszopiclone, a longer-acting benzodiazepine receptor agonist, is FDA approved for the treatment of chronic insomnia.

### CHRONIC LOWER EXTREMITY EDEMA

The differential for chronic **bilateral lower extremity edema** includes the following:

- **Venous insufficiency:** The most important risk factor for venous insufficiency is prior DVT or phlebitis. Other risk factors include obesity, age, injury, and a history of pregnancy. Varicose veins may be the only finding in the early stages. Brawny edema, skin changes, and ulcerations (medial ankle) are later findings.
- **Lymphedema:** Can be idiopathic (due to a congenital abnormality of the lymphatic system) or secondary to lymphatic obstruction (eg, from tumor, filariasis, lymph node dissection, or radiation). The dorsum of the foot is commonly affected. Late changes include a nonpitting “peau d’orange” appearance.
- Varicose veins: May occur with or without chronic venous insufficiency.
- Right-sided heart failure.
- Low albumin states: Nephrotic syndrome, cirrhosis, or protein-losing enteropathy.
- Inferior vena cava obstruction, including from pregnancy.
- Medications, including amlodipine.

The differential for **unilateral lower extremity edema** is as follows:

- **Venous insufficiency:** Post-vein graft for CABG, prior DVT, leg injury.
- **Complex regional pain syndrome:** Hyperesthesia and hyperhidrosis that occur a few weeks after trauma; changes in skin texture and/or color and pain out of proportion to the exam (see below).
- **DVT:** Usually acute edema.

- Infection: Cellulitis or fasciitis.
- Inflammation: Gout; ruptured Baker cyst (posterior knee).

### Diagnosis

- Depending on the history and exam, consider an echocardiogram, UA, liver enzymes, and abdominal/pelvic imaging to rule out systemic causes of edema or venous obstruction.
- Lower extremity ultrasound with Doppler can rule out DVT and demonstrate venous incompetence.
- Radionuclide lymphoscintigraphy is the gold-standard test for lymphedema.

### Management

- Treat the underlying causes, including discontinuation of contributing medications.
- Compression stockings. Below-knee stockings ↓ postthrombotic syndrome in proximal DVT.
- Lifestyle modification (↓ salt) and leg elevation.
- Surgery and sclerotherapy are options for advanced varicosities.
- For lymphedema, gradient pressure stockings, massage therapy, and external pneumatic compression. Avoid diuretics given risk for intravascular volume depletion.

### COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) is a rare condition characterized by autonomic and vasomotor instability in the affected extremity. Previously known as reflex sympathetic dystrophy, the syndrome is usually preceded by **direct physical trauma**, which may be minor. Surgery on the affected limb may also precede the development of CRPS. Most commonly affects the **hand**.

### Symptoms/Exam

Presents as:

- Diffuse pain of the affected extremity that is often burning, intense, and worsened by light touch.
- Swelling.
- Disturbances of color and temperature.
- Dystrophic changes of affected skin and nails.
- Limited ROM.
- The shoulder-hand variant presents with hand symptoms along with limited ROM at the ipsilateral shoulder. May occur after MI or neck/shoulder injury.

### Diagnosis

- No specific diagnostic tests are available, but **bone scan** is sensitive and reveals ↑ uptake in the affected extremity. MRI may also be helpful.
- Later in the course, x-rays reveal generalized **osteopenia**.

### Management

- Early mobilization and physical therapy after injury/surgery/MI ↓ the chance of developing CRPS and improves the prognosis once it has occurred. There is also evidence for vitamin C in patients undergoing distal limb surgery or with distal limb fractures for prevention of CRPS.
- Tricyclic antidepressants (TCAs) are first-line pharmacologic therapy; neuropathic pain medications (gabapentin, topical lidocaine), local steroid injections, oral glucocorticoids, bisphosphonates, and calcitonin may also be used.
- Regional nerve blocks and dorsal column stimulation are helpful as well.



### QUESTION

A 32-year-old man presents with burning pain in his right arm, which started 8 months earlier when he sustained an injury while waiting tables at a restaurant. Exam reveals brawny edema and excess sweat in the arm as well as ↑ muscle tone. What is the most likely diagnosis and workup?

**KEY FACT**

Exceptions to the requirement for informed consent include life-threatening emergencies or circumstances in which patients waive their right to participate in the decision-making process.

**KEY FACT**

A diagnosis of dementia does not necessarily imply that the patient lacks capacity to make decisions as long as the patient can satisfy the requirements of decision-making capacity.

**Medical Ethics**

Medical ethics are based on a group of fundamental principles that should guide the best practice (Table 2.14).

**DECISION MAKING**

- Decisions about medical care should be **shared** between the patient (or surrogate) and the provider. **Informed consent** can be verbal but should be put in writing for high-risk treatments. Patients give informed consent when they demonstrate **decision-making capacity** by:
  - The ability to communicate a choice.
  - Understanding the medical condition and the treatment being proposed.
  - Appreciating the situation and its consequences (ie, potential risks, benefits, and alternatives).
  - Being reasonable about treatment options (ie, making decisions that are rational and consistent over time and with their values).
- Patients should be evaluated for delirium and other potential impairments to decision-making capacity. If a patient lacks the capacity to make decisions, his or her advance directive or assigned surrogate should guide decisions. See the Psychiatry chapter for more about advance directives.

**CONFIDENTIALITY**

- **HIPAA**, the Health Insurance Portability and Accountability Act of 1996, provides specific guidelines governing when and how the sharing of confidential patient information is acceptable.

**TABLE 2.14. Guiding Principles in Biomedical Ethics**

PRINCIPLE	EXPLANATION	EXAMPLE
Beneficence	Act in patients' best interest	A physician counsels a hyperlipidemic patient on lifestyle modifications.
Nonmaleficence	Do no harm to your patient	A physician advises against epidural steroid injection for chronic back pain due to spinal stenosis because it is unlikely to benefit the patient.
Justice	The equitable distribution of resources within a population	UNOS system for organ transplantation.
Autonomy	The right of patients to make their own decisions about their health care	A patient gives informed consent for (or refuses) surgery.
Fidelity	Truthful disclosure to patients	A physician informs a patient that pneumothorax occurred during thoracentesis.

**A****ANSWER**

CPRS is the most likely diagnosis based on a history of trauma followed by hyperalgesia and autonomic and vasomotor changes in the affected part of the body. No tests can diagnose CRPS definitively, but an x-ray of the affected limb may show osteopenia from disuse, and a bone scan may be helpful.

- Exceptions to the rule of confidentiality include:
  - Child or elder abuse or domestic violence.
  - Reportable diseases (eg, STIs, conditions that could impair driving).
  - Threats by the patient to their own or others' lives.
- When confidentiality must be broken, physicians should, when possible, discuss the need for disclosure with the patient in advance.

### ERROR REPORTING

Patients who have been injured, even if no error occurred, should be informed promptly and completely about what has happened.

### IMPAIRED PHYSICIANS

- Physicians who are impaired must not take on patient care responsibilities that they may not be able to perform safely and effectively.
- Causes include substance use (alcohol, other drugs), psychiatric illness, advanced dementia, or physical illness that interferes with the cognitive and/or motor skills needed to deliver care.
- Physicians have an ethical responsibility to protect patients from other physicians they know to be impaired. Legal reporting requirements vary by locality.

### FUTILE CARE

- Physicians are not obliged to provide care that they believe is futile. Futility is difficult to define quantitatively, but generally accepted futile conditions are as follows:
  - CPR in a patient who fails maximal life-support measures (eg, a patient who suffers cardiac arrest due to hypotension refractory to multiple vasopressors).
  - An intervention that has already been tried and failed (eg, if cancer worsened despite a complete course of chemotherapy, there would be no obligation to provide another course of the same therapy).
  - Treatment with no physiologic basis (eg, plasmapheresis for septic shock).
- Ethical "gray zones" in futility include discontinuing life-sustaining support because the chance of success is small or because the patient's best outcome would be a low quality of life. **Discussions with families and ethics consultations** are often required to sort through these complex situations.

### HIGH-VALUE CARE

- High-value care (HVC) is care that seeks to improve patient outcomes by balancing the clinical benefit of medical interventions with costs and potential harms.
- Physicians should use health resources judiciously and appropriately (ie, they should avoid unnecessary tests, medications, procedures, and consults).
- A physician's 1° responsibility is to his/her patient, and larger resource allocation decisions should be made at the societal or policy level. Individual physicians should identify system-level improvements that can reduce harm and waste and improve patient outcomes.
- In practicing HVC, physicians should be mindful of benefits, costs, and harms of care and work to choose interventions that maximize benefits while decreasing costs and potential harms. Physicians must also use a patient-centered approach and incorporate patient values.

## Lesbian, Gay, Bisexual, and Transgender Health

Sexual practices, not orientation, determine the risk of infections and cancers. Patients in same-sex relationships may have had opposite-sex relationships in the past (and vice versa), and specific high-risk practices (eg, receptive anal intercourse) may occur in patients who self-identify as gay, straight, bisexual, or transgender.

### RISKS

- There is an ↑ risk of anal cancer (caused by HPV) in men who have sex with men (MSM), particularly in those who are HIV-positive.
- There may be a ↓ risk of cervical cancer and HPV among women who have sex with women; however, many women who self-identify as lesbian have had sex with men, and rates of HPV infection are similar in lesbian women and the heterosexual population.
- HIV, gonorrhea, chlamydia, syphilis, hepatitis A, and hepatitis B are ↑ among MSM.

### SCREENING

- **In MSM:**
  - Screen for HIV and HBV, urethritis (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*), and proctitis (*N gonorrhoeae*, *C trachomatis*), HSV, and syphilis.
  - Offer HBV and HAV vaccines.
  - **Anal Pap smear:** In HIV-positive MSM, results of this test and cervical Pap smear have similar characteristics.
- **In women who have sex with women:** Cervical cancer screening should proceed according to standard guidelines (see the discussion of Cancer Screening above) even if patients have never had heterosexual contact.
- **In transgender patients:** Recommendations for screening and preventative care are the same as the general population for those not on hormone therapy. In individuals on hormone therapy or who have received surgery, recommendations depend on hormonal and surgical status. This is especially important in cancer risk assessment and assessing CVD risk (particularly ↑ CVD risk in male-to-female patients taking estrogen).

### KEY FACT

A highly **Sensitive** test, when **Negative**, rules **out** the disease (**SnNout**).

A highly **Specific** test, when **Positive**, rules **in** the disease (**SpPin**).

### KEY FACT

Sensitivity and specificity are characteristics of the diagnostic test itself. They do not depend on the population being tested or on disease prevalence.

### KEY FACT

Unlike sensitivity and specificity (which describe the test itself), the PPV and NPV of a test vary depending on the prevalence of the disease in the population being tested.

## Evidence-Based Medicine

### MAJOR STUDY TYPES

Table 2.15 outlines the major types of studies seen in the medical literature.

### TEST PARAMETERS

Test parameters measure the clinical usefulness of a test. These include the following:

- **Sensitivity (Sn)** (“PID”—Positive in Disease): The probability that a given test will be  $\oplus$  in someone who has the disease in question.
- **Specificity of a test (Sp)** (“NIH”—Negative in Health): The probability that a given test will be  $\ominus$  in someone who does not have the disease in question.
- **Positive predictive value (PPV):** The probability that a disease is present in a person with a  $\oplus$  test result.
- **Negative predictive value (NPV):** The probability that a disease is absent in a person with a  $\ominus$  test result.

TABLE 2.15. Statistical Study Types

STUDY TYPE	EXPLANATION	EXAMPLE	ADVANTAGES	DISADVANTAGES
Randomized controlled trial	Assigns exposure to subjects and observes disease outcome	Assigning patients with hypertension to one of two treatments: diuretics or ACEIs	True experiment erases unforeseen confounders; the optimal study type for assessing the effects of a particular intervention/exposure.	Expensive; the study population may be homogeneous, limiting the ability to generalize the results to the overall population.  Small sample sizes limit the power to detect small but potentially important differences between groups.
Cohort study	Identifies exposure subjects first and <b>then follows</b> for disease outcomes	Identifying obese adults and following them for development of hypertension	The most robust observational study type; evaluates multiple exposures.	May take a long time to develop disease; confounding and unmeasured variables may lead to incorrect conclusions.
Case-control study	Identifies cases and noncases of the disease outcome <b>before</b> determining exposure	Identifying children born with a rare birth defect and looking at possible in utero exposures	Inexpensive; fast; good for rare diseases and for generating hypotheses to subject to more rigorous study.	Prone to reporting biases due to differential recall between cases and non cases.
Cross-sectional study	Identifies exposure and outcome <b>at the same time</b> for each subject within a specified population	Determining how many patients hospitalized with an upper GI bleed have a history of recent NSAID use	Inexpensive; helpful for determining accuracy of diagnostic test since patients typically have both "gold standard" test and test being studied.	No ability to detect temporal relationship between exposure and outcome.
Systematic review	Summarizes the results of multiple individual trials addressing the same (or similar) research questions	Qualitative review of all trials of omega-3 fatty acids for the prevention of cardiovascular disease	Sets forth rigorous criteria to determine which studies will be included or excluded from the review; this helps limit bias in the summary conclusions.	Studies are often too small or too heterogeneous to apply rigorous statistical methods to the summary analysis; qualitative summary conclusions are substituted for numeric data.
Meta-analysis	A subset of systematic reviews; quantitative compilation of data from multiple small studies to generate a pooled result	Cochrane review of all randomized trials comparing glucosamine with placebo or other treatments for patients with osteoarthritis	Provides an estimate of treatment effect, including magnitude of effect, when individual studies are too small to derive robust conclusions.	Uses a variety of statistical methods; different meta-analyses of the same data can produce different results.  When component studies are heterogeneous, it is difficult to interpret/use a pooled result.

- **Likelihood ratio (LR):** The proportion of patients **with** a disease who have a certain test result divided by the proportion of patients **without** the disease in question who have the same test result (“WOWO”—With Over WithOut). **Example:** A high-probability V/Q scan has an LR of 14. The odds of a PE are ↑ by 14 times in patients with a  $\oplus$  V/Q relative to those with a  $\ominus$  V/Q.

### Calculating PPV, NPV, and LRs

Create a  $2 \times 2$  table of test results and disease status to calculate PPV and NPV, as well as  $\oplus$  and  $\ominus$  LRs, when sensitivity and specificity are known (Table 2.16):

- Sensitivity =  $a / a + c$ .
- Specificity =  $d / b + d$ .
- PPV =  $a / a + b$ .
- NPV =  $d / c + d$ .
- LR (+) = (sensitivity) / (1 – specificity).
- LR (–) = (1 – sensitivity) / (specificity).

An illustrative example of how to calculate PPV, NPV, and LRs, and how they depend on disease prevalence, is outlined below.

- For a given disease, the diagnostic test under consideration has the following characteristics:
  - Sensitivity = 90%.
  - Specificity = 95%.
- For this test, then, the **likelihood ratios** of  $\oplus$  and  $\ominus$  results are as follows:
  - LR (+) =  $0.90 / (1 - 0.95) = 18$ .
  - LR (–) =  $(1 - 0.90) / 0.95 = 0.105$ .
- Since the LRs are far from 1, this test appears to be useful both for ruling disease in and for ruling it out. However, disease prevalence in the population has a crucial effect on test performance, as seen below.

*Example:*

- Suppose the disease prevalence in the population in question is 20%. Given a total population of 1000 individuals, the  $2 \times 2$  table of disease status/test result can be constructed as shown in Table 2.17.
- From this table, one can calculate PPV and NPV:
  - PPV =  $a / a + b = 180/220 = 81.8\%$ .
  - NPV =  $d / c + d = 760/780 = 97.4\%$ .
- In this population, 81.8% of  $\oplus$  results occur in people who truly do have the disease (true  $\oplus$ s), while 97.4% of  $\ominus$  results occur in people who truly do not have the disease (true  $\ominus$ s).
- For the same diagnostic test with the same sensitivity and specificity, **if the disease prevalence were 2%, the values in the  $2 \times 2$  table would change** (Table 2.18). In this population, the PPV and NPV are different:
  - PPV =  $a / a + b = 18/67 = 26.9\%$ .
  - NPV =  $d / c + d = 931/933 = 99.8\%$ .

TABLE 2.16. Calculating PPV and NPV

	DISEASE PRESENT	DISEASE ABSENT
Test $\oplus$	True $\oplus$ <b>a</b>	False $\oplus$ <b>b</b>
Test $\ominus$	False $\ominus$ <b>c</b>	True $\ominus$ <b>d</b>

TABLE 2.17. 2 × 2 Table, Assuming 20% Disease Prevalence

	DISEASE PRESENT	DISEASE ABSENT	TOTALS
Test +	180 a	40 b	220
Test -	c 20	d 760	780
Totals	200	800	1000

- In this population, only 26.9% of  $\oplus$  results occur in people who truly have the disease; 99.8% of  $\ominus$  results occur in people who truly do not have the disease.
- This example illustrates that when a disease is rare in the population being tested, even a fairly sensitive and specific test will have a low PPV. False  $\oplus$ s will be far more common than true  $\oplus$ s in this population.

### Absolute and Relative Risk

Risk comparisons compare the rates of events in two groups.

- Absolute risk:** Probability of event happening during a specific period (event rate).
- Relative risk:** Ratio of the probability of an outcome with a risk factor present to the probability of an outcome without the risk factor present. Used in RCTs and cohort studies.
- Absolute risk reduction:** Difference in event rates between control and experimental group.
- Relative risk reduction:** Ratio of absolute risk reduction (experimental group event rate minus control group event rate) to control group event rate.

### Number Needed to Treat

Defined as the number of patients who must receive the treatment in question to achieve one additional favorable outcome (or avoid one additional adverse outcome) compared to the control treatment. The lower the number needed to treat (NNT), the more effective the treatment.  $NNT = 1 / \text{absolute risk reduction}$ .

- A randomized trial finds that subjects treated with a placebo have a 25% incidence of adverse outcome X. Subjects treated with drug A have a 14% incidence of the same adverse outcome.
- The absolute reduction in risk for adverse outcome X with drug A versus placebo is  $25\% - 14\% = 11\%$ . Thus,  $NNT = 1/0.11 = 9.09$ .
- This means that approximately nine patients would have to be treated with drug A instead of the placebo to prevent one case of adverse outcome X.

TABLE 2.18. 2 × 2 Table, Assuming 2% Disease Prevalence

	DISEASE PRESENT	DISEASE ABSENT	TOTALS
Test +	18 a	49 b	67
Test -	c 2	d 931	933
Totals	20	980	1000

### KEY FACT

Disease		
	+	-
Test	+	a b
	-	c d

$$\text{Sensitivity} = \frac{a}{a+c}$$

$$\text{Specificity} = \frac{d}{b+d}$$

### KEY FACT

$PPV = \frac{a}{a+b}$
$NPV = \frac{d}{c+d}$

## THREATS TO VALIDITY

Table 2.19 and the discussion below delineate factors that can adversely affect the outcome of a statistical study.

- **Lead-time bias:** The time by which a screening test advances the date of diagnosis from the usual symptomatic phase to an earlier, presymptomatic phase (see Figure 2.20).
- **Example:** A new screening test for pancreatic cancer is able to detect disease in a presymptomatic stage.
- Unfortunately, the poor overall prognosis for the disease remains the same. Screened patients know about their diagnosis sooner and live with the disease longer because of this knowledge, but their death is not truly postponed because no treatment exists to alter the outcome for patients diagnosed earlier in the course of illness.
- **Length-time bias:** Because cases vary in the lengths of their presymptomatic phase, screening will overdetect cases of slowly progressing disease (longer duration in the asymptomatic phase) and will miss rapidly progressing cases.
- **Example:** In Figure 2.21, mammography is able to detect two cases of slowly growing breast cancer because of the long period between disease onset and symptoms, but two cases with rapid progression from onset to symptoms are missed. This type of bias occurs with every screening test.
- Because more slowly progressive cases are more likely to be detected by the screening test, patients with screen-detected disease appear to have better outcomes than those with inherently aggressive disease diagnosed because of symptoms.

## KEY FACT

Screen-detected patients will always live longer than clinically detected patients even if early detection and treatment confer no benefit. This is due to lead-time and length-time biases.

TABLE 2.19. Threats to the Validity of Statistical Studies

	EXPLANATION	EXAMPLES
Confounding	Another variable (confounding factor) is associated with the predictor variable and the outcome variable without being in the causal pathway.	Coffee drinking is associated with a risk of MI. This does not mean that coffee causes MI; rather, coffee drinking (the confounder) is associated with smoking (the true predictor variable), and smoking causes MI.
Measurement (misclassification) biases	When the method of measuring an exposure or outcome misclassifies subjects either at random or in a systematic way. <b>Random misclassification:</b> When participants are placed in the wrong group (either with or without exposure/disease) in a random fashion; this biases the results to the null. <b>Nonrandom misclassification:</b> When placement into the correct vs incorrect exposure group is dependent on disease status; recall bias is a common type of nonrandom misclassification. <b>Recall bias:</b> Self-reporting by study subjects is influenced by knowledge of the study hypothesis, or knowledge of subjects' own disease status.	Misclassification bias occurs if subjects provide inaccurate information. For example, subjects may underreport behaviors perceived as socially unacceptable, such as heavy alcohol use; if the likelihood of underreporting alcohol intake is independent of disease status, random misclassification of subjects occurs. Recall bias: In a case-control study, cancer patients may think harder than healthy controls about past toxic exposures, are more likely to recall them, and are thus more likely to be categorized as "exposed."
Selection bias	Study subjects are selected into (or drop out of) a study in a way that misleadingly changes the degree of association.	Subjects recruited into a study from a subspecialty referral center are more likely to have severe forms of illness than those from a broader community-based sample. Subjects who drop out of a study after recruitment may have different disease characteristics or associations than those who continue the study.

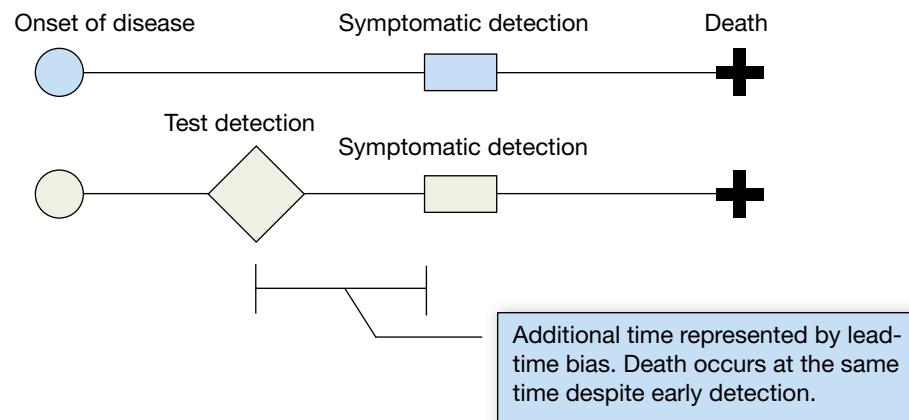


FIGURE 2.20. Lead-time bias.

**HYPOTHESIS TESTING**

- **P value:** A quantitative estimate of the probability that a particular study result could occur by chance alone if in fact there is no difference between groups or no treatment effect.
- A result with a  $P < .05$  signifies that the probability of the results occurring by chance is  $< 1$  in 20 and thus considered to be “statistically significant.”
  - **Example:** A study finds that treatment A, compared to placebo, causes a 20% reduction in the chance of outcome B, with a  $P$  value  $<.05$ . This means that there is less than a 5% chance that the difference in treatment effect between the two drugs is due to chance alone.
- **Confidence interval (CI):** If a given study were repeated an infinite number of times, in  $x\%$  of those trials would the effect estimate fall between the upper and lower limit of the  $x\%$  CI. In the medical literature, the 95% CI is generally used (ie, the range into which results would fall in 95 out of 100 repeats of the study in question).
  - **Example:** A study finds that the LR of a diagnostic test is 6.7.
  - The 95% confidence interval for this result is 5.0-8.2. This finding is abbreviated as  $LR = 6.7$  (95% CI, 5.0-8.2).

**KEY FACT**

A narrower CI around a result indicates a more precise result. Larger studies generally produce narrower CIs.

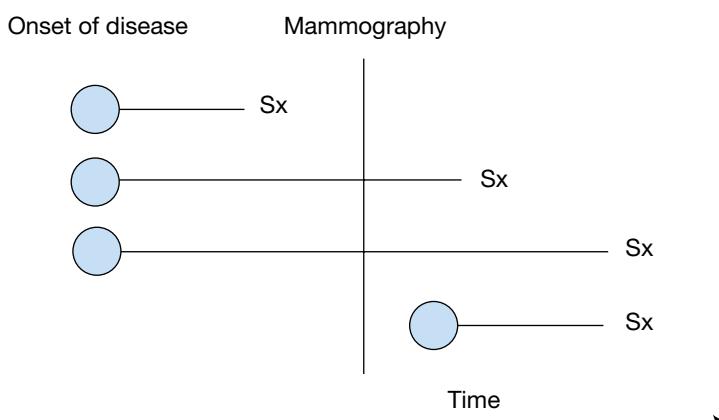


FIGURE 2.21. Length-time bias. Two cases of breast cancer with brief time between disease onset and symptom appearance (top and bottom cases) are missed by routine mammography. Two other cases, with longer presymptomatic phases, are detected by mammography.

## NOTES

## CHAPTER 3

# Cardiovascular Disease

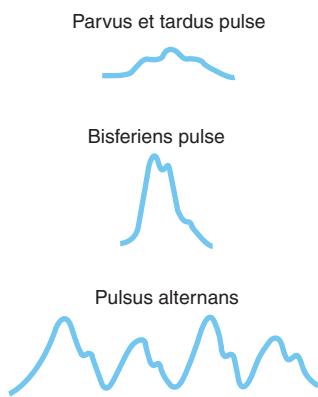
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## Cardiac Diagnosis and Testing

You should know this topic well, as it is an extremely high-yield area for boards testing, and within clinical vignettes, the physical exam findings can help discriminate among answer choices.



**FIGURE 3.1. Arterial pulse**

**waveforms.** (Modified with permission from Fuster V, et al. *Hurst's the Heart*, 12th ed. New York: McGraw-Hill, 2008, Fig. 12-43.)

### KEY FACT

**Boards clue for Corrigan (water-hammer) pulse:** A large pulse pressure!

### KEY FACT

**Kussmaul sign** is an ↑ in JVP during inspiration. Seen in chronic constrictive pericarditis.

### THE PHYSICAL EXAM

#### Arterial Pulsations

Know these examples of abnormal arterial pulsations and the disorders with which they are commonly associated (Figure 3.1).

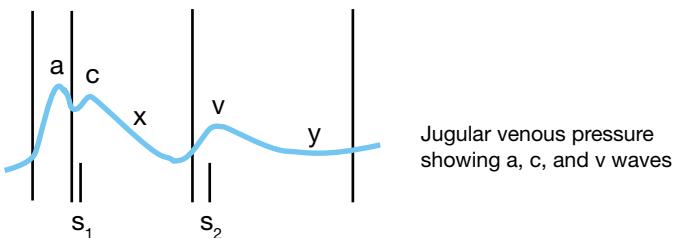
- **Asymmetric pulses:** Occur in aortic dissection.
- **Brachio-femoral delay:** Delay between brachial and femoral palpable peaks. Seen in coarctation of the aorta.
- **Carotid pulsations:**
  - **Parvus et tardus pulse:** Weak and delayed upstroke; occurs in aortic stenosis.
  - **Bisferiens pulse:** Two palpable peaks during systole; occurs in aortic regurgitation and hypertrophic cardiomyopathy.
  - **Pulsus alternans:** Only every other beat generates a strong pulse. Occurs in low cardiac output states with reduced ejection fraction (EF). A sign of poor cardiac output.
- **Peripheral pulse:** Corrigan (water-hammer) pulse, characterized by a rapid rise and fall of the radial pulse accentuated by wrist elevation. Occurs in chronic, hemodynamically significant aortic regurgitation. Boards clue will be a **large pulse pressure!**
- **Pulsus paradoxus:** Defined as a ↓ in BP of >10 mm Hg during normal inspiration. Occurs in cardiac tamponade, severe asthma, and chronic obstructive pulmonary disease (COPD).

#### Venous Pulsations

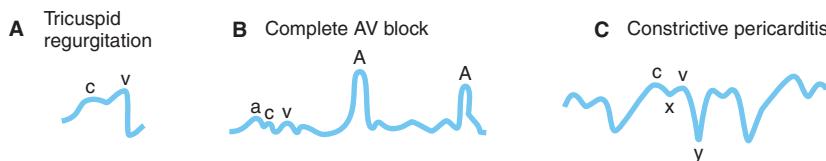
Normal jugular venous pulsations (Figure 3.2):

- **a wave:**  $\oplus$  wave due to contraction of the right atrium.
- **c wave:**  $\oplus$  deflection due to bulging of the tricuspid valve toward the atria at the onset of ventricular contraction.
- **x descent:**  $\ominus$  deflection due to atrial relaxation.
- **v wave:**  $\oplus$  deflection due to filling of the right atrium against the closed tricuspid valve during ventricular contraction.
- **y descent:**  $\ominus$  deflection due to passive emptying of the right atrium upon ventricular relaxation.
- **Jugular venous pressure (JVP):** During inspiration, the JVP declines.

High-yield abnormal patterns of jugular venous pulsations are shown in Figure 3.3.



**FIGURE 3.2. Normal jugular venous pulse waveforms.**



**FIGURE 3.3.** Abnormal jugular venous pulse waveforms. (A) Large v wave: Tricuspid regurgitation. (B) Cannon a waves: Atrioventricular (AV) dissociation. (C) Rapid y descent: Constrictive pericarditis; restrictive cardiomyopathy. (Modified with permission from Fuster V, et al. *Hurst's the Heart*, 12th ed. New York: McGraw-Hill, 2008, Fig. 12-46.)

### KEY FACT

Handgrip ↑ vascular resistance and can help distinguish mitral valve prolapse (MVP) from hypertrophic obstructive cardiomyopathy (HOCM); MVP murmurs get louder, whereas HOCM murmurs diminish.

## Heart Murmurs

Table 3.1 differentiates systolic murmurs on the basis of their response to various physiologic maneuvers. These maneuvers are most useful in distinguishing tricuspid regurgitation, mitral valve prolapse, and hypertrophic obstructive cardiomyopathy.

## Heart Sounds

The following are examples of normal and abnormal heart sounds.

- **S<sub>1</sub>:**
  - Heard when the mitral and tricuspid valves close.
  - Soft with severe LV systolic dysfunction and mitral regurgitation.
  - ↑ with rheumatic mitral stenosis (the mitral valve slams shut).
- **S<sub>2</sub>:**
  - Heard when the aortic (A<sub>2</sub>) and pulmonic (P<sub>2</sub>) valves close. In normal hearts, A<sub>2</sub> comes before P<sub>2</sub>.
  - A<sub>2</sub> is ↓ or absent (only hear a single S<sub>2</sub> sound) in severe aortic stenosis. P<sub>2</sub> ↑ in any form of pulmonary hypertension (HTN).
- **Split S<sub>2</sub>:**
  - **Physiologic splitting:** The time between A<sub>2</sub> and P<sub>2</sub> ↑ during inspiration. This is normal. See Figure 3.4.
  - **Paradoxical splitting:** A<sub>2</sub> is now significantly after P<sub>2</sub> with splitting that then disappears with inspiration as P<sub>2</sub> moves closer to A<sub>2</sub>. Etiologies include ↑ LV ejection time or conduction abnormality in conditions such as aortic stenosis, left bundle branch block (LBBB), paced rhythm. See Figure 3.4.
  - **Fixed splitting:** Atrial septal defect (ASD).

**TABLE 3.1.** Effects of Physiologic Maneuvers on Systolic Murmurs

MANEUVER	TRICUSPID REGURGITATION	AORTIC STENOSIS	MITRAL REGURGITATION	MITRAL VALVE PROLAPSE	HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY
Inspiration	↑	—	—	—	—
Squatting/straight leg raise	—	—	—	↓	↓
Valsalva/standing	↓	↓	↓	↑	↑
Handgrip/transient arterial occlusion	—	—	↑	↑	↓

### KEY FACT

There are often clues in the history that guide your exam interpretation! Patients who have lived internationally: Think rheumatic heart disease. Post-MI: Think mechanical complications of MI (MR, VSD). Cancer patients: Think pericardial disease or chemo-related cardiomyopathy. Young patients: Think congenital heart disease.

### KEY FACT

Given the physiologic changes of pregnancy, including ↑ blood volume and ↑ stroke volume, there will also be changes on physical exam. Findings may include brisk carotids, elevated JVP, displaced apical impulse, 2-3/6 early peaking systolic flow murmur, S<sub>3</sub>.

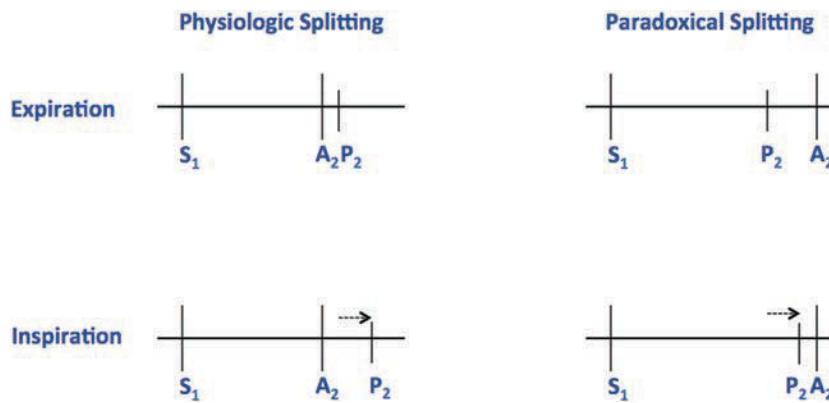
### KEY FACT

Inspiration (↑ venous return to the right atrium) ↑ right-sided murmurs but ↓ left-sided murmurs.



### QUESTION

A 37-year-old man with a bicuspid aortic valve is admitted to the hospital for endocarditis. On hospital day 3, he is noted to have ↑ fatigue, a slow pulse, and examination of his jugular vein reveals occasional prominent a waves. What is his ECG likely to show?



**FIGURE 3.4.** Schematic of physiologic (normal) and paradoxical (abnormal) splitting of  $S_2$ .  $S_2$  is comprised of  $A_2$  and  $P_2$ . With inspiration,  $P_2$  occurs later. (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Atif Qasim.)

- **Variable/wide splitting:** ↑ resistance to RV ejection, ↑ RV ejection time or conduction abnormality. Etiologies: pulmonic stenosis, pulmonary HTN, ventricular septal defect (VSD), and right bundle branch block (RBBB).
- $S_3$ :
  - A low-pitched sound heard in diastole just after  $S_2$ . Usually best heard at the apex.
  - Occurs as a result of sudden limitation of blood flow during ventricular filling.
  - Can be a normal finding in healthy young adults.
  - Abnormal in older adults; suggests ↑ filling pressures. Associated with enlargement of the ventricle, heart failure and severe mitral regurgitation/aortic regurgitation.
- $S_4$ :
  - A low-pitched sound heard in diastole just before  $S_1$ . Coincides with atrial systole ("atrial kick").
  - Occurs as a result of a stiff left ventricle with ↑ ventricular filling during atrial systole.
  - Can be a normal finding with advancing age due to loss of ventricular compliance.
  - Pathologic causes include long-standing HTN, aortic stenosis, and hypertrophic cardiomyopathy.
- **Additional diastolic sounds:**
  - **Opening snap:** A high-frequency, early diastolic sound most frequently caused by **mitral stenosis**.
  - **Pericardial knock:** High-pitched early diastolic sound seen in **constrictive pericarditis**. Occurs earlier in diastole and has a higher pitch than an  $S_3$ .

#### KEY FACT

Because an  $S_4$  is a result of atrial systole against stiff ventricle,  $S_4$  is **absent in AF**.

#### KEY FACT

Early diastolic sounds can be heard in atrial myxoma as tumor "plops" into ventricle. This is the most common tumor of the heart and can mimic mitral stenosis with intermittent mitral valve obstruction. Treatment is surgical resection.



#### ANSWER

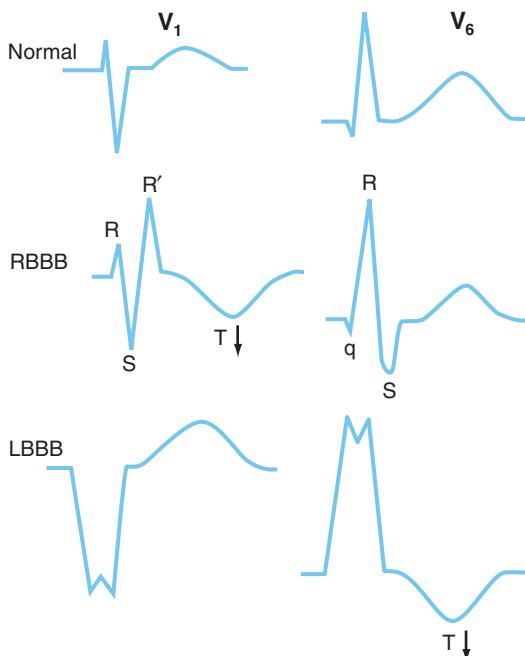
Complete heart block. This patient likely has aortic endocarditis given his bicuspid aortic valve, which predisposes him to aortic disease. Progression to heart block is a known sequela of aortic valve endocarditis. The finding of prominent a waves refers to cannon a waves often found with complete heart block as the atria are contracting against closed valves.

#### ELECTROCARDIOGRAPHY INTERPRETATION

- The following are fundamentals of ECG interpretation:
- **Dimensions (one small box):** Height: 0.1 mV = 1 mm; duration: 40 msec = 1 mm.
  - **Rate:** The normal HR is 60 to 100 bpm ( $300 \div \text{number of large boxes} = \text{rate}$ , when rhythm is regular). If irregular, the entire ECG is 10 secs, so count the number of QRS complexes and multiply by 6).
  - **QRS axis:** A normal axis is  $-30^\circ$  to  $+110^\circ$ . An axis less than  $-30^\circ$  is left axis deviation; an axis more than  $+110^\circ$  is right axis deviation. Use QRS in leads I and II to determine axis. Upright in I and II = normal axis; upright in I and downward in II = left axis deviation; downward in I and upright in II = right axis deviation; downward in I and II = extreme axis deviation.

■ **Intervals:**

- PR: Normal 120 to 200 msec (3-5 small boxes).
- QRS: Normal <120 msec (<3 small boxes).
- QT: Normal <1/2 RR interval (rule of thumb).
- QTc: Normal <440 msec.
- Right atrial abnormality (only one criterion is needed):
  - Lead II: P >2.5 mm (P-wave height >2.5 small boxes).
  - Lead V<sub>1</sub>: P >1.5 mm (P-wave height >1.5 small boxes).
- Left atrial abnormality (only one criterion is needed):
  - Lead II: P >120 msec with notches separated by at least one small box.
  - Lead V<sub>1</sub>: P wave has a ⊖ terminal deflection that is ≥40 msec by 1 mm (one small box by one small box).
- **Left ventricular hypertrophy (LVH):** There are numerous criteria for LVH, three of which are listed below. All are specific but insensitive, so fulfillment of one criterion is sufficient for LVH in patients **>35 years of age**:
  - R aVL >9 mm in women and >11 mm in men.
  - R aVL + S V<sub>5</sub> >20 mm in women and >25 mm in men.
  - S V<sub>1</sub> + (R V<sub>5</sub> or R V<sub>6</sub>) >35 mm.
- **Right ventricular hypertrophy (RVH):** The following findings suggest RVH:
  - Right axis deviation.
  - R V<sub>1</sub> + S V<sub>6</sub> >11 mm (or simply look for a deep S wave in V<sub>6</sub>).
  - R:S ratio >1 in V<sub>1</sub> (in the absence of RBBB or posterior MI).
- **RBBB** (Figures 3.5 and 3.6):
  - QRS >120 msec.
  - Wide S wave in I, V<sub>5</sub>, and V<sub>6</sub>.
  - Second R wave (R') in right precordial leads, with R' greater than the initial R (look for “rabbit ears” in V<sub>1</sub> and V<sub>2</sub>).
- **LBBB** (Figures 3.5 and 3.7):
  - QRS >120 msec, broad R wave in I and V<sub>6</sub>, broad S wave in V<sub>1</sub>, and a normal axis **or**
  - QRS >120 msec, broad R wave in I, broad S wave in V<sub>1</sub>, RS in V<sub>6</sub>, and left axis deviation.

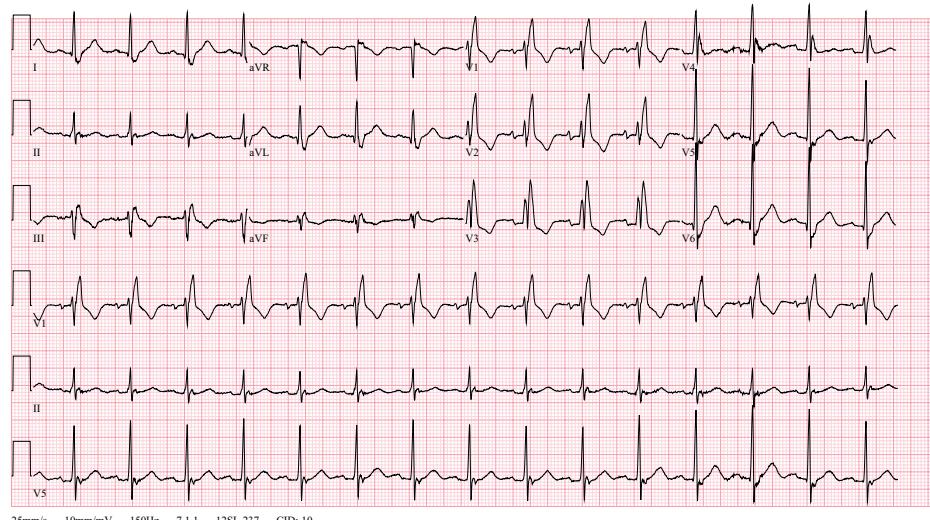


**FIGURE 3.5. Bundle branch blocks.** (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 221-10.)



**QUESTION**

A 75-year-old man with history of CAD and NSTEMI s/p stent placement 3 years earlier is presenting with light-headedness. HR is 160 bpm and BP is normal. He is mentating and is without chest pain. ECG shows wide-complex tachycardia. What is the most appropriate next step in management?



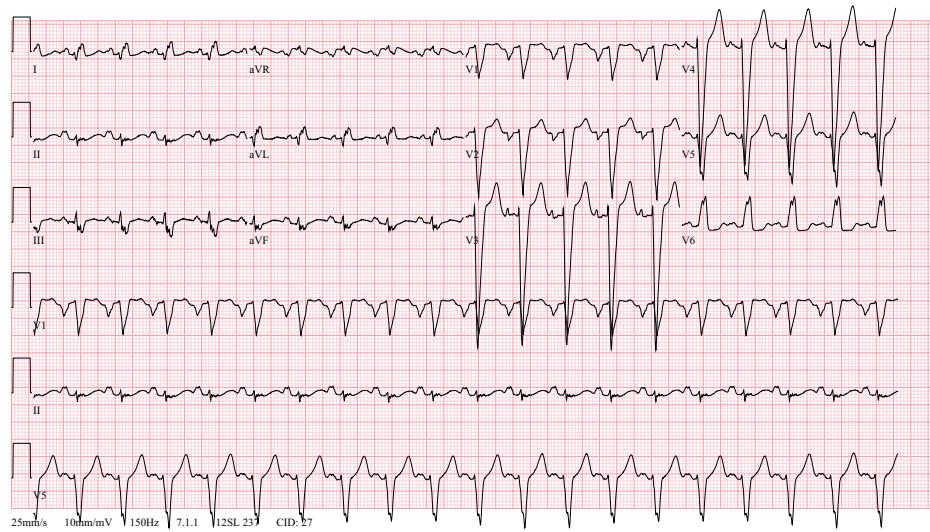
**FIGURE 3.6. Right bundle branch block.** (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Atif Qasim.)

- **Wide-complex tachycardia:** >100 bpm and QRS >120 msec. Differential includes supraventricular rhythm with aberrant conduction, paced rhythms or ventricular tachycardia (VT). Clues to VT:
  - Northwest axis ( $\oplus$  in aVR).
  - Concordant in precordial leads (QRS all up or down, no RS wave).
  - AV dissociation.
  - Capture or fusion beats.

### NONINVASIVE CARDIAC TESTING

#### Cardiac Stress Testing

Given possibility of false-negatives and false-positives, cardiac stress testing is most useful in the patient with intermediate risk (as opposed to high risk or low risk). Table 3.2 summarizes the various cardiac stress tests.



**FIGURE 3.7. Left bundle branch block.** (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Atif Qasim.)



#### KEY FACT

If someone has a history of CAD or an MI and presents with a wide-complex tachycardia, it is very likely to be VT as opposed to supraventricular tachycardia with aberrancy.



#### KEY FACT

Exercise treadmill testing should not be performed in those with LBBB or a paced rhythm, even if the patient is capable of exercise, since there is an  $\uparrow$  risk of a false-positive imaging test (nuclear or echo). Instead, a vasodilator nuclear test is preferred in this setting.



#### KEY FACT

Choice of pharmacologic agent for stress test should be deliberate. **Contraindications** for using dobutamine include uncontrolled HTN or recent clinically significant arrhythmia. A **contraindication** to the use of dipyridamole, adenosine, or regadenoson is active COPD or asthma, as all agents can cause bronchoconstriction.



#### ANSWER

Given the history, this is most likely a stable ventricular tachycardia. First step in management would be pharmacotherapy with amiodarone. If the patient becomes unstable, he should have synchronized cardioversion.

TABLE 3.2. Cardiac Stress Testing

TEST	INDICATION	OUTPUT	ADVANTAGE	LIMITATION
<b>Exercise treadmill ECG</b>	Patients with symptoms suggestive of CAD with normal resting ECG Exercise ↑ myocardial O <sub>2</sub> demand and unmasks ↓ coronary flow reserve in patients with stenosis	Duke score calculated based on exercise tolerance, presence of angina, and ST deviation	Better understanding of functional status, symptomatology and hemodynamics during exercise	Cannot quantify location or extent of ischemia so less useful in patients with preexisting CAD and revascularization Indeterminate if patient's peak HR is not at least 85% of the maximum predicted rate (220 – age)
<b>Stress echocardiography</b>	Used to determine regional wall motion abnormalities in patients with a relatively normal resting echocardiogram and signs or symptoms of ischemic heart disease Stress with exercise or dobutamine	Exercise data along with echo imaging	Allows for imaging of valve function and pulmonary pressures Lower cost than nuclear protocols	Difficult to assess wall motion abnormalities if baseline abnormalities Less sensitive if single vessel disease or delay from exercise to imaging May also be difficult to access appropriate windows in some patients
<b>Myocardial perfusion imaging</b>	Evaluates for presence and distribution of areas of myocardial ischemia based on differences in myocardial perfusion Exercise or pharmacologic stress (dipyridamole, adenosine, or regadenoson) is used to induce coronary vasodilation, which ↑ flow to the myocardium perfused by healthy coronary arteries but fails to ↑ flow in the distribution of a hemodynamically significant stenosis	Perfusion images show defects in areas where blood flow is relatively ↓ (low radioisotope uptake) If a perfusion defect on the initial (stress) imaging improves on repeat (rest) imaging after 3-24 hours, the area is presumably still viable (ie, it is a reversible defect) A fixed defect suggests myocardial scar tissue (or hibernating myocardium)	Highest sensitivity and specificity	Radiation exposure Artifact from breast tissue or obesity

## Echocardiography

A noninvasive ultrasound imaging modality used to identify anatomic abnormalities of the heart and great vessels, to assess the size and function of cardiac chambers, and to evaluate valvular function.

- **Resting:** Indicated for evaluation of heart failure, cardiomyopathy, and pericardial disease. Can demonstrate regional LV wall motion abnormalities (hypokinesis, akinesia) that may suggest coronary artery disease and culprit coronary artery.
- **Doppler:** Indicated for evaluation of valves and aorta.
- **Bubble study:** Injection of agitated normal saline to diagnose right-to-left shunts. Indicated for evaluation of patent foramen ovale or ASD (bubbles flow directly from



## QUESTION

A 57-year-old woman with history of HTN reports a history of intermittent epigastric burning pain. The pain is variably associated with exertion or with food. She is still able to participate in yoga once weekly. Her baseline ECG has no abnormality. What is the most appropriate diagnostic test?

**KEY FACT**

Consider familial hypercholesterolemia or secondary causes of hyperlipidemia, including hypothyroidism and DM in those with  $\text{LDL} \geq 190 \text{ mg/dL}$ .

**KEY FACT**

If multiple drugs must be used to control the BP, a diuretic should be included.

**MNEMONIC****Causes of 2° hypertension—ABCDE**

**A**ldosteronism, obstructive sleep **A**pnea

**B**ruits (renal artery stenosis), **B**ad kidneys (CKD; most common)

**C**ushing syndrome, **C**oarctation, **C**atecholamines (pheochromocytoma)

**D**rugs (NSAIDs, OCPs, decongestants, cocaine, methamphetamine)

**E**ndocrine (thyroid or parathyroid disease), **E**rythropoietin

**KEY FACT**

An  $\uparrow$  in Cr level of 25% to 30% from baseline is generally considered acceptable when starting an ACEI.

**KEY FACT**

If patients develop a cough with an ACEI, it is acceptable to try an ARB, which is associated with a lesser risk of cough.

**ANSWER**

Exercise ECG is the best diagnostic test in an individual with intermediate cardiac risk, ability to exercise, and no ST-T wave abnormalities on resting ECG. Exercise provides additional prognostic information.

the right to the left atrium) or intrapulmonary shunt (delayed appearance of bubbles in the left atrium).

- **Transesophageal echocardiography (TEE):** A small ultrasound probe placed into the esophagus that allows for higher-resolution images, especially of **posterior** cardiac structures. Common indications include the detection of left atrial thrombi, valvular vegetations, prosthetic valve function and thoracic aortic dissection.

**Other Noninvasive Tests**

- **Coronary CT angiography:** Visualization of coronary anatomy using radiocontrast. Sensitive for atherosclerosis but does not allow assessment of hemodynamics. May be effective in ruling out CAD in those with intermediate risk (high  $\ominus$  predictive value) but if  $\oplus$ , patient will likely need further evaluation with stress testing or angiography. Should not be used in asymptomatic patients or in symptomatic patients with very low or high probability of CAD. Cannot be used in someone with a high coronary artery calcium score (poor image quality due to artifact).
- **Cardiac MRI:** A useful adjunctive test for assessing left and right ventricular morphology and function, myocardial viability, CAD, valvular heart disease, nonischemic cardiomyopathy, cardiac masses, congenital heart disease, and pericardial disease in selected patients. Limitations: not available everywhere, expensive, patient must be able to lie flat and do several breath-holds.

**Hypertension****Diagnosis**

Diagnosed when systolic BP is persistently  $\geq 140 \text{ mm Hg}$  or diastolic BP is  $\geq 90 \text{ mm Hg}$  (Table 3.3). HTN is associated with an  $\uparrow$  risk of MI, heart failure, stroke, and kidney disease. Diagnosis requires multiple BP readings above 140/90 mm Hg on at least two different occasions, unless end-organ damage is present or BP is  $\geq 220/115 \text{ mm Hg}$ . HTN screening is recommended for all adults.

**2° HTN:**

- Consider 2° causes in the setting of severe or refractory HTN (refractory to three antihypertensives of different classes) or if age of onset is  $<30$  years in non–African American patients without a family history.
- Clinical clues to etiology of 2° HTN:
  - **Renal artery stenosis:** Unexplained deterioration of kidney function during antihypertensive therapy, particularly angiotensin-converting enzyme inhibitor (ACEI), diffuse atherosclerosis, unexplained renal atrophy, systolic-diastolic abdominal bruit lateralizing to one side.
  - **1° aldosteronism:** Hypokalemia due to renal potassium wasting.
  - **Sleep apnea syndrome:** Obese, snoring, daytime somnolence.

**TABLE 3.3. Blood Pressure Classification**

BP CATEGORY	SYSTOLIC BP (MM HG)	DIASTOLIC BP (MM HG)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	$\geq 160$	or $\geq 100$

## Management

- Lifestyle modifications (Table 3.4) for all patients, including those with pre-HTN.
- BP goal:
  - Adults <60 years: Treat if  $\geq 140$  mm Hg **or** diastolic BP is  $\geq 90$  mm Hg.
  - Adults  $\geq 60$  years: Treat if  $\geq 150$  mm Hg **or**  $\geq 90$  mm Hg.
  - Diabetes and/or renal disease: Goal of BP management is  $< 130/80$  mm Hg.
- Pharmacotherapy (Table 3.5):
  - General non-black population: Thiazide diuretic, ACEI, calcium-channel blocker (CCB).
  - Black population: Thiazide or CCB.

## Hyperlipidemia

Hyperlipidemia is a risk factor for CAD, stroke, and peripheral vascular disease.

## Diagnosis

- Obtain a fasting total cholesterol, LDL, HDL, and TG.
- Screen starting age  $\geq 35$  years for all men and  $\geq 45$  years for women at ↑ risk for CAD. Begin screening at age 20 if any major cardiovascular risk factors are present.

## Management

- Different online calculators exist to estimate an individual patient's risk for CAD based on lipid levels and CAD risk factors to determine whether to start cholesterol-lowering medications. A commonly used risk calculator is the 10-year American College of Cardiology/American Heart Association (ACC/AHA) risk calculator for patients 40 to 75 years of age; this includes risk factors such as HTN and diabetes:
  - If no diabetes: Treat with 10-year CAD risk  $\geq 7.5\%$  with moderate- to high-intensity statin therapy.
  - If diabetes: LDL level doesn't matter. Treat with at least a moderate-intensity statin.
  - Additionally, if LDL  $\geq 190$  mg/dL treat with high-intensity statin therapy and consider use of nonstatin drugs to further ↓ LDL.
- Therapeutic lifestyle changes are indicated for all patients with an LDL above the goal LDL level. Such changes include a low-saturated-fat, low-cholesterol, high-fiber diet; plant stanols/sterols (eg, vegetable oil, nuts, legumes, whole grains); and ↑ physical activity.

**TABLE 3.4. Lifestyle Modifications for Hypertension**

MEASURE	COMMENTS
Sodium restriction	No added salt or low-sodium diet
DASH diet (Dietary Approaches to Stop Hypertension)	A diet rich in fruits, vegetables, and low-fat dairy products with ↑ saturated and unsaturated fat
Weight reduction	If over the ideal BMI
Aerobic physical activity	AHA recommends 40 minutes of aerobic exercise of moderate to vigorous intensity three to four times a week
Limitation of alcohol consumption	Limit to <2 drinks per day for men and <1 drink per day for women

## KEY FACT

CK is not routinely measured in statin therapy. This should only be checked if patient has muscle symptoms.

## KEY FACT

Special indications:

- **Post-MI:** β-blocker, ACEI.
- **CHF:** β-blocker, ACEI (ARB if intolerant of ACEI).
- **Diabetes:** ACEI or ARB ± thiazide.
- **CKD:** ACEI or ARB ± diuretic (thiazide and/or loop).

## KEY FACT

Calculate a patient's baseline 10-year CV risk; if  $\geq 7.5\%$ , treat with at least a moderate-intensity statin.

## KEY FACT

Atorvastatin and rosuvastatin are high-intensity statins at appropriate doses. At lower doses, these medications are also moderate-intensity statins, as are simvastatin, lovastatin, pravastatin, and fluvastatin.

## QUESTION 1

A 60-year-old woman with diet-controlled type 2 DM and HTN presents to clinic for routine follow-up. On exam, BP is 150/90 mm Hg. On her last visit, her BP had been 148/85 mm Hg. What is the best next step in management?

## QUESTION 2

A 55-year-old healthy man with well-controlled HTN on hydrochlorothiazide has a total cholesterol level of 280 mg/dL, LDL 200 mg/dL, HDL 40 mg/dL, and triglycerides (TG) 150 mg/dL. What is your first-line treatment?

TABLE 3.5. Antihypertensive Medications

	THIAZIDES	$\beta$ -BLOCKERS	ACEIS	ARBs	CCBs
<b>Indications as first-line drug</b>	Used in most patients as mono- or combination therapy (stage 1 or 2 HTN)	<b>MI; high CAD risk; heart failure with reduced ejection fraction (HFrEF)</b>	<b>DM with micro-albuminuria/ proteinuria; MI; HFrEF;</b> non-DM-related proteinuria (ie, <b>CKD</b> )	ACEI cough (but not <b>angioedema</b> ) in patients who would otherwise have indications for ACEIs	Angina
<b>Side effects</b>	Hypokalemia, hyperuricemia	Bronchospasm, bradycardia/AV node blockade, erectile dysfunction	Cough (10%), hyperkalemia, renal failure, angioedema	Small chance of cough but likely safe; less hyperkalemia, renal failure, angioedema	Conduction defects (nondihydropyridines); lower-extremity edema (dihydropyridines)

**KEY FACT**

Myalgias occur in a minority of patients who take statins, but myositis with ↑ CK and rhabdomyolysis with renal failure are rare. Myositis is more common when fibrates (often used for a ↑ TG level), and possibly niacin, are used with a statin.

**KEY FACT**

If patient is intolerant to one statin, attempting an alternate statin or ↓ dosage often eliminates side effects.

**ANSWER 1**

In addition to diet and exercise counseling, begin an antihypertensive agent to meet the goal of <130/80 mm Hg in diabetic patients. An ACEI would be an excellent choice given the patient's coexisting DM. Check a chemistry panel prior to initiation of the ACEI, and repeat the panel within 1 week of starting the medication to rule out acute renal failure and hyperkalemia.

**ANSWER 2**

Counsel the patient on lifestyle modifications and begin high-intensity statin therapy.

- Cholesterol-lowering medications are appropriate for patients who are at high or moderately high risk for CAD or for those who have not reached their LDL goal after 3 months of lifestyle modifications. HMG-CoA reductase inhibitors (“statins”) are considered first-line therapy (Table 3.6).
- For fasting TG levels >500 mg/dL, use statins (fibrates second line: gemfibrozil, fenofibrate) to reduce levels and thus ↓ risk of pancreatitis.

TABLE 3.6. Drugs Used for the Treatment of Hyperlipidemia

DRUG CLASS	EXAMPLES/COMMENTS	LDL	HDL	TG	APPLICATIONS	ADVERSE EFFECTS
HMG-CoA reductase inhibitors	Statins	↓↓	↑	↓	<b>First-line to reduce risk of cardiovascular events in most patients requiring lipid-lowering medication</b> Primarily lower LDL	Elevated LFTs, myositis <b>Myositis is more common when fibrates, and possibly niacin, are used with a statin</b>
Niacin (nicotinic acid)	B vitamin; ↓ lipoprotein (a)	↓	↑↑	↓	Raise HDL; lower TG and LDL ( <b>near-ideal effects on lipid profile</b> )	<b>Flushing</b> limits use (affects >50% of patients; ↓ with ASA) Can exacerbate gout, PUD; cause elevated liver enzymes and BG
Fibrates	Gemfibrozil, fenofibrate	↓	↑	↓↓	Used in severe hypertriglyceridemia	Abdominal pain, myositis
Ezetimibe	Add-on therapy	↓	—	—	For patients on maximal dose statin who are not meeting cholesterol goals	Abdominal pain, myositis, LFT abnormality
Bile acid sequestrants	Cholestyramine	↓↓	—	↑	Lower LDL; used as monotherapy or in combination with statin	Nausea, bloating, constipation, LFT abnormality
Omega-3 fatty acids	FDA approved as an adjunct to diet	—	↑	↓	Lower TG	Bloating

## Coronary Artery Disease

### ACUTE CORONARY SYNDROMES

Acute coronary syndromes encompass ST-segment elevation MI (STEMI), non-ST-segment-elevation MI (NSTEMI), and unstable angina. Etiologies include unstable plaques with nonocclusive thrombosis (unstable angina and NSTEMI) and thrombotic occlusion of an epicardial coronary artery (STEMI).

#### Symptoms

Ischemic chest pain is often described as dull or squeezing substernal pain or left-sided discomfort with radiation down the left arm or into the neck or jaw associated with dyspnea, nausea, diaphoresis. Unlikely to be sharp, pinpoint, or of seconds duration.

#### Exam

- S<sub>4</sub>: Acute ischemia with stiff left ventricle.
- Elevated JVP: RV systolic dysfunction.
- Murmur of acute mitral regurgitation: ischemic papillary muscle rupture.
- Ventricular arrhythmia.
- Pulmonary edema, S<sub>3</sub>: Ischemic systolic dysfunction.

#### Diagnosis

Based primarily on **risk factors**, **troponin level**, and **ECG during chest pain** (Table 3.7).

#### Management

- **STEMI:**
  - 1° PCI within 90 minutes is generally preferred if it is available.
  - Pharmacologic thrombolysis is also considered first-line therapy if it is administered **within 12 hours** of chest pain onset. It should be utilized if PCI is unavailable and time to transfer and complete PCI is >120 minutes. Other medical management includes:
    - Antiplatelet therapy: Aspirin and clopidogrel (or prasugrel, ticagrelor).
    - Anticoagulation agents: Unfractionated heparin or LMWH.
    - Antianginal therapy (BP and HR control): Nitrates, β-blockers, and/or ACEI if not hypotensive.
    - Lipid lowering medication: Statin.

**TABLE 3.7. Acute Coronary Syndromes**

	UNSTABLE ANGINA	NON ST ELEVATION MI	ST ELEVATION MI
Angina symptoms	1) Acute onset without evidence of infarction 2) Much worse in severity than patient's usual angina due to known CAD 3) Occurs at rest	Unstable angina like symptoms	Unstable angina like symptoms ± possible symptomatic evidence of infarction (ie, hypotension, bradycardia, HF)
Troponin	⊖	⊕	⊕ (if initial is not, subsequent will be)
ST-segment elevation on ECG	No  May have T wave inversions or nonspecific ST-T changes	No  May have T wave inversions or nonspecific ST-T changes	Yes, in ≥2 contiguous leads or new LBBB, implying transmural infarction

#### KEY FACT

Fibrates, ezetimibe, and bile acid sequestrants are only indicated in high-risk patients who fail to respond to statin or are unable to tolerate statins.

#### KEY FACT

If the chest pain is pleuritic, positional or reproducible, it is less likely to be ischemic.

#### KEY FACT

There are several populations that can present with MI and no or atypical chest pain. Those populations are: women, elderly persons, patients with diabetes.

#### KEY FACT

Not all ST-segment elevations are caused by a STEMI. Consider pericarditis, Takotsubo cardiomyopathy, LV aneurysm, or vasospasm.

**KEY FACT**

Prinzmetal angina is vasospasm of the coronary arteries, which can mimic ACS due to elevated cardiac biomarkers and classic ECG changes. Cardiac catheterization rules out ACS and can occasionally demonstrate active vasospasm with provocation. Treatment is CCB.

**KEY FACT**

Avoid  $\beta$ -blockers if patient has bradycardia, AV nodal blockade, or concern for acute RV infarct. Avoid nitrates in the setting of hypotension, RV infarct, or recent phosphodiesterase inhibitor use.

**KEY FACT**

If reduced EF post-MI, consider the addition of eplerenone/spironolactone.

**KEY FACT**

Drug-eluting stents  $\downarrow$  the incidence of restenosis with the use of antiproliferative agents (eg, sirolimus and paclitaxel) but require more prolonged treatment with clopidogrel.

- **Absolute contraindications to thrombolysis** are as follows:

- Active internal bleeding.
- A history of hemorrhagic stroke.
- Ischemic strokes within 1 year.
- A known CNS neoplasm or lesion.
- Suspected aortic dissection.

- **NSTEMI and unstable angina:**

- **Medical therapy** includes the following:

- Antiplatelet medication: ASA 325 mg  $\times$  1 then 81 mg daily, clopidogrel/prasugrel or ticagrelor at loading dose and then at maintenance dosing following. GPIIb/IIIa inhibitors considered in high-risk patients.
- Anticoagulation agents: LMWH or unfractionated heparin.
- Lipid-lowering medication: High-intensity statin.
- Antianginal therapy: Nitrates and  $\beta$ -blockers if not hypotensive.

- **Angiography:**  $\uparrow$  evidence supports an early aggressive strategy (cardiac catheterization within 48 hours) for high-risk patients who present with unstable angina or NSTEMI. Guidelines for risk stratification are included in Table 3.8. TIMI Risk Score Calculation in Table 3.9.

**REVASCULARIZATION FOR MANAGEMENT OF CAD****Cardiac Catheterization**

Indications for cardiac catheterization include evaluation/treatment of acute and chronic CAD and evaluation of cardiogenic shock, heart failure, pulmonary HTN, suspected valvular disease, and congenital heart disease.

**Coronary Angiography**

- **STEMI:** 1° initial reperfusion therapy. Rescue therapy after failed thrombolysis (if there is ongoing chest pain and  $<50\%$   $\downarrow$  in ST-segment elevation after thrombolysis).
- **Elective (diagnostic):** For patients with known or suspected CAD who are candidates for coronary revascularization.

**TABLE 3.8. Unstable Angina and NSTEMI Risk Stratification**

LOW RISK	INTERMEDIATE RISK	HIGH RISK
Atypical cardiac chest pain	Typical cardiac chest pain	Typical cardiac chest pain
Few cardinal cardiac risk factors	Many cardinal cardiac risk factors	Many cardinal cardiac risk factors
Chest pain subsides	Chest pain subsides	Angina pain reoccurs Patient becomes symptomatic with HF, hypotension, bradycardia, or new murmur
Normal or unchanged ST segment on ECG from baseline <b>and</b> $\ominus$ cardiac enzymes	ST depression or T wave inversion <b>or</b> $\oplus$ cardiac enzymes	ST depression or T wave inversion <b>and</b> $\oplus$ cardiac enzymes
TIMI Risk Score 0-2	TIMI Risk Score 3-4	TIMI Risk Score 5-7
Stress test in 24 hours Cardiac catheterization if $\oplus$	Stress test in 24 hours Cardiac catheterization if $\oplus$	Cardiac catheterization in 24-48 hours

## Coronary Stents

Antiplatelet therapy following UA/NSTEMI or coronary stent placement:

- UA/NSTEMI with or without stent: Aspirin for life and clopidogrel or ticagrelor for 1 year.
- Bare metal stent: Aspirin for life and clopidogrel/prasugrel/ticagrelor for at least 1 month.
- Drug-eluting stent: Aspirin for life and clopidogrel/prasugrel/ticagrelor for at least 6 months.

## Indications for Coronary Artery Bypass Graft

- Left main stenosis.
- Symptomatic two-vessel disease with proximal LAD disease and a ↓ ejection fraction (EF) or diabetes.
- Symptomatic three-vessel CAD.

## Complications During Percutaneous Coronary Intervention

- **Coronary arterial complications:**
  - Distal microembolization of the coronary artery.
  - Vessel perforation or dissection.
  - **Abrupt closure:** Usually due to dissection or thrombosis.
  - **Subacute thrombotic occlusion of coronary stent within 2 to 14 days.**
  - **Gradual restenosis:** Defined as ≥50% narrowing of the luminal diameter within 1 to 6 months.
- **Vascular complications:**
  - Retroperitoneal bleeding: Look for hypotension or ↓ hemoglobin after PCI with femoral access.
  - Femoral hematoma, pseudoaneurysm, or fistula formation.
  - **Atheroembolic kidney disease:** Look for eosinophilia, livedo reticularis, eosinophiluria, hypocomplementemia, and distal embolic complications ("blue toes").
  - **Stroke:** Either embolic (disruption of atherosomatous plaque) or hemorrhagic (antiplatelets and anticoagulation).
- **Other complications:**
  - **Contrast nephropathy:** Usually occurs 24 to 48 hours after contrast load. Diabetes and preexisting renal insufficiency are the most important risk factors.

## COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

See Table 3.10.

## CHRONIC STABLE ANGINA

The hallmark of chronic stable angina is reproducible, exercise-induced chest discomfort that is relieved by rest and nitroglycerin. Unlike unstable angina and MI, stable angina is thought to involve a **fixed** coronary stenosis that limits myocardial O<sub>2</sub> delivery; angina results when demand outstrips supply. The most important CAD risk factors are diabetes, smoking, hyperlipidemia, HTN, age (>45 years man, >55 years woman), and a family history of premature CAD (<45 years man, <55 years woman).

**TABLE 3.9. TIMI Risk Score Calculation**

Age ≥65 years (1 point)
Three or more CAD risk factors (1 point)
Known CAD with >50% stenosis (1 point)
Aspirin use in the past 7 days (1 point)
Severe angina in the preceding 24 hours (1 point)
Elevated cardiac markers (1 point)
ST-segment elevation >0.5 mm (1 point)

## KEY FACT

Prasugrel has more bleeding when compared to clopidogrel; risk factors for this bleeding is age >75 years, low weight, or history of TIA or stroke.

## QUESTION 1

A 76-year-old man with a history of tobacco use and type 2 DM presents to the hospital with 30 minutes of crushing substernal chest pain with diaphoresis and sensation of shortness of breath. ECG demonstrates ST elevation in inferior leads. The nearest facility with percutaneous coronary intervention (PCI) capability is >120 minutes away. Which of the following is the next appropriate step in management?

## QUESTION 2

An 85-year-old man undergoes coronary angiography and has drug-eluting stents placed into his left circumflex artery. On day 1 post-angiography, routine lab results show an elevated Cr level and a normal WBC count (50% neutrophils, 20% eosinophils). Exam reveals cold toes with a slight bluish discoloration. What is the most likely diagnosis?

TABLE 3.10. Complications of Acute MI

COMPLICATION	TIMING	SYMPTOMS/EXAM	DIAGNOSIS	TREATMENT
Papillary muscle rupture	2-7 days after MI	Acute pulmonary edema with exam revealing a new systolic murmur, heard loudest at the apex, that radiates to the axilla	Echocardiography	Vasodilators and surgical correction
Ventricular septal defect	3-7 days after MI	Acute CHF symptoms Holosystolic murmur that radiates from left to right over the precordium, heard loudest over the left lower sternal border	Echocardiography; right heart catheterization	Vasodilators and surgical correction
LV free wall rupture	5-14 days after MI	Dyspnea, hypotension Signs of tamponade ( $\uparrow$ JVP, pulsus paradoxus, diminished heart sounds)	Echocardiography	Urgent pericardiocentesis and thoracotomy Surgical correction
LV aneurysm	Chronic and persist for >6 weeks after MI	Large, diffuse PMI; $S_3$ may be present	ECG (Q waves in $V_{1-3}$ with persistent ST-segment elevation), echocardiography, cardiac MRI	<ul style="list-style-type: none"> <li>■ Acute: Treat associated cardiogenic shock</li> <li>■ Chronic: Anticoagulate with heparin/warfarin if mural thrombus is present; consider a defibrillator if the LV EF is &lt;35% or there are documented ventricular arrhythmias</li> </ul>

(continues)

**A****ANSWER 1**

Administer tenecteplase for ST-elevation MI when there is not accessible PCI within 120 minutes. Continued chest pain, failure of ST elevation to improve, or hemodynamic instability may indicate failed therapy; patient should then be prepared for transport to center with PCI capability.

**A****ANSWER 2**

This patient likely has atheroembolic disease stemming from catheterization, which is manifesting with typical symptoms of renal failure, eosinophilia, and emboli to the distal digits. Although renal failure is more commonly associated with contrast nephropathy, the remaining findings make atheroembolic disease more likely. Treatment is largely supportive.

**TABLE 3.10. Complications of Acute MI (continued)**

COMPLICATION	TIMING	SYMPOMTS/EXAM	DIAGNOSIS	TREATMENT
Early pericarditis	1-4 days after MI	Pain worsens when patients are supine and radiates to the trapezius ridge Pericardial friction rub	ECG with diffuse ST elevation and PR depression Echocardiography may reveal pericardial effusion	ASA Avoid NSAIDs and corticosteroids, which may interfere with the healing of infarcted myocardium
Late pericarditis	1-8 weeks after MI	Fever, pericardial friction rub	ECG with diffuse ST elevation and PR depression Echocardiography may reveal pericardial effusion	If >4 weeks have elapsed since the MI, NSAIDs and/or steroids can be used
Reperfusion arrhythmia	24-48 hrs after MI	Often asymptomatic	ECG with transient accelerated idioventricular arrhythmia	Does not warrant antiarrhythmic therapy

### Symptoms

Ischemic chest pain is often described as dull or squeezing substernal or left-sided discomfort associated with dyspnea and diaphoresis, with radiation down the left arm or into the neck.

### Differential

GERD, esophageal spasm, herpes zoster, costochondritis, coronary vasospasm.

### Diagnosis

- If patient is high probability, treat empirically for CAD.
- If patient is intermediate probability, noninvasive stress testing with or without imaging (nuclear imaging or echocardiography).
- Invasive cardiac catheterization (angiography) only if symptoms persist despite optimal medical therapy, reduced LV function, or high-risk criteria on noninvasive stress test.

### Management

- **Risk factor reduction:** Includes smoking cessation and aggressive treatment of HTN, hyperlipidemia, and diabetes (see the Ambulatory Medicine chapter).
- **Antianginal medical therapy:** Nitrates,  $\beta$ -blockers, CCBs.
- **2° prevention:** ASA, statins, and ACEIs have been shown to reduce cardiovascular events in patients with chronic CAD.
- **Revascularization:** Percutaneous coronary intervention (PCI) or CABG only if symptoms persist despite optimal medical therapy, reduced LV function or high-risk criteria on noninvasive stress test.

### KEY FACT

For the boards, risk factors are important in determining etiology of chest pain in patients <55 years of age or premenopausal women.

### KEY FACT

An ACEI should be prescribed for patients with chronic stable angina and HTN, diabetes, or LV dysfunction.

### QUESTION

A 52-year-old man presents to the hospital with new chest pain and fever 2 weeks after having been admitted for an MI. The pain worsens when he is supine and is unrelenting. On exam, he is mildly tachycardic with a normal BP. Lab results show WBC count of 12,000/mL and  $\downarrow$  troponin level; bedside echocardiogram reveals a small pericardial effusion. What is the treatment of choice for this patient?

## Heart Failure

Table 3.11 and the discussion that follows outline the stages, types, and clinical characteristics of heart failure. Each stage has goal-directed therapy. The New York Heart Association (NYHA) also classifies heart failure into four categories (class I-IV), from no limitation in physical activity to symptoms at rest.

### KEY FACT

A normal BNP (<100 pg/mL) excludes heart failure. Don't order BNP to monitor heart failure.

**TABLE 3.11. Stages of Heart Failure**

STAGE	DESCRIPTION	TREATMENT
A	Patients who are at risk for heart failure because of comorbidities strongly associated with the development of heart failure (eg, HTN, CAD, DM)  No structural or functional abnormalities of the valves or ventricles	ACEIs/ARBs; treat the underlying condition (eg, HTN, CAD)
B	Patients who have structural heart disease that is strongly associated with the development of heart failure but no symptoms or history of heart failure (eg, LVH; enlarged, dilated left ventricle; asymptomatic severe valvular heart disease; previous MI)	ACEIs/ARBs, $\beta$ -blockers, implantable defibrillator if EF is low (<35%) despite medical therapy
C	Patients who have current or prior symptoms of heart failure associated with underlying structural heart disease  Represents the largest group of patients with clinical evidence of heart failure	As in stage B plus salt restriction, diuretics Selected patients may be given nitrates/hydralazine, digoxin, aldosterone antagonists, or cardiac resynchronization therapy
D	Patients who have marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions  Examples include patients with recurrent hospitalizations as well as those who are in hospital awaiting heart transplantation, on continuous IV support for symptom relief, on a mechanical circulatory assist device, or in hospice	As in stage C, consider mechanical support, experimental surgery/drugs, transplantation, or hospice

A

### ANSWER

ASA. This patient probably has Dressler syndrome, a late-onset pericarditis that follows acute MI. Although pericarditis normally responds well to NSAIDs, the potential effect of NSAIDs on wound healing makes them an unfavorable choice.

(Modified with permission from Fuster V, et al. *Hurst's the Heart*, 12th ed. New York: McGraw-Hill, 2008, Table 26-1.)

- Exam may reveal S<sub>3</sub>, pulmonary crackles, JVP, pulsatile liver, hepatomegaly, ascites, peripheral edema.
- Laboratory examination may reveal hypervolemic hyponatremia, renal failure due to vascular congestion, hepatic congestion, and elevated BNP and/or troponin levels.
- Management:
  - Acute exacerbation of chronic heart failure: Most often heart failure patients present warm (adequate perfusion) but with volume overload. The mainstay of treatment for these patients is diuresis, nitrates (to reduce preload) and afterload reduction (ACEI/ARB, hydralazine, nitrates). If patient has been on β-blocker, reasonable to continue this medication. However, generally β-blockers are not initiated in this setting.
  - See below for other types of heart failure and their respective treatments.

### HEART FAILURE WITH REDUCED EF (SYSTOLIC HEART FAILURE)

- Clinically defined as evidence of a ↓ EF (typically <40%) in the setting of symptoms and signs of heart failure. Affects all ages; more common in men.
- Etiologies:
  - Ischemic: Coronary artery disease (very common).
  - Nonischemic: Idiopathic versus HTN, valvular disease, toxins, hyper/hypothyroidism, myocarditis (Chagas disease), end-stage HIV/AIDS, vitamin deficiencies (thiamine), peripartum.
- Management:
  - Diuretics: Can utilize loop diuretics with addition of thiazide diuretics. Helps maintain euvoolemia, reduces readmission, but does not confer mortality benefit.
  - ACEIs (**lisinopril**): Mortality benefit in all classes of heart failure. If ACEIs are not tolerated because of cough, switch to an ARB.
  - β-blockers (metoprolol, carvedilol): Mortality benefit in all classes of heart failure. Do not begin new β-blocker in acute heart failure exacerbation but safe to continue if patient already taking.
  - Hydralazine with nitrates: Mortality benefit but confers less benefit than ACEIs. In African American patients, can achieve an additional mortality benefit when added to ACEI/ARB therapy.
  - Aldosterone antagonist (spironolactone, eplerenone): Mortality benefit in class II-IV heart failure.
  - Angiotensin receptor—neprilysin (valsartan-sacubitril): Mortality benefit in patients with chronic symptomatic HFrEF (NYHA class II or III). Consider this as an alternative to ACEI or ARB therapy in these patients. **Do not use** this medication in ADDITION to an ACEI.
  - Implantable cardioverter-defibrillator (ICD): Mortality benefit for 1° prevention. Used in patients with heart failure NYHA class II or III while on optimal pharmacologic therapy and ischemic cardiomyopathy >40 days post-MI or nonischemic cardiomyopathy with EF <35%.
  - Cardiac resynchronization therapy (CRT): Mortality benefit. Pacemaker-based therapy (with leads in the right atrium, the right ventricle, and a branch of the coronary sinus to pace the left ventricle) is used in patients with systolic heart failure (NYHA class II-IV on optimal pharmacotherapy), an EF of <35%, and a wide QRS (>150 msec) on ECG. Improves ventricular synchrony and cardiac output.
  - Advanced therapies: Mechanical circulatory support (intra-aortic balloon pump [IABP], LV assist device) or cardiac transplantation.

#### KEY FACT

Takotsubo cardiomyopathy (stress-induced cardiomyopathy, also known as “broken heart” syndrome) is a nonischemic cardiomyopathy characterized by sudden-onset ECG changes consistent with an acute MI and heart failure with ventricular ballooning. This can be triggered by emotional stress. Management is supportive. LV function usually returns to baseline quickly.

#### KEY FACT

If asked about mortality benefit in systolic heart failure, correct answer may include ACEI, ARBs, hydralazine, β-blockers, spironolactone, CRT (biventricular pacemaker), or ICD. If you see two of these answers as possibilities, one must be contraindicated (eg, β-blockers contraindicated in severe asthma, ACEI/ARB contraindicated in hyperkalemia, CRT not indicated if normal QRS).

#### KEY FACT

Chemotherapy agents associated with cardiac toxicity include doxorubicin, epirubicin, daunorubicin.



#### QUESTION

A 63-year-old man with HTN and HFrEF is transferring his care. He has good exercise capacity, no other comorbidities, and takes only lisinopril. He appears euvolemic on exam. BP is 130/80 mm Hg. Of amlodipine, furosemide, or metoprolol, initiation of which medication will improve his mortality?

**KEY FACT**

Patients who have had an MI with heart failure (EF <40%) will derive a mortality benefit from the addition of eplerenone, an aldosterone antagonist.

**KEY FACT**

In patients with isolated diastolic dysfunction, always consider underlying myocardial or pericardial causes of a stiff left ventricle (eg, infiltrative diseases, constrictive pericarditis, restrictive cardiomyopathies).

**KEY FACT**

Even with maximal medical therapy (eg, ACEIs,  $\beta$ -blockers), patients with an EF of  $\leq 35\%$  still have a  $\downarrow$  in the incidence of sudden death with placement of an ICD.

**A****ANSWER**

Metoprolol. A patient with HFrEF should be taking a  $\beta$ -blocker and an ACEI or ARB regardless of functional status or degree of heart failure. These medications improve mortality. Furosemide, while an important part of volume management and symptom relief in heart failure, does not confer mortality benefit.

**HEART FAILURE WITH PRESERVED EF (DIASTOLIC HEART FAILURE)**

- Clinically defined as a normal EF (>50%) in the setting of symptoms and signs of heart failure. This is due to impaired diastole (ability of the heart to relax). Affects elderly patients; occurs more often in women. Comorbidities include HTN, DM, obesity, obstructive sleep apnea, and CKD.
- **Etiologies:**
  - **Myocardial:** Impaired relaxation or  $\uparrow$  passive stiffness (ischemia, hypertrophy 2/2 age/HTN, high output cardiac failure, restrictive cardiomyopathies, hypertrophic cardiomyopathy).
  - **Pericardial:** Constrictive pericarditis.
- **Management:** BP control and maintenance of euvoolemia are the mainstays of treatment.

**DIASTOLIC DYSFUNCTION**

Very common. Often coexists with systolic dysfunction; frequently associated with HTN and ischemic heart disease. Diastolic dysfunction (based on echocardiographic findings) does not equal diastolic heart failure. Many patients have asymptomatic diastolic dysfunction (which is a risk factor for future morbidity and mortality), but diastolic heart failure denotes *symptomatic* heart failure in the setting of diastolic dysfunction.

**CARDIOGENIC SHOCK**

Failure of RV or LV to pump adequate amount of blood to perfuse vital organs. **Etiologies** include:

- LV systolic dysfunction.
- Acute or acute-on-chronic RV failure: Acute RV MI, decompensated pulmonary HTN, acute pulmonary embolism.
- Acute, severe valvular insufficiency.
- Cardiac tamponade.

**Symptoms/Exam**

- Hypotension (systolic BP <90 mm Hg) or relative hypotension (a large  $\downarrow$  in systolic BP in a chronically hypertensive patient), tachycardia, tachypnea.
- Signs of hypoperfusion: altered mental status (acute delirium), cyanosis, poor peripheral pulses,  $\downarrow$  urine output.

**Management**

- If the underlying etiology is ischemic, proceed immediately to revascularization (PCI or coronary artery bypass graft [CABG]).
- If signs of volume overload, pursue aggressive diuresis or ultrafiltration (in setting of anuric/oliguric renal failure).
- **Supportive care:**
  - Vasopressor therapy usually consists of dopamine and dobutamine. Norepinephrine can also be used in cases of refractory hypotension.
  - Mechanical ventilation.
  - Placement of an IABP  $\downarrow$  afterload and improves coronary perfusion in diastole. It is contraindicated in patients with severe peripheral vascular disease and hemodynamically significant aortic insufficiency.
  - For ischemia-induced cardiogenic shock, nitrates and nitroprusside can be used, but only with extreme caution. Nitroprusside can cause coronary steal phenomenon and exacerbate ischemia. IABP is a more effective therapy for coronary ischemia in these patients and is the treatment of choice.

## Cardiomyopathies and Myocarditis

Tables 3.12 and 3.13 and the discussion below outline the etiologies, classification, and evaluation of cardiomyopathies.

### RESTRICTIVE CARDIOMYOPATHY

**Pathogenesis** includes infiltration or fibrosis of the myocardium causing impaired ventricular filling with preserved systolic function. In end-stage disease, systolic dysfunction may develop. Causes include amyloidosis, sarcoidosis, hemochromatosis, scleroderma, and radiation.

- **Symptoms/Exam:** Signs and symptoms of heart failure.
- **Differential:** Constrictive pericarditis, cardiac tamponade (see Table 3.13).
- **Diagnosis:**
  - ECG: Conduction system disease, low QRS voltage.
  - **Echocardiography:** Restrictive filling pattern with a preserved EF and batrial enlargement. Infiltrative causes can present with the characteristic granular appearance of myocardium.
  - **Right heart catheterization:** Dip-and-plateau ventricular filling pressure (“square root” sign), respiratory concordance of the right and left ventricles.
  - **MRI:** Global LV late gadolinium enhancement.
  - **Myocardial biopsy:** Infiltrative diseases such as amyloidosis.
- **Management:**
  - Treat the underlying disease process (eg, amyloidosis, sarcoidosis).
  - Control HR (to ↑ filling time), reduce venous pressures, correct conduction disturbances:
    - **β-blockers/CCBs:** May improve diastolic function early in the disease process by slowing HR and ↑ ventricular filling time. However, in more advanced disease, may be dependent on HR to ↑ cardiac output in the setting of a fixed stroke volume.
    - **Diuretics:** ↓ symptoms from venous congestion.

### HYPERTROPHIC CARDIOMYOPATHY

An autosomal dominant disorder of myocardial structural proteins that causes premature, severe LVH. A subset of hypertrophic cardiomyopathy (HCM) cases may have asymmetric septal hypertrophy and dynamic outflow tract obstruction.

TABLE 3.12. Clinical Classification of Cardiomyopathies

CATEGORY	CHARACTERISTICS
Dilated	Left and/or right ventricular enlargement, impaired systolic function
Restrictive	Endomyocardial scarring or myocardial infiltration resulting in restriction to left and/or right ventricular filling
Hypertrophic	Disproportionate LVH, typically involving the septum more than the free wall, with or without an intraventricular systolic pressure gradient; usually of a nondilated left ventricular cavity

(Modified with permission from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1408.)

### KEY FACT

For hypertrophic obstructive cardiomyopathy, unlike for most other cardiomyopathies, ACEIs and other vasodilators should be avoided. Diuretics should be used with caution.

### KEY FACT

When you encounter low voltage on ECG, think infiltrative disease or pericardial effusion.

### KEY FACT

Restrictive cardiomyopathy causes severe diastolic dysfunction with preserved EF.

### KEY FACT

Look for extracardiac clues to amyloid causing restrictive cardiomyopathy, including vocal hoarseness, carpal tunnel, and peripheral weakness.



### QUESTION

A 74-year-old man presents to the ED with shortness of breath. On evaluation, he has mild hypotension and tachycardia but is afebrile. Exam reveals an elevated JVP that ↓ with inspiration; ECG is notable for non-specific ST- or T-wave changes, a prolonged PR interval, and low voltages. Lab results show nephrotic-range proteinuria. What is the next best diagnostic test?

TABLE 3.13. Constrictive Pericarditis, Restrictive Cardiomyopathy, and Cardiac Tamponade

VARIABLE	CONSTRICITIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY	CARDIAC TAMPONADE
History	TB, cardiac surgery, radiation therapy, collagen vascular disease, trauma, prior pericarditis	Amyloidosis, hemochromatosis, sarcoidosis	Prior pericardial effusion, cardiac surgery, malignancy (eg, breast cancer), recent MI
Physical exam:			
Pulsus paradoxus	May be present	Rare	Frequent
JVP	Prominent x and y descents; Kussmaul sign often present	Prominent x and y descents; Kussmaul sign sometimes present	Absent or diminished y descent
Heart sounds	Pericardial knock	Prominent S <sub>4</sub>	Muffled
Murmurs	Not typically present	Mitral and tricuspid regurgitation are often present	Not typically present
ECG	Nonspecific	Right or left atrial enlargement; AV conduction delay; bundle branch block; may have low voltage	Low voltage; electrical alternans
CXR	Pericardial calcification	Nonspecific	Enlarged cardiac silhouette
Echocardiography	Pericardial thickening; pericardial effusion may be present; ventricular septal flattening with inspiration	Atrial enlargement; moderate or severe diastolic dysfunction	Pericardial effusion present; RV collapse during diastole
Hemodynamics			
Equalization of diastolic pressures	Present	Left-sided pressures are often higher than right-sided pressures	Present
Dip-and-plateau sign ("square root" sign)	Present	Present	Not typically present
Respiratory variation in LV/RV pressure tracings	Discordant peak RV and LV pressures	Concordant peak RV and LV pressures	Variable

### Symptoms/Exam

- Presents with dyspnea, chest pain, and syncope.
- Murmur: The obstructive form presents with a systolic crescendo-decrescendo murmur that intensifies with a ↓ in preload (eg, standing, Valsalva maneuver) and diminishes with an ↑ in preload (eg, raising the legs when the patient is in a supine position).
- S<sub>4</sub> and a sustained apical impulse.
- Carotid upstrokes are **bifid** owing to midsystolic obstruction.



### ANSWER

Fat pad biopsy to assess for amyloid deposition. This patient's hypotension, tachycardia, and low voltages on ECG point to an infiltrative process that has resulted in restrictive cardiomyopathy. The presence of nephrotic-range proteinuria limits the differential but makes amyloidosis a possible diagnosis. If high suspicion for amyloid deposition but fat pad biopsy is ⊖, proceed to cardiac biopsy or MRI.

### Differential

- **Valvular aortic stenosis:** The murmur of aortic stenosis radiates to the neck and ↑ with ↑ ventricular volume. Aortic stenosis also has weak and delayed carotid upstrokes (parvus et tardus).
- **Hypertensive heart disease:** Not typically associated with asymmetric septal hypertrophy or outflow tract obstruction.

## Diagnosis

- **ECG:** Left atrial enlargement and LVH with a broad, deep Q wave in leads I and II and in the left precordial leads (pseudoinfarction pattern).
- **Echocardiogram:** LVH with asymmetrically hypertrophied septum. The LV cavity is small and hypercontractile often with diastolic dysfunction. Systolic anterior motion of the mitral valve and LV outflow tract obstruction also seen.
- **Genetic testing:** Not routinely done, but has the potential to identify the genotype (which has prognostic value) and screen family members.

## Management

- **Avoid strenuous exercise.**
- **$\beta$ -blockers or verapamil:** Improve symptoms by  $\ominus$  inotropy, which  $\downarrow$  the outflow tract gradient and slows HR to  $\uparrow$  filling time.
- **Electrophysiologic study and ICD placement:** Indicated for patients with syncope or a family history of sudden cardiac death.
- **Septal reduction:** Via surgical myectomy/percutaneous alcohol septal ablation. Removes tissue from hypertrophic septum and relieves outflow tract obstruction. Improves symptoms but does not  $\downarrow$  the rate of sudden cardiac death.

## Screening for HCM in Young Athletes

- It is difficult to assess patients for risk factors of sudden cardiac death because these conditions are rare and because millions of young athletes need to be screened.
- Although screening usually involves history taking and physical examination, these measures alone lack the sensitivity to detect even the most common causes of sudden cardiac death in athletes (eg, HCM).
- In patients with a suggestive history or physical examination or in patients with 1st degree relative with HCM, further workup with ECG and echocardiography is warranted.

## ACUTE MYOCARDITIS

Patients are typically young and healthy, and many present with heart failure after a viral upper respiratory illness. Can be a cause of sudden cardiac death.

- **Etiologies** are as follows:
  - **Infectious:** **Most commonly viral** (coxsackievirus, HIV), but can be caused by numerous pathogens, including *Trypanosoma cruzi* (Chagas disease and Lyme disease).
  - **Immune mediated:** Sarcoidosis, scleroderma, SLE.
  - **Toxic:** Medications (anthracyclines), alcohol, heavy metals.
- **Symptoms/Exam:** Flulike symptoms, fever, arthralgias, and malaise. In more severe cases, patients can present with chest pain, dyspnea, and symptoms of heart failure. Exam reveals evidence of heart failure.
- **Diagnosis:**
  - The gold standard is **endomyocardial biopsy**, but because of patchy involvement of the myocardium, yield is not great and the test can be insensitive. By the time most patients seek medical care, fibrosis is the only finding on biopsy.
  - **ECG:** May have ST-segment changes and q waves; may have variety of arrhythmias. Lyme/sarcoid more likely to be associated with heart block.
  - **Cardiac biomarkers:** Elevated in the acute phase.
  - **Echocardiography:** Focal wall motion abnormalities and/or  $\downarrow$  EF.
  - **Cardiac catheterization:** To exclude CAD.
- **Management:** Support and evidence-based heart failure treatment.

## KEY FACT

Patients with HCM who have any of the following should undergo risk stratification (electrophysiologic testing) and possible ICD placement:

- Prior cardiac arrest
- Family history of sudden death
- Syncope (especially if recurrent or exertional)
- Nonsustained VT on Holter monitoring
- 3-cm thickness of the interventricular septum
- $\downarrow$  BP with exercise

## KEY FACT

Agents that  $\downarrow$  LV volume, such as nitrates and diuretics,  $\uparrow$  the outflow tract gradient and  $\uparrow$  murmur intensity and are thus contraindicated in patients with hypertrophic cardiomyopathy.

## KEY FACT

Consider the diagnosis of myocarditis in young patients who present after a viral illness. They commonly have no coronary risk factors and have  $\oplus$  cardiac enzymes but normal coronary arteries on cardiac catheterization.

## Pericardial Disease

### ACUTE PERICARDITIS

Pericardial inflammation that results in chest pain, a pericardial friction rub, diffuse ST-segment elevation. **Common etiologies** are idiopathic (often assumed to be viral illness), iatrogenic (procedural), connective tissue disease, and post-MI.

- **Symptoms/Exam:** Sharp, pleuritic chest discomfort that worsens while supine and lessens while leaning forward. Exam reveals a pericardial **friction rub**.

#### Diagnosis:

- Need at least two of the following three:
  - Chest pain typical of acute pericarditis.
  - Presence of friction rub on exam.
  - Typical ECG changes (diffuse ST-segment elevation, PR-segment depression) **not compatible with a single coronary distribution**; PR-segment elevation in aVR (Figure 3.8).
- May also have echocardiography with pericardial effusion.

#### Management:

- NSAIDs at high dose with prolonged course (4-6 weeks).
- Colchicine reduces recurrence when combined with NSAIDs.
- Steroids are often used when patients do not respond to other therapies/other therapies contraindicated; these ↑ risk for recurrence and have substantial side effects.

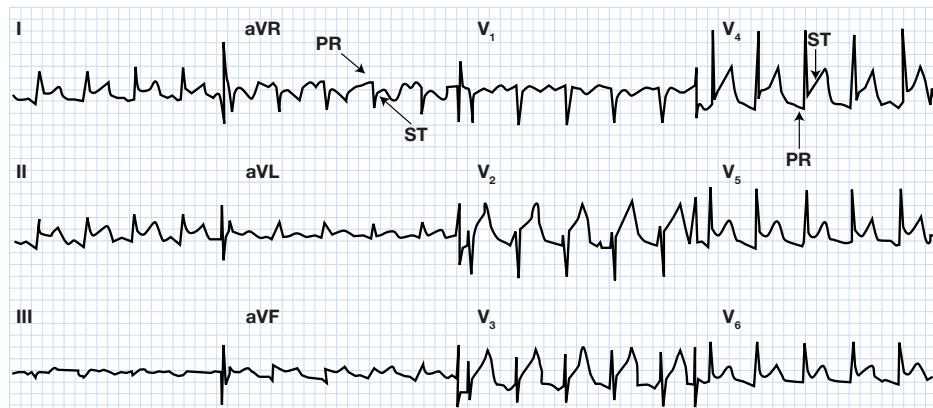
### CONSTRICITIVE PERICARDITIS

Impaired ventricular filling due to thickening and scarring of pericardium.

- **Etiologies:** Recurrent episodes of acute pericarditis, prior radiation therapy, TB, collagen vascular disease, and post-cardiac surgery.

#### Symptoms/Exam:

- Insidious onset of systemic venous congestion and ↓ cardiac output (fatigue, dyspnea, peripheral edema).
- **Kussmaul sign** (↑ JVP during inspiration).
- There are prominent  $x$  and  $y$  descents on jugular venous pulsation exam, leading to an M-shaped contour. Pulsus paradoxus may be present.
- A pericardial knock (a high-pitched third heart sound heard shortly after  $A_2$ ) may be heard following  $S_2$ , representing rapid cessation of early diastolic filling.



**FIGURE 3.8. Acute pericarditis on ECG.** (Modified with permission from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 232-1.)

■ Diagnosis:

- CXR: Shows pericardial calcifications (on lateral view) in approximately 25% of patients; bilateral pleural effusions are often present.
- Echocardiogram: Demonstrates pericardial thickening and adhesions, ventricular septal bounce during diastole, and a plethoric IVC without inspiratory collapse.
- Right heart catheterization: Equalization of diastolic pressures and dip-and-plateau pattern (“square root” sign) that reflects early diastolic filling followed by constraint from fixed pericardial volume. Interventricular discordance is specific for pericardial constriction.
- MRI: The most sensitive imaging modality for measuring abnormal pericardial thickness.
- Management: Initial therapy is diuresis, but surgical pericardectomy is the treatment of choice.

**KEY FACT**

While constrictive pericarditis presents similarly to heart failure, BNP level is typically normal.

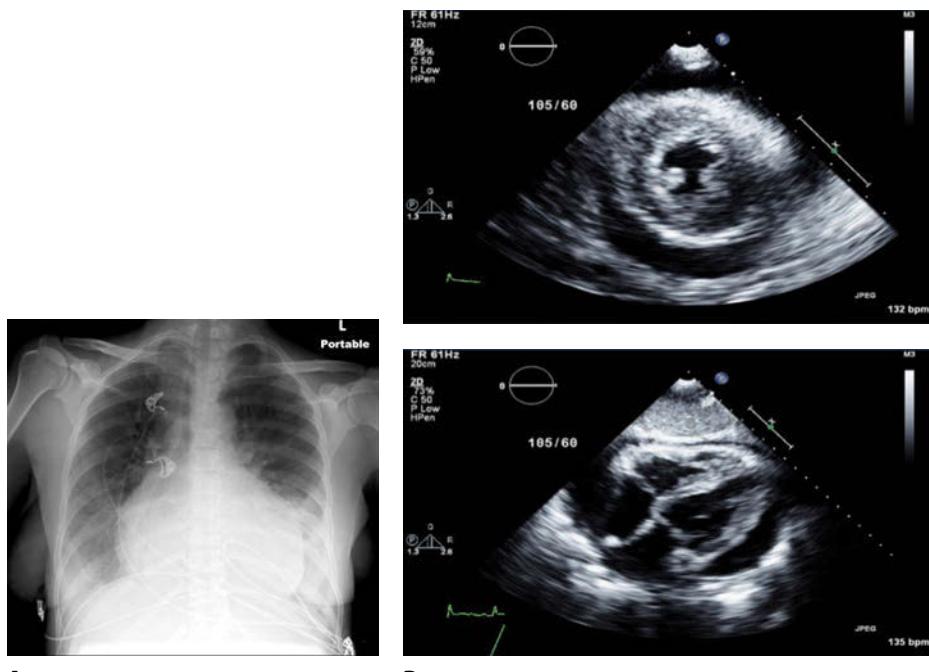
**PERICARDIAL EFFUSION**

Etiologies include pericarditis, iatrogenic (post-procedure), trauma, malignancy, MI, ESRD with uremia, and infection. Most common symptoms include dyspnea, chest pain, chest fullness.

Exam reveals muffled heart sounds and ↑ jugular venous pulsations.

■ Diagnosis:

- ECG: Low voltage; electrical alternans (beat-to-beat variation in the height of the QRS complex due to oscillation of heart in pericardial fluid).
- CXR: Cardiomegaly with a characteristic “boot-shaped” or “water-bottle” heart (Figure 3.9A).
- Echocardiography: Visualize effusion and evaluate for tamponade physiology (Figure 3.9B).



**FIGURE 3.9. Pericardial effusion and tamponade.** (A) Frontal CXR shows enlargement of the cardiac silhouette with a “water-bottle heart” configuration in a patient with a pericardial effusion. (B) Transthoracic echocardiogram images show a large pericardial effusion with collapse of the right atrium and right ventricle in early diastole in a patient with cardiac tamponade. (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Katie Raffel.)



**QUESTION 1**

A 56-year-old man with history of TB with mild effusive pericarditis s/p treatment presents with ↑ abdominal girth and edema. HR 98 bpm, BP 100/70 mm Hg. Exam reveals bibasilar crackles, elevated JVP with prominent y descent, extra diastolic sound, and peripheral edema. What is the most likely diagnosis?



**QUESTION 2**

A 42-year-old woman with history of metastatic breast cancer presents with subacute dyspnea and chest fullness and is found to have ↓ heart sounds, elevated JVP, and hypotension. Pulsus paradoxus is 15 mm Hg. CXR demonstrates water-bottle heart. How would you treat this condition?

**KEY FACT**

If fluid from a bloody pericardial effusion clots on drainage, the fluid is likely coming from an acute or subacute ruptured myocardium or blood vessel. In other forms of bloody pericardial fluid (eg, renal failure or malignancy), the fluid does not clot.

**KEY FACT**

Cardiac tamponade is more closely related to the rate of pericardial fluid accumulation than to the size of the effusion. A small effusion may cause tamponade if it is acute.

**KEY FACT**

Rule out myocardial ischemia in cases of polymorphic VT with a normal QT interval on baseline ECG.

**A****ANSWER 1**

Constrictive pericarditis. Features include insidious onset of ascites and edema with physical exam demonstrating ↑ JVP with prominent y descent,  $\oplus$  Kussmaul sign, pericardial knock. Chronic pericardial effusion such as that from TB can cause constrictive pericarditis. Treatment is predominantly diuresis and volume management with surgical pericardectomy in refractory cases.

**A****ANSWER 2**

Pericardiocentesis for pericardial effusion with tamponade. Elevated pulsus paradoxus ( $>10$  mm Hg) has a high likelihood ratio for tamponade. Transthoracic echocardiogram may confirm your suspicion but, ultimately, this is a clinical diagnosis.

- **Pericardiocentesis:** Can help diagnose underlying cause of the effusion (cytology, culture).
- **Management:** Treat underlying pathology and if patient is unstable, consider tamponade (next section).

**CARDIAC TAMPONADE**

An accumulation of pericardial fluid under pressure that impedes ventricular filling. Symptoms include dyspnea, chest pain, and light-headedness.

- **Symptoms/Exam:** Reveals tachycardia and hypotension with diminished heart sounds, ↑ JVP with blunting or absence of the y descent and pulsus paradoxus  $>10$  mm Hg.
- **Differential:**
  - **Constrictive pericarditis:** Has a slow, insidious onset. Kussmaul sign is usually present. Echocardiogram shows pericardial thickening without large effusion.
  - **Tension pneumothorax:** Can also present with tachycardia, hypotension, and elevated neck veins with **pulsus paradoxus**. Loss of unilateral breath sounds, pneumothorax on CXR and, if ventilated, ↑ ventilator pressures make tension pneumothorax more likely.
- **Diagnosis:**
  - **ECG:** Low voltage and/or electrical alternans.
  - **Echocardiogram:** Pericardial effusion with right atrial systolic collapse, RV diastolic collapse, a plethoric IVC that does not collapse with inspiration and/or ↑ respiratory variation of mitral and tricuspid inflow patterns.
  - **Cardiac catheterization:** Equalization of diastolic pressures (right atrial, RV, pulmonary arterial, PCWP).
- **Management:**
  - **IV fluids:** ↑ preload and improve ventricular filling.
  - **Pericardiocentesis:** Usually first line unless patient with reaccumulation of previously drained effusion or coagulopathic.
  - **Pericardial window:** Fistula between pericardial and pleural space that is surgically placed to prevent reaccumulation of fluid.

**Electrophysiology****VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION**

Commonly caused by ischemia/infarction, cardiomyopathy, electrolyte abnormalities, and drug toxicity. Types of VT are as follows (see also Figure 3.10):

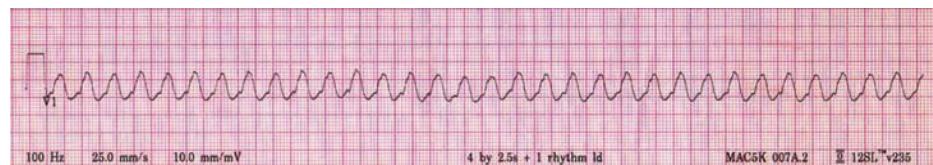
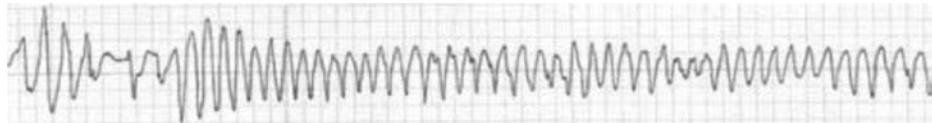
- **Monomorphic:** Characterized by a uniform QRS pattern; most commonly associated with myocardial scar.
- **Polymorphic:** Bizarre and changing QRS morphology as seen in torsades de pointes; may be precipitated by myocardial ischemia. Torsades is most often associated with medications such as type IC and type III antiarrhythmics, electrolyte abnormalities that prolong the QT interval, hypomagnesemia, hypocalcemia, and hypokalemia or channelopathies/long QT syndromes.

**Symptoms**

Chest pain, dyspnea, presyncope or syncope due to poor systemic perfusion are common. The initial manifestation of VT/VF in many patients is sudden cardiac death.

**Exam**

**Cannon A** waves on jugular venous pulsation are seen during VT as a result of AV dissociation.

**A****B**

**FIGURE 3.10. Monomorphic and polymorphic ventricular tachycardia.** (A) Rhythm strip shows wide-complex tachycardia with no clearly discernible P waves. (B) Rhythm strip shows torsade de pointes—a rapid polymorphic tachycardia with characteristic “twisting” of the QRS complexes around the baseline. (Image A source: Singh A. Monomorphic ventricular tachycardia. *West J Emerg Med*. 2008 Nov; 9(4):216. Image B source: Yates C, et al. Utility of the electrocardiogram in drug overdose and poisoning: theoretical considerations and clinical implications. *Curr Cardiol Rev*. 2012;8(2):137-151.)

### Differential

Supraventricular tachycardia (SVT) with aberrant conduction or SVT with accessory pathway.

### Diagnosis

- For stable patients, the Brugada criteria can be used to distinguish SVT with aberrancy from VT. Major criteria are as follows:
  - Northwest axis ( $\oplus$  in aVR).
  - Concordant in precordial leads (QRS all up or down, no RS wave).
  - AV dissociation.
  - Capture or fusion beats.
- For unstable patients, always assume VT until proven otherwise.

### Management

- Unstable VT (hypotension, dyspnea, chest pain, confusion): **Electrical cardioversion**.
- Stable VT: Amiodarone is first-line therapy; lidocaine second-line.
- Polymorphic VT (including torsades de pointes): Rapid magnesium infusion and overdrive pacing.
- Catheterization should be pursued in any patient with suspected ischemia as precipitant of ventricular arrhythmia.
- ICD placement is indicated for patients whose etiologies are not thought to be transient or reversible.

### ATRIAL FIBRILLATION

The most common arrhythmia in the general population. Prevalence ↑ with age. **Etiologies** include valvular heart disease, heart failure, pulmonary disease, hyperthyroidism, alcohol or cocaine use, untreated obstructive sleep apnea, cardiac surgery.

### Symptoms/Exam

Can be asymptomatic or manifest as palpitations, fatigue, dyspnea, presyncope, and/or symptoms of heart failure.



### KEY FACT

Many medications may cause prolonged QTc and torsade de pointes. Some of these include: antibiotics, antipsychotics, prokinetic agents, antiarrhythmic agents, and methadone.



### QUESTION 1

A 55-year-old man is brought to the ED by ambulance after he collapsed at work. He is in monomorphic VT and is successfully cardioverted. He has no acute lesions on coronary angiography. Cardiac imaging reveals an area of nonreversible perfusion defect laterally. EF on echocardiography is 35%. What intervention is likely to have the greatest effect on his survival?



### QUESTION 2

A 64-year-old man with history of diabetes presents with atrial fibrillation (AF) and is found to have dilated cardiomyopathy with an EF of 40%. An echocardiogram shows left atrial enlargement, chamber dilation, and no obvious intracardiac thrombus. What would be the optimal initial treatment for his condition?

### Differential

**Irregular tachycardias:** Atrial flutter with variable block, multifocal atrial tachycardia, any tachycardia with frequent premature atrial or ventricular contractions.

### KEY FACT

In patients >65 years of age, maintaining sinus rhythm with antiarrhythmics is no more effective than rate control and anticoagulation in reducing the incidence of stroke or mortality.

### Diagnosis

- **ECG:** AF is the most common cause of an irregularly irregular rhythm on ECG (Figure 3.11). **Look for the absence of P waves.**
- **Echocardiogram:** Used to evaluate etiology including valvular disease.

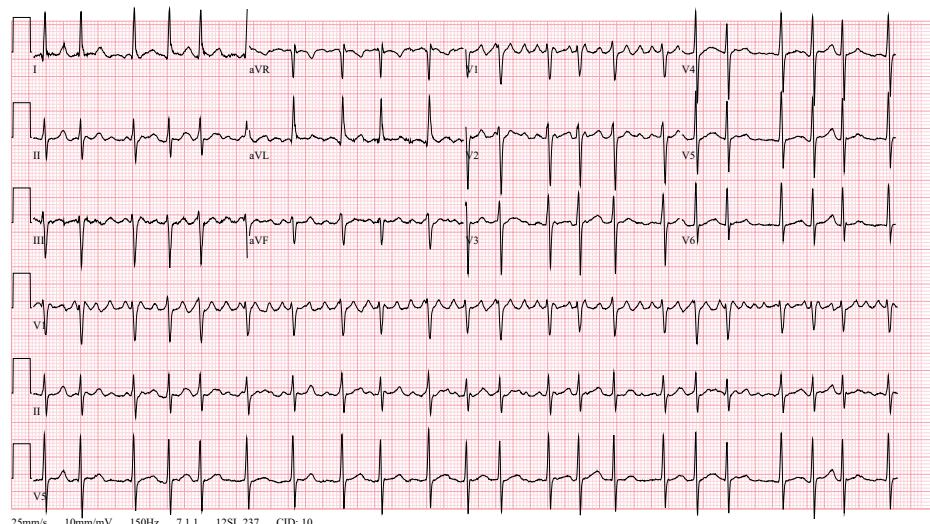
### Management

- **Unstable patients:** Proceed directly to cardioversion.
- **Rate control:**  $\beta$ -blockers or centrally acting nondihydropyridine CCBs (diltiazem, verapamil) are first line. For a  $\downarrow$  EF, avoid CCB. Digoxin can be added to these if needed.
- **Rhythm control:** Guidelines suggest flecainide, propafenone, or sotalol as first-line therapy in patients without heart disease. Patients with LVH, CAD, CHF can be started on amiodarone or dofetilide. Flecainide, propafenone are contraindicated in

A

### ANSWER 1

Placement of an ICD. This patient has a high chance of recurrence given that he had monomorphic VT from his associated scar from a prior MI (nonreversible).



A

A

### ANSWER 2

Rate control and anticoagulation. The patient is unlikely to benefit from cardioversion, as the duration of his AF is unknown, and he already has structural heart disease that will likely lead to a recurrence of AF. Given his  $\downarrow$  EF, a  $\beta$ -blocker would be optimal long-term treatment for both his HFrEF and AF rate control. This patient's CHADS2VASc score (one point for DM and one point for CHF) indicates that therapeutic anticoagulation and not ASA would be appropriate anticoagulation in this case.



B

**FIGURE 3.11. Atrial fibrillation and atrial flutter.** (A) Atrial fibrillation. (B) Atrial flutter with classic “sawtooth” appearance. (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Atif Qasim.)

those with CAD. Both dofetilide and sotalol can prolong QT and require inpatient monitoring for five doses with initiation. They are cleared by the kidney so not for those with CKD.

- **Wolfe-Parkinson-White (WPW) syndrome patients who present in AF with rapid ventricular response:** If baseline ECG shows a delta wave or if the current ECG shows wide, bizarre QRS complexes during AF, **avoid AV nodal blocking agents** ( $\beta$ -blockers, CCBs, adenosine, digoxin). The treatment of choice is IV procainamide or ibutilide, which slows conduction in the entire atrium. **If AV nodal blocking agents are given in this situation, the atrial impulses in rapid AF can proceed down the accessory pathway and cause VF and death.**
- **Anticoagulation:**
  - CHADS2  $\geq 2$  (1 point for CHF, Hypertension, Age  $>60$  years, Diabetes; 2 points for prior Stroke, or TIA) should be **anticoagulated** with warfarin or direct oral anticoagulant (DOAC) including factor Xa inhibitors (rivaroxaban and apixaban) and direct thrombin inhibitors (dabigatran) to **prevent stroke**. Notably, the DOACs should be dose-reduced or used with caution in the elderly, of low body weight or with renal insufficiency.
  - CHADS2VASc  $<2$ : Risk/benefit should be tailored to patient. Warfarin, DOAC or ASA can be used.
  - Anticoagulation may not be needed if AF is new onset and the duration is  $<48$  hours.
- **Anticoagulation in setting of cardioversion:**
  - If AF is  $>48$  hours or if  $<48$  hours and associated with rheumatic mitral valve disease, anticoagulate for 3 to 4 weeks prior to cardioversion and following for 4 weeks.
  - **TEE-guided cardioversion:** Confirmation of absence of thrombus. Anticoagulation for 24 hours prior to cardioversion and anticoagulation following cardioversion for 4 weeks.
- **Post-cardiac surgery AF:** Most common after mitral valve surgery; occurs on post-operative days 2 to 3. Cardioversion is the most effective therapy. If AF recurs after cardioversion, treat with rate control and anticoagulation. Prophylaxis includes perioperative  $\beta$ -blockers or amiodarone.

## ATRIAL FLUTTER

After AF, atrial flutter is the most common atrial arrhythmia. It is most commonly caused by a macro-reentrant circuit within the **right atrium**.

- **Symptoms/Exam:** Can be asymptomatic or manifest as palpitations, fatigue, dyspnea, presyncope, and/or symptoms of heart failure.
- **Diagnosis:**
  - Always consider the diagnosis of atrial flutter in patients who have a HR of approximately 150 bpm, since atrial flutter usually presents with a 2:1 AV block.
  - **Typical flutter:** The most common type of atrial flutter. ECG will generally show a **sawtooth pattern in the inferior leads** (II, III, aVF; see Figure 3.11). Look for discrete, upright, P-wave-like deflections in lead V<sub>1</sub> (the P-wave rate should be approximately 300 bpm).
- **Management:** In the acute setting, three treatment options exist for the restoration of sinus rhythm:
  - **Unstable rhythm:** Cardioversion.
  - **Stable:**
    - **Antiarrhythmic drugs** such as ibutilide, flecainide, propafenone. Ibutilide is approximately 60% effective in restoring sinus rhythm but carries the risk of torsades de pointes due to QT prolongation.
    - Rate control can be achieved with centrally acting CCBs,  $\beta$ -blockers, or digoxin.

## KEY FACT

The efficacy of DOACs has not been proven in pregnancy or with mechanical valves.

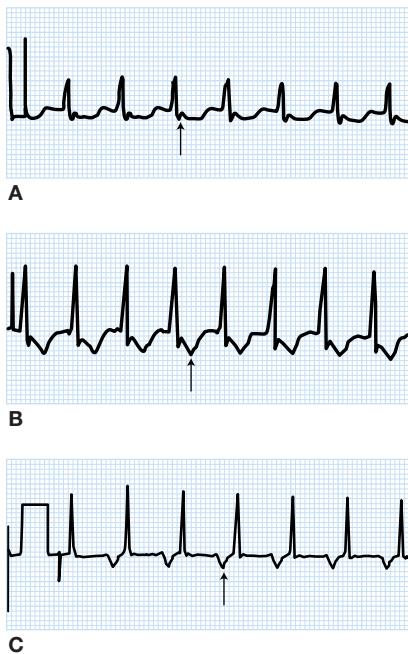


## QUESTION

An 83-year-old woman with a history of aortic stenosis and AF with rapid ventricular response presents to the ED with 3 days of nausea, vomiting, and confusion. Medications are metropolol, digoxin, and apixaban. She is afebrile with a pulse of 45 bpm and BP 123/67 mm Hg. Cr is 2.3, K is 5. ECG shows AF with complete heart block. What is the next best step in management?

### KEY FACT

If asked about pharmacotherapy for wide-complex tachycardia, adenosine is the wrong answer.



**FIGURE 3.12. Examples of supraventricular tachycardia.** Arrows indicate P waves. (A) AV nodal reentry. Upright P waves are visible at the end of the QRS complex. (B) AV reentry using a concealed bypass tract. Inverted retrograde P waves are superimposed on the T waves. (C) Automatic atrial tachycardia. Inverted P waves follow the T waves and precede the QRS complex.

(Modified with permission from Kasper DL, et al.

*Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1349.)



### ANSWER

Stop digoxin. Digoxin toxicity manifests as altered mental status, vision change, GI symptoms, and **arrhythmia**, including AV nodal block. Digoxin cannot be dialyzed; if the patient becomes unstable from her digoxin-related arrhythmia, administer digoxin-specific antibody fragments.

- For long-term treatment: Radiofrequency ablation is highly effective. Alternative treatments include antiarrhythmic drugs or rate control. These treatments generally require long-term anticoagulation to ↓ the risk of thromboembolism.

### PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

The most common type of paroxysmal SVT is **atrioventricular nodal reentry tachycardia (AVNRT)**, which is not commonly associated with structural heart disease.

- Atrial tachycardia:** Tachycardia arising from an ectopic atrial focus (↑ automaticity).
- Atrioventricular reentry tachycardia (AVRT):** Reentry via an AV bypass tract (WPW syndrome if a delta wave is present on ECG).
- AVNRT:** Reentry within the AV node.
- Multifocal atrial tachycardia:** Multiple p wave morphologies, often irregular. Associated with pulmonary disease.

### Symptoms

Can be asymptomatic or manifest as palpitations, fatigue, dyspnea, presyncope, or syncope. Paroxysms usually begin in young adulthood and ↑ with age. Attacks begin and end suddenly and may last a few seconds or persist for hours.

### Differential

Based on the ECG:

- If **QRS is narrow and regular:** AVRT, AVNRT, and atrial tachycardia.
- If **QRS is wide:** Paroxysmal SVT with aberrancy versus VT.
- If **QRS is wide and the rhythm is irregular with bizarre QRS complexes:** AF conducting via an accessory pathway.

### Diagnosis

- ECG (Figure 3.12).**
  - AVRT is a macro-reentrant circuit with retrograde P waves (short RP).
  - AVNRT is a micro-reentrant circuit with P waves buried in QRS (very short RP).
  - AT has a “long RP” relationship, with P waves preceding each QRS.
- Holter or event monitoring is essential if episodes are not documented on a 12-lead ECG.
- An electrophysiologic study can be used for diagnosis and ablative therapy.

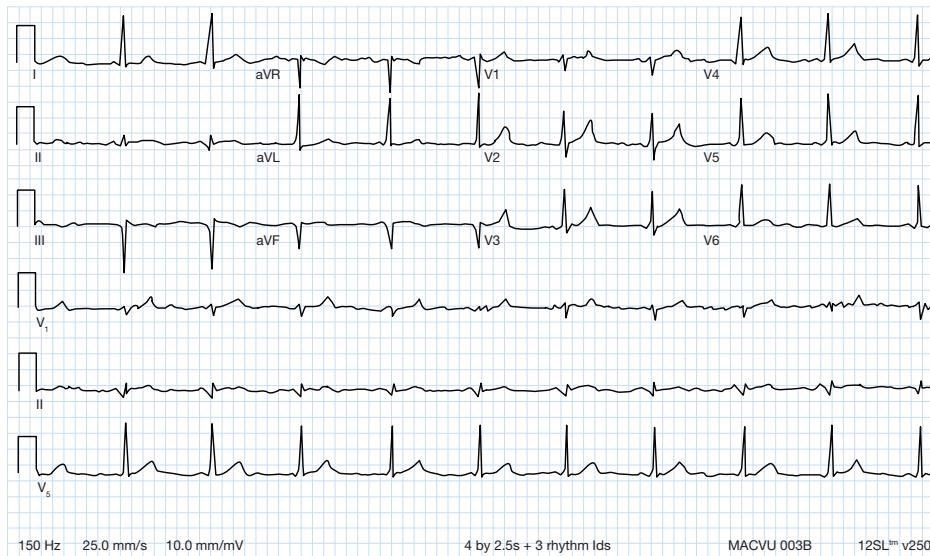
### Management

- Acute termination can occur with carotid massage or rapid administration of adenosine.
- Medical management consists of AV nodal blocking agents (eg, β-blockers). Can also use antiarrhythmics such as propafenone or flecainide in the absence of structural heart disease.
- Curative therapy consists of catheter-based ablation.

### WOLFF-PARKINSON-WHITE SYNDROME

In patients with WPW syndrome, an accessory pathway exists between the atria and ventricles as a result of a defect in the separation of the atria and ventricles during fetal development. WPW syndrome may be found incidentally on routine ECG. However, patients with WPW syndrome are at risk for tachyarrhythmias and even sudden cardiac death.

- Diagnosis:** If the accessory pathway allows **anterograde conduction**, electrical impulses from the atria can conduct down the accessory pathway into the ventricles, causing ventricular preexcitation with a short PR interval and **classic delta waves on ECG** (slurring of the upstroke on the QRS, best seen in lead V<sub>1</sub>; see Figure 3.13).



**FIGURE 3.13. Classic Wolff-Parkinson-White ECG.** Note the short PR interval and classic delta waves on ECG (slurring of the upstroke of the QRS best seen in  $V_4$ ).

- **Management:** If acutely unstable, cardiovert. If AF with RVR, use procainamide or ibutilide. Electrophysiologic study and catheter ablation of the bypass tracts is the treatment of choice for patients with WPW syndrome.

## BRADYCARDIA

Incidence ↑ with age. Etiologies include:

- **Intrinsic causes:** Idiopathic senile degeneration; ischemia (usually involving the inferior wall); infectious processes (endocarditis, Chagas disease, Lyme disease); infiltrative diseases (sarcoidosis, amyloidosis, hemochromatosis); autoimmune disease (SLE, RA, scleroderma).
- **Extrinsic causes:** Autonomic (neurocardiac, carotid sinus hypersensitivity, situational), medications ( $\beta$ -blockers, CCBs, clonidine, digoxin, antiarrhythmics), metabolic (electrolyte abnormalities, hypothyroidism, hypothermia), neurologic ( $\uparrow$  ICP, obstructive sleep apnea).

### Symptoms/Exam

Patients may be asymptomatic or may present with light-headedness, weakness, fatigue, or loss of consciousness (syncope). Look for evidence of ↓ pulse rate and evidence of the underlying cause of bradycardia. Look for **cannon A** waves in cases of complete AV dissociation (complete heart block).

### Diagnosis

- **ECG:** Look for the origin of the rhythm and whether dropped beats or AV dissociation is present (evidence of AV block; see Table 3.14 and Figures 3.14 and 3.15).
- **Telemetry, event monitors, and electrophysiologic studies** can also be helpful.

### Management

- If possible, treat the underlying cause (eg, metabolic abnormality, hypothermia). Glucagon for  $\beta$ -blocker overdose; calcium for CCB overdose.
- **Unstable rhythm:** If the patient is unstable, give atropine with escalation to dopamine or epinephrine gtt. If complete heart block, will likely need transvenous pacing.
- **Stable rhythm:** Discontinue any AV nodal blocking agents. Monitor and ensure pacing pads are accessible.

### KEY FACT

Do not treat atrial fibrillation with WPW with AV nodal blocking agents or you may precipitate a ventricular arrhythmia.

### KEY FACT

If left untreated, Lyme disease can cause varying degrees of AV conduction block at any time in the disease course.

### KEY FACT

Remember the association between hyperkalemia and bradycardia!

### KEY FACT

Remember that eye drops (like timolol) with  $\beta$ -blocker properties can have systemic affects and contribute to bradycardia.

### QUESTION

A 63-year-old woman presents to the hospital with palpitations and is found to have AF with a rate of 145 bpm. She is hemodynamically stable; ECG is notable for AF with rapid ventricular response and prominent delta waves. What is the appropriate therapy for this patient?

TABLE 3.14. ECG Findings with AV Block

TYPE OF BLOCK	ECG FINDINGS
First degree	Prolonged PR interval (>200 msec)
Second degree type I (Wenckebach)	Progressive prolongation of the PR interval until there is a dropped QRS Progressive shortening of the RR interval and a constant PP interval are other signs
Second degree type II	Regularly dropped QRS (eg, every third QRS complex is dropped) Constant PR interval (no prolongation) Usually associated with bundle branch blocks
Third degree	Complete dissociation of P waves and QRS complexes (P-wave rate > QRS rate)

### INDICATIONS FOR PERMANENT PACING

Indications for permanent cardiac pacing, based on expert guidelines, are classified as follows: I (definite indications), II (indications with conflicting evidence or opinion), or III (not indicated or harmful). All indications assume that transient causes such as drugs, electrolytes, and ischemia have been corrected or excluded.

#### Class I (Definite Indications)

- Third-degree AV block and advanced second-degree AV block with or, at times, symptomatic bradycardia.
- Symptomatic bradycardia.
- Arrhythmias or other conditions requiring medications that result in symptomatic bradycardia.
- Documented asystole of >3 seconds or escape rates of <40 bpm in **awake**, asymptomatic patients.

#### Class III (Not Indicated)

- Asymptomatic first-degree AV block.
- Asymptomatic type I second-degree AV block.
- AV block that is expected to resolve and/or is not likely to recur.



A



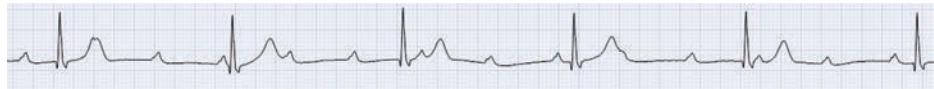
B

A

### ANSWER

IV procainamide. Because the patient is hemodynamically stable, she does not need urgent cardioversion. The presence of delta waves implies a bypass tract, which may be indicative of WPW syndrome. Treatment with  $\beta$ -blockers or CCBs may  $\uparrow$  conduction through the bypass tract, and therefore IV procainamide is the treatment of choice.

FIGURE 3.14. Second-degree heart block. (A) Type 1. (B) Type 2. (Source: Wikimedia commons; courtesy of Npatchett.)



**FIGURE 3.15. Third-degree (or complete) heart block.** Note the AV dissociation. (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Atif Qasim.)

## Implantable Cardioverter-Defibrillators

### 2° Prevention

- **Goal:** To prevent recurrent sudden cardiac death in patients with a history of VT or VF.
- **Indications:**
  - Hemodynamically unstable VT or history of VF arrest.
  - Patients with structural heart disease and spontaneous sustained VT.

### 1° Prevention

- **Goal:** To prevent sudden cardiac death in patients who have no history of VT and/or VF.
- **Indications:**
  - Patients with EF  $\leq$ 30% in patients with prior MI (at least 40 days prior).
  - Patients with nonischemic heart failure, EF  $\leq$ 35%, and NYHA class II or III (must have been treated with 3 months of evidence-based pharmacotherapy).

## Valvular Heart Disease

Table 3.15 summarizes common presentations of valvular heart disease.

### AORTIC STENOSIS

The most common types of aortic stenosis are senile calcific aortic stenosis and congenital bicuspid aortic valve. Rheumatic aortic stenosis is usually not hemodynamically significant and **almost always occurs in the presence of mitral valve disease**.

#### Symptoms/Exam

- Presents with a long asymptomatic period and may be picked up by exam first. Otherwise, the initial presenting complaint is usually dyspnea on exertion. The classic triad of symptoms associated with ↑ mortality include **angina, syncope, and eventually heart failure**. The normal valve area is  $3 \text{ cm}^2$ , and symptoms usually do not develop until the area is  $<1 \text{ cm}^2$ .
- Exam reveals crescendo-decrescendo systolic murmur heard at the base of the heart with radiation to the carotid arteries, delayed carotid upstrokes, sustained PMI, diminished A<sub>2</sub>.

#### Differential

- **Sub- or supravalvular stenosis:** Due to LV outflow tract membrane or fibromuscular ring (rare).
- **Hypertrophic obstructive cardiomyopathy:** Murmur accentuated with Valsalva or standing and ↓ by hand grip.



#### KEY FACT

In severe aortic stenosis, aortic valve replacement should be performed as soon as symptoms develop to prevent cardiac death.



#### KEY FACT

Aortic stenosis has been associated with an ↑ risk of GI bleeding, which is now thought to be due to acquired von Willebrand disease from disruption of von Willebrand factor multimers as they pass through the stenotic aortic valve.

TABLE 3.15. Valvular Heart Disease

	MITRAL STENOSIS	MITRAL REGURGITATION	AORTIC STENOSIS	AORTIC REGURGITATION
Inspection	—	Prominent apical impulse to the left of the midclavicular line (MCL)	Sustained point of maximal impulse (PMI) LV heave Delayed carotid upstroke	Hyperdynamic PMI to the left of the MCL Wide pulse pressure with a diastolic pressure of <60 mm Hg Bisferins arterial pulse
Heart sounds	<b>Opening snap</b> in early diastole	Prominent $S_3$ Midsystolic <b>click</b> may be present	<b>Paradoxical splitting of <math>S_2</math></b> ; prominent $S_4$	$S_3$
Murmurs	Diastolic low-pitched, rumbling murmur	Pansystolic blowing murmur Mid to late systolic murmur (with MVP)	Midsystolic crescendo-decrescendo harsh murmur	Early diastolic blowing murmur
Optimal auscultation	Apex	Apex, radiating to axilla	Right upper sternal border, radiates to carotid	Left lower sternal border
Indications for intervention	Symptoms Pulmonary HTN: Pulmonary arterial systolic pressure (PASP) $\geq 50$ mm Hg	Symptoms LV EF <60% LV ESD >40 mm Pulmonary HTN: PASP $\geq 50$ mm Hg New AF	Symptoms LV EF <50%	Symptoms LV EF <50%

(Data from McPhee SJ, et al. *Current Medical Diagnosis & Treatment 2010*. New York: McGraw-Hill, 2010, Table 10-2.)

### Diagnosis

- **Echocardiography:**
  - **Mild disease:** A valve area  $<1.5 \text{ cm}^2$ , mean gradient  $<25 \text{ mm Hg}$ .
  - **Moderate disease:** A valve area 1.0 to  $1.5 \text{ cm}^2$ , mean gradient 25 to  $40 \text{ mm Hg}$ .
  - **Severe disease:** A valve area  $<1 \text{ cm}^2$ , mean gradient  $>40 \text{ mm Hg}$ .
- **Follow-up echocardiography:** Recommended every year for severe aortic stenosis; every 2 years for moderate aortic stenosis; and every 3 to 5 years for mild aortic stenosis.
- **Cardiac catheterization:** Required to exclude significant coronary stenoses in symptomatic patients who are scheduled for surgery and are at risk for CAD. Also needed to confirm the severity of aortic stenosis when there is a discrepancy between clinical and noninvasive data.
- **Dobutamine stress testing:** Used in cases of low-gradient aortic stenosis (severe aortic stenosis by valve area, but mean gradient  $<40 \text{ mm Hg}$ ) to distinguish true stenosis from pseudostenosis caused by ↓ systolic function. If true aortic stenosis is present, the gradient will ↑ and the valve area will remain unchanged. If pseudostenosis is present, the valve area will ↑ with dobutamine.

### Management

Indicated in the setting of symptomatic aortic stenosis, asymptomatic severe aortic stenosis with LV dysfunction and asymptomatic aortic stenosis in setting of CAD and CABG:

- **Aortic valve replacement:** Replacement can now be done surgically or percutaneously in the right patients via transcatheter aortic valve replacement.
- **Aortic valvuloplasty:** May be effective in young adults with congenital aortic stenosis. Less effective in patients with degenerative aortic stenosis, and should be considered palliative therapy or a bridge to surgery.

## AORTIC REGURGITATION

Native aortic regurgitation can be caused by destruction or malfunction of the valve leaflets (infective endocarditis, bicuspid aortic valve, rheumatic valve disease) or dilatation of the aortic root such that the leaflets no longer coapt (Marfan syndrome, aortic dissection).

### Symptoms/Exam

- **Acute aortic regurgitation:** Presents with rapid onset of cardiogenic shock.
- **Chronic aortic regurgitation:** A long asymptomatic period followed by progressive dyspnea on exertion and other signs of heart failure.
- Exam reveals a soft or absent A<sub>2</sub> with a decrescendo blowing diastolic murmur at the base, wide pulse pressure and water-hammer peripheral pulses.
- Other peripheral signs include a bruit over the femoral artery; nail-bed pulsations (Quincke pulse); and a popliteal-brachial BP difference of >20 mm Hg.

### Diagnosis

- **Echocardiography:** Essential for determining LV size and function as well as the structure of the aortic valve. TEE is often necessary to rule out endocarditis in acute aortic regurgitation.
- **Cardiac catheterization:** Aortography can be used to estimate the degree of regurgitation if noninvasive studies are inconclusive. Coronary angiography is indicated to exclude CAD in patients at risk prior to surgery.

### Management

- In asymptomatic patients with normal LV function, afterload reduction may be considered, but evidence supporting its benefit is lacking. ACEIs or other vasodilators may ↓ LV volume overload and slow progression to heart failure.
- **Aortic valve replacement:** Should be considered in symptomatic patients or in those without symptoms who have worsening LV dilatation and systolic failure.
- **Acute aortic regurgitation:** Surgery is the definitive therapy, since mortality is high in this setting. IV vasodilators may be used as a bridge to surgery.

## MITRAL STENOSIS

Almost exclusively due to **rheumatic heart disease**, with rare cases due to congenital lesions, RA/SLE, and calcification of the mitral annulus. The normal mitral valve area is 4-6 cm<sup>2</sup>. Severe mitral stenosis occurs when the valve area is <1 cm<sup>2</sup>.

### Symptoms/Exam

- Characterized by a long asymptomatic period followed by gradual onset of dyspnea on exertion and findings of right heart failure and pulmonary HTN.
- Hemoptysis and thromboembolic stroke are late findings.
- Hoarseness from recurrent laryngeal nerve compression or dysphagia due to esophageal compression by an enlarged left atrium may be seen in late presenting cases.
- Exam reveals a loud S<sub>1</sub> and an opening snap of stenotic leaflets after S<sub>2</sub> followed by an apical diastolic rumble, signs of pulmonary HTN (loud P<sub>2</sub>) and RV failure (↑ JVP and hepatic congestion). AF is also common.

### KEY FACT

Valvuloplasty is not the appropriate management in adults!

### MNEMONIC

**To remember survival by symptom in the setting of aortic stenosis:**

**SASH**

Survival: **A**ngina 5 years, **S**yncope 3 years, **A**rt failure 2 years.

### KEY FACT

Indications for valve replacement in aortic regurgitation: development of symptoms or LV systolic failure/LV dilation even in the absence of symptoms.

### QUESTION 1

A 72-year-old man with a history of AF has dyspnea on exertion and 3/6 crescendo-decrescendo systolic murmur located at right upper sternal border. Echocardiogram shows normal systolic function and aortic valve area of 0.7 cm<sup>2</sup>, mean gradient of 44 mm Hg. What is the most appropriate next step in management?

### QUESTION 2

A 43-year-old woman from Vietnam presents with shortness of breath. On exam, she has an ↑ JVP, a loud P<sub>2</sub>, and an apical diastolic rumble following an opening snap. Her ECG shows right-axis deviation, RVH, and batrial enlargement. What is the diagnosis?

### Diagnosis

- **CXR:** Enlarged left atrium with normal LV. Prominent pulmonary arteries.
- **Echocardiography:** Used to estimate valve area and to measure the transmитral pressure gradient. Mitral valve morphology on echocardiography determines a patient's suitability for percutaneous valvuloplasty.
- **TEE:** To better assess mitral valve anatomy, valve area, and appropriateness for balloon valvuloplasty.
- **Cardiac catheterization:** Can be used to directly measure the valve gradient through simultaneous recording of PCWP and LV diastolic pressure.

### Management

- **Percutaneous mitral balloon valvotomy:** Unlike aortic valvuloplasty, balloon dilatation of the mitral valve has proven to be a successful strategy in patients without concomitant mitral regurgitation, atrial thrombus or severe annular calcification.
  - Consider this intervention in symptomatic patients with isolated mitral stenosis and an effective valve area of  $<1.0 \text{ cm}^2$ .
- **Mitral valve replacement:** For patients who are not candidates for valvuloplasty.

### Complications

- Left atrial enlargement and AF with resultant stasis is common and can result in left atrial thrombus formation and embolic stroke. All patients with AF and mitral stenosis should be anticoagulated.
- Pulmonary HTN and 2° tricuspid regurgitation.

### MITRAL REGURGITATION

Common causes of mitral regurgitation are 1° valve issues (mitral valve prolapse with myxomatous mitral valve disease, endocarditis, rheumatic heart disease) or secondary to problems with surrounding structures such as LV dysfunction (causing annular dilation or leaflet tethering) or acute ischemia (with papillary muscle dysfunction).

### Symptoms/Exam

- **Acute mitral regurgitation:** Abrupt onset of dyspnea due to pulmonary edema. Can be associated with hypotension; murmur may be early systolic.
- **Chronic mitral regurgitation:** Can be asymptomatic. In severe cases, can present with dyspnea and symptoms of heart failure.
- Exam reveals a soft S<sub>1</sub> and a holosystolic, blowing murmur heard best at the apex with radiation to the axilla. S<sub>3</sub> can be due to mitral regurgitation alone (in the absence of systolic heart failure), and its presence suggests severe mitral regurgitation.

### Diagnosis

- **Early detection of mitral regurgitation is essential because treatment should be initiated before symptoms occur.**
- **Exercise stress testing:** Document exercise limitation before symptoms occur at rest.
- **Echocardiography:** Transthoracic echocardiography is important for diagnosis as well as for grading the severity of mitral regurgitation. TEE is useful in patients who may need surgical repair or mitral valve replacement.
- **Catheterization:** To exclude CAD prior to surgery.

### KEY FACT

In patients with rheumatic heart disease, the mitral valve is typically involved. Isolated involvement of the aortic or tricuspid valve with sparing of the mitral valve is exceedingly rare in these patients.

### KEY FACT

In patients with mitral regurgitation, the intensity of the murmur on physical exam does not correlate with disease severity. In patients with acute myocardial ischemia, even a low-intensity murmur of mitral regurgitation should alert the physician to the possibility of papillary muscle rupture.

A

### ANSWER 1

Aortic valve replacement. This patient has symptomatic severe aortic stenosis, which is an indication for intervention.

A

### ANSWER 2

Rheumatic mitral valve disease. This patient likely has mitral stenosis, as indicated by her exam findings of an apical diastolic rumble and an opening snap. This is likely long-standing mitral stenosis that has led to pulmonary HTN, resulting in RVH and a loud P<sub>2</sub>. Given that she grew up in Asia, rheumatic heart disease is the most likely etiology.

## Management

- **Medications:** ACEIs are useful in patients with LV dysfunction or HTN.
- **Surgical intervention:** Indications for surgery include 1° mitral regurgitation disease with symptoms related to mitral regurgitation or severe asymptomatic mitral regurgitation with LV dysfunction, LV dilation, AF, or pulmonary HTN. If the mitral regurgitation is due to a problem with the surrounding structures and the leaflets themselves are normal, there are no clear guidelines as of yet for surgical correction. Mitraclip is reserved for patients who have 1° degenerative mitral regurgitation who are too high risk for surgery. Optimal timing of surgery is early in the disease course. Surgical outcomes are best in patients who have an EF of >60% and a LV end-systolic diameter of <4.5 cm.
- **Mitral valve replacement:** For symptomatic patients with an EF of >30% when the mitral valve is not technically repairable.
- **Patients with EF <30%:** Medical therapy is the mainstay of treatment. In refractory cases associated with severe symptoms, surgical repair or valve replacement has variable success; therefore, LV assist devices and cardiac transplantation are the treatment options.

## MITRAL VALVE PROLAPSE

- Defined by a displaced and abnormally thickened, redundant mitral valve leaflet that projects into the left atrium during systole. Mitral valve prolapse may be complicated by chordal rupture or endocarditis, both of which can lead to severe mitral regurgitation. It can be associated with connective tissue disease and Marfan syndrome.
- **Symptoms/Exam:** Most patients have no symptoms, and the diagnosis is often found incidentally on physical exam or echocardiography. However, some patients may present with atypical chest pain, palpitations, or TIAs. Exam reveals a midsystolic click followed by a midsystolic murmur with characteristic response to maneuvers ( $\uparrow$  with handgrip or Valsalva).
- **Diagnosis:** Echocardiography should be used for initial assessment; then follow every 3 to 5 years unless symptomatic or associated with mitral regurgitation.
- **Management:** Watchful waiting and then repair or replacement of the mitral valve when there is significant regurgitation, as per guidelines above.

## PROSTHETIC VALVES

### Indications for Placement

- **Bioprosthetic valves:** Older patients or those who cannot take long-term anticoagulant therapy (eg, bleeding diathesis, high risk of trauma, poor compliance).
- **Mechanical valves:** Young patients; patients with a prolonged life expectancy of >20 years or with other indications for chronic anticoagulation (eg, AF).

### Anticoagulation

- No anticoagulation is needed for porcine valves after 3 months of warfarin therapy. ASA can be used in patients with high bleeding risk.
- For patients with mechanical valves, **anticoagulation with warfarin** is indicated indefinitely. The level of anticoagulation depends on the location and type of valve; valves in the mitral and tricuspid position and older caged-ball valves are most prone to thrombosis. Goal INR 2.5 to 3.5 for mitral/tricuspid valves and 2 to 3 for aortic valves.

### Complications of Prosthetic Valves

- **Arrhythmia:** AF, conduction disturbances.
- **Endocarditis:**
  - **Early prosthetic valve endocarditis:** Occurs during the first 60 days after valve replacement, most commonly due to *Staphylococcus epidermidis*; often fulminant and associated with high mortality rates.
  - **Late prosthetic valve endocarditis:** Most often occurs in patients with multiple valves or bioprosthetic valves. Microbiology is similar to that of native valve endocarditis.
- **Hemolysis:** Look for schistocytes on peripheral smear. Usually occurs in the presence of a perivalvular leak.
- **Thrombosis:**
  - Presents clinically as heart failure, poor systemic perfusion, or systemic embolization.
  - Diagnose with echocardiography.
  - For small thrombi (<5 mm) that are nonobstructive, IV heparin should be tried initially. For large thrombi (>5 mm), use more aggressive therapy such as fibrinolysis or valve replacement.
- **Perivalvular leak:** Rare. In severe cases, look for hemolytic anemia and valvular insufficiency causing heart failure.
- **Emboi:** Typically present as stroke, but can present as intestinal or limb ischemia.
- **1° valve failure:** Most common with bioprosthetic valves; usually occurs after 10 years, but newer valves may last >20 years.

#### KEY FACT

Consider reproductive health in patients with congenital cardiac malformations. Pregnancy is well tolerated in VSD and ASD (in the absence of pulmonary HTN). Pregnancy is poorly tolerated in patients with coarctation of aorta, right-to-left shunt, pulmonary HTN, or severe stenosis of aortic/mitral/pulmonary valve.

#### KEY FACT

Complications of ASD include paradoxical embolism, atrial arrhythmias, and pulmonary HTN progressing to Eisenmenger syndrome.

## Adult Congenital Heart Disease

Congenital heart disease comprises 2% of adult heart disease. Only the most common noncyanotic heart defects will be presented here.

### ATRIAL SEPTAL DEFECT

There are three major types of atrial septal defect (ASD): ostium secundum (most common), ostium primum, and sinus venosus. Associated with Down syndrome.

#### Symptoms/Exam

- Most cases are asymptomatic and are either diagnosed incidentally on echocardiography or found during workup of paradoxical emboli. Large shunts can cause dyspnea on exertion and orthopnea.
- **Fixed wide splitting of S<sub>2</sub>** with a loud P<sub>2</sub> as pulmonary HTN develops.
- Exam reveals a systolic flow murmur (usually best heard at the left upper sternal border) due to ↑ flow across the pulmonic valve, and occasionally a diastolic rumble across the tricuspid valve due to ↑ flow.

#### Diagnosis

- **ECG:** Right atrial enlargement, RBBB, RVH.
- **CXR:** Prominent pulmonary artery, enlarged right atrium, and enlarged right ventricle.
- **Echocardiography with agitated saline bubble study:** Can be used to visualize the intracardiac shunt.
- **Cardiac catheterization:** May be needed to determine the ratio of pulmonary-to-systemic blood flow ( $Q_p/Q_s$ ) and to aid in decision for closure.

## Management

Closure if  $Q_p/Q_s > 1.5:1$ , severe pulmonary HTN, RV enlargement, or symptoms from ASD (dyspnea, AF, paradoxical embolus). This is contraindicated in right-to-left shunt.

### COARCTATION OF THE AORTA

Proximal narrowing of the descending aorta just beyond the left subclavian artery with development of collateral circulation involving the internal mammary, intercostal, and axillary arteries. A bicuspid aortic valve is present in >50% of patients with coarctation of the aorta. Also associated with Turner syndrome.

#### Symptoms/Exam

- Presents with headache, dyspnea, fatigue, and leg claudication.
- Exam reveals diminished femoral pulses with a radial-to-femoral-pulse delay and a systolic scapular murmur due to collateral flow that may become continuous with ↑ severity. May hear click of bicuspid aorta.

#### Diagnosis

- CXR: “Figure 3” sign (dilation of aorta proximal and distal to coarctation), rib notching from enlarged collaterals.
- ECG: LVH.
- Echocardiography: Bicuspid aortic valve, LVH, coarctation of aorta.
- Cardiac catheterization with aortography: Can define stenosis and measure gradient.
- MRI/MRA: Offer excellent visualization of the location and extent of coarctation along with collateral circulation (Figure 3.16).

#### Management

Surgical correction is appropriate for patients <20 years of age and in older patients with upper extremity HTN and a gradient of ≥20 mm Hg.

#### Complications

- Severe HTN.
- LVH due to ↑ afterload.
- Premature CAD.
- Aortic dissection or rupture.
- SAH due to rupture of aneurysms of the circle of Willis (rare).

### PATENT DUCTUS ARTERIOSUS

Uncommon in adults. Risk factors for patent ductus arteriosus (PDA) include premature birth and exposure to rubella virus in the first trimester.

#### Symptoms/Exam

- Usually asymptomatic, but moderate to large shunts can cause dyspnea, fatigue, and LV overload (due to ↑ pulmonary blood flow). In late stages, large shunts can cause signs and symptoms of pulmonary HTN and right heart failure (Eisenmenger syndrome).
- Continuous “machinery-like” murmur at the left upper sternal border and bounding peripheral pulses due to rapid aortic runoff to the pulmonary artery.
- In the presence of pulmonary HTN (Eisenmenger syndrome), the murmur is absent or soft, and there is differential cyanosis involving the lower extremities and sparing the upper extremities.



**FIGURE 3.16. Aortic coarctation.**

Parasagittal cine-MRI sequence showing a coarctation of the aorta (arrow) just distal to the origin of the left subclavian artery (S). (Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

Coarctation of the aorta is commonly associated with congenital bicuspid aortic valve.



#### QUESTION 1

A 46-year-old woman presents with intermittent palpitations. On exam, HR is 70 bpm and BP 130/70 mm Hg, normal JVP, widely and fixed split S<sub>2</sub> and 3/6 systolic ejection murmur at base. ECG reveals RBBB. What is the next most appropriate test?



#### QUESTION 2

A 37-year-old woman with difficult-to-treat HTN presents with fever, chills, and shortness of breath. Exam shows ↓ pedal pulses, a l/V diastolic murmur at the sternal border, and crackles bilaterally. CXR shows mild pulmonary edema and rib notching bilaterally. What condition does this patient have that predisposes her to the development of endocarditis?

**KEY FACT**

Differential cyanosis of the fingers (pink) and toes (blue and clubbed) is pathognomonic for Eisenmenger syndrome caused by an uncorrected PDA.

**Diagnosis**

- **ECG:** Left atrial enlargement, LVH; RVH in late stages.
- **Echocardiography:** Can be used to calculate the shunt fraction and to estimate pulmonary artery systolic pressure. Abnormal ductal flow can be visualized in the pulmonary artery.
- **Cardiac MRI:** The gold-standard test with which to diagnose PDA (cardiac CT can also be used).

**Management**

Closure if left atrial enlargement, LVH, or presence of left-to-right shunting. If severe pulmonary HTN, unable to close.

**Complications**

**Eisenmenger syndrome** with pulmonary HTN and shunt reversal; infective endocarditis.

**KEY FACT**

**Eisenmenger syndrome:** Long-standing left-to-right shunting causes pulmonary vascular hyperplasia, resulting in pulmonary arterial HTN and shunt reversal (development of right-to-left shunt). Clues on physical exam include cyanosis or clubbing; on ECG, right atrial enlargement or RVH.

**VENTRICULAR SEPTAL DEFECT**

Most common congenital heart defect at birth; some spontaneous closure by adulthood.

- **Symptoms/Exam:**

- Most patients diagnosed in adulthood are asymptomatic, but insidious heart failure symptoms may develop.
- A holosystolic murmur is heard at the left lower sternal border with a RV heave and prolonged splitting of  $S_2$ .
- As pulmonary arterial pressure  $\uparrow$ , a loud  $P_2$  and tricuspid regurgitation can also be appreciated.
- Cyanosis, clubbing, and signs of right heart failure can appear with the development of Eisenmenger syndrome.

- **Diagnosis:**

- Echocardiography with an agitated saline bubble study can be used to visualize the intracardiac shunt, determine size, and ascertain  $Q_p/Q_s$ .
- Cardiac catheterization: To determine  $Q_p/Q_s$  ratio.
- ECG: Left atrial enlargement, LVH; right atrial enlargement, RVH, and RBBB with pulmonary HTN.
- CXR: Cardiomegaly and enlarged pulmonary arteries.

- **Management:** Surgical correction is appropriate for patients with significant shunt ( $Q_p/Q_s > 1.7:1$ ); once Eisenmenger syndrome has developed, no longer able to close surgically.

- **Complications:** Eisenmenger syndrome, paradoxical embolism leading to TIAs or stroke; infective endocarditis.

**A****ANSWER 1**

Contrast echocardiogram. This patient is young, has fixed split  $S_2$ , a systolic murmur, RBBB on ECG, and intermittent palpitations. This makes us suspicious for possible congenital heart disease, specifically atrial septal defect.

**Vascular Pathology****A****ANSWER 2**

Bicuspid aortic valve. This patient has a diastolic murmur suggestive of aortic regurgitation as well as fevers and chills, making aortic endocarditis likely. Patients with rib notching, difficult-to-treat HTN, and  $\downarrow$  pedal pulses may have undiagnosed aortic coarctation, which is often associated with a bicuspid aortic valve.

**AORTIC DISSECTION**

Aortic dissection is associated with uncontrolled HTN, medial degeneration of the aorta (Marfan syndrome, Ehlers-Danlos syndrome), coarctation, congenital bicuspid valve, trauma, cardiac surgery. **Type A = proximal dissection; type B = distal dissection** (the dissection flap originates distal to the left subclavian artery).

## Symptoms

- Classically presents as a sudden-onset “tearing” or “ripping” sensation originating in the chest and radiating to the back. Unlike MI, pain is maximal at the onset and is not gradual in nature.
- Can present with organ hypoperfusion due to occlusion of arteries by the dissection flap (eg, coronary ischemia, stroke, intestinal ischemia, renal failure, limb ischemia).
- Other presentations include cardiac tamponade, aortic insufficiency, and acute MI (typically due to involvement of the right coronary artery) in cases of proximal aortic dissection.

## Exam

- BP is ↑ (although hypotension can be seen with proximal dissections associated with tamponade).
- Diastolic murmur of aortic insufficiency.
- Pulse deficits or unequal pulses between the right and left arms.
- Focal neurologic deficits (from associated cerebrovascular infarct) or paraplegia (from associated anterior spinal artery compromise).

## Diagnosis

- Three major clinical predictors are sudden, tearing chest pain; differential pulses or BPs between the right and left arms; and abnormal aortic or mediastinal contour on CXR.
- CXR:** Look for a widened mediastinum.
- TEE:** The fastest and most portable method for unstable patients, but may not be available at all hospitals.
- Chest CT:** Gold standard. Has a sensitivity and specificity up to 98%. See Figure 3.17.
- MRI:** Good for following patients with type B dissections but slower and less accessible than chest CT.

## Management

- Type A:** Surgical repair.
- Type B:** Admit to the ICU for medical management of HTN. Treat first with IV β-blockers (esmolol, labetalol) and then with IV nitroprusside. Avoid anticoagulation. Surgery is indicated for complications of dissection, end-organ damage, contained rupture, penetrating ulceration of significant size or extension despite medical therapy.

## Aortic Aneurysm

- Risk factors include ↑ age, male sex, smoking history, and history in first-degree relative. Men who have ever smoked should be screened with one time abdominal ultrasound between age 65 and 75 years.
- Management:** Elective repair at 5.5 cm or with expansion of >0.5 cm/year.

## PERIPHERAL ARTERIAL DISEASE

- Atherosclerosis of the peripheral arterial system is associated with the same clinical risk factors as coronary disease (smoking, diabetes, HTN, and hyperlipidemia).
- Symptoms/Exam:** Intermittent claudication is reproducible pain in the lower extremity muscles that is brought on by exercise and relieved by rest; however, most peripheral arterial disease is asymptomatic. Presents with poor distal pulses, femoral bruits, loss of hair in the legs and feet, slow capillary refill, and poor wound healing (chronic ulceration).

### KEY FACT

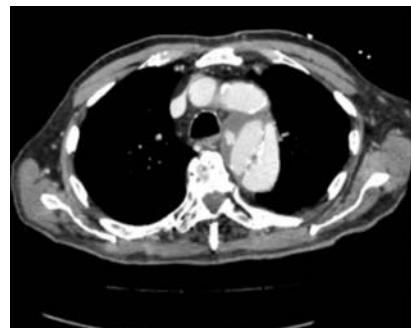
Proximal (type A) aortic dissection can present as acute inferior or right-sided MI due to involvement of the right coronary artery (prone to occlusion by the dissection flap).

### KEY FACT

Proximal (type A) aortic dissection is managed with surgical repair, and distal (type B) with aggressive BP management.

### KEY FACT

A nonarterial cause of limb pain may be spinal stenosis (pseudoclaudication). Spinal stenosis is relieved by sitting down but not by standing still!



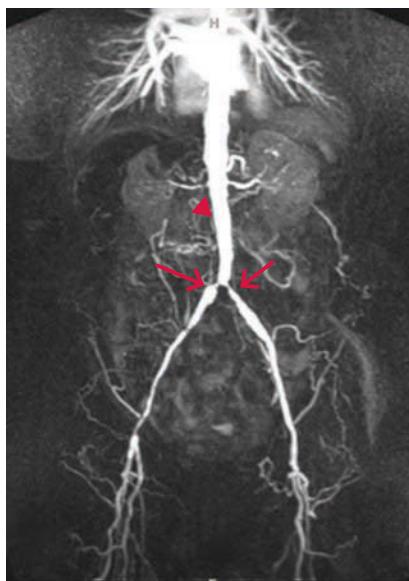
**FIGURE 3.17. Aortic dissection.**

Enhanced CT showing true (medial) and false (lateral) lumens within the aortic arch and descending aorta. (Reproduced with permission from USMLE-Rx.com.)



### QUESTION

A 55-year-old man with poorly controlled HTN and tobacco use presents with upper abdominal pain radiating to the back. BP is 170/100 mm Hg; cardiac exam reveals S<sub>4</sub>. Troponin is 0.3 ng/mL. ECG demonstrates LVH. CT angiography of the chest/abdomen demonstrates aortic dissection originating distal to the left subclavian artery and without major aortic branch involvement. What is the most appropriate next step in management?



**FIGURE 3.18. Peripheral arterial disease.** Coronal contrast-enhanced MRA shows multifocal atherosclerotic disease that is most severe at the origins of the common iliac (arrows) and right renal (arrowhead) arteries. (Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

Cilostazol has structural association with milrinone and is contraindicated in heart failure.

#### KEY FACT

If defined as an ABI of <0.90, most peripheral arterial disease is asymptomatic but still confers a high risk of adverse cardiovascular events and death.

A

#### ANSWER

Medical management with aggressive HR/BP control using IV  $\beta$ -blocker is indicated for Type B dissections, a dissection originating distal to left subclavian artery. If the dissection becomes complicated (propagation of dissection with end-organ ischemia, aneurysmal expansion or rupture), emergent surgical repair is warranted.

#### ■ Diagnosis:

- Ankle-brachial index (ABI) <0.90 (the highest ankle systolic pressure measured by Doppler divided by the highest brachial systolic pressure). <0.4 is severe.
- MRA and CT angiography of the lower extremities are useful noninvasive diagnostic tests (Figure 3.18).
- Lower-extremity angiography is the gold standard.

#### ■ Management:

- Aggressive cardiac risk factor reduction, including control of smoking, HTN, diabetes, and hyperlipidemia.
- Initiate a structured exercise rehabilitation program.
- **Pharmacotherapy:**
  - **Antiplatelet agents:** ASA is first-line therapy for overall cardiovascular event reduction, but data also support the use of ticlopidine, clopidogrel, and dipyridamole in peripheral arterial disease.
  - **Statins.**
  - **Cilostazol:** Phosphodiesterase inhibitor that inhibits platelet aggregation and promotes lower arterial vasodilation. Max benefit takes weeks to months.
- **Surgery:** Percutaneous transluminal angioplasty and lower extremity revascularization bypass surgery should be used only for severe symptoms such as resting pain/ischemia or threatened limb refractory to above interventions.

#### Acute Limb Ischemia

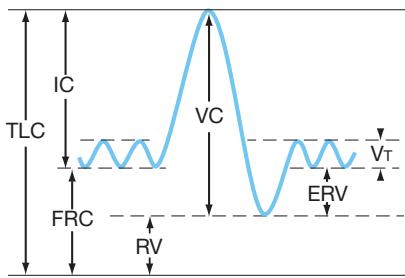
- May occur from progression of underlying atherosclerosis, from embolic phenomenon (endocarditis, LV thrombus, atrial thrombus in AF, cholesterol) or superimposed thrombosis.
- **Symptoms** include cool, painful limb.
- **Exam** reveals absent or ↓ pulses, weakness, sensory deficit (varying degrees).
- **Management:** Antiplatelet and systemic heparin therapy with emergent vascular consultation.

## CHAPTER 4

# Pulmonary and Critical Care

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**FIGURE 4.1. Lung volumes shown by spirogram tracing.**

## Physiology Primer

### LUNG VOLUMES

Common definitions are as follows (Figure 4.1 shows volumes in spirogram tracing):

- **Residual volume (RV):** Volume of air left in the respiratory system after maximal expiration.
- **Expiratory reserve volume (ERV):** Volume of air that can still be exhaled after normal expiration.
- **Tidal volume (VT):** Volume of air that enters and exits the lungs during normal respirations; approximately 500 mL in healthy patients.
- **Functional reserve capacity (FRC):**  $RV + ERV$ .
- **Total lung capacity (TLC):**  $RV + ERV + VT + IRV$  (inspiratory reserve volume).
- **Inspiratory capacity (IC):**  $VT + IRV$ .
- **Vital capacity (VC):** Volume of air that can be exhaled from full inhalation by exhaling as forcefully and rapidly as possible.

## Diagnostics in Pulmonary Medicine

### PULMONARY FUNCTION TESTS

PFTs are useful in the workup for unexplained pulmonary symptoms such as cough, dyspnea or wheezing and for monitoring the progression of known disease.

#### Spirometry Interpretation

Spirometry measures  $FEV_1$ , FVC, and reversibility by bronchodilators. Body plethysmography is one method to assess lung volumes. Table 4.1 outlines the steps in the evaluation of obstructive and restrictive lung disease and changes in lung function associated with obstruction and restriction. Table 4.2 lists common pulmonary disorders by category.

#### Flow Volume Loop Interpretation

Flow volume loops are visual representations (versus the numerical representation in spirometry) of obstructive and restrictive lung disease. For the Boards, it is important to be able to recognize intrathoracic, extrathoracic, and fixed obstruction on flow volume loops (Figure 4.2).

### ABG INTERPRETATION

The ABG is important in interpreting acid-base status (see the Nephrology chapter) as well as calculating the alveolar-arterial (A-a) gradient (see the Hypoxemia section below).

**TABLE 4.1. Obstructive vs Restrictive Lung Disease**

OBSTRUCTION	RESTRICTION
<p><b>Step 1: Is obstruction to airflow present?</b></p> <p>Look at FEV<sub>1</sub>/FVC:</p> <ul style="list-style-type: none"> <li>■ &lt;70% = obstructive lung disease.</li> </ul> <p><b>Step 2: How severe is it?</b></p> <p>Look at FEV<sub>1</sub>:</p> <ul style="list-style-type: none"> <li>■ 70% predicted but less than the lower limit of normal: Mild.</li> <li>■ 60%-69% predicted: Moderate.</li> <li>■ 50%-59% predicted: Moderately severe.</li> <li>■ 35%-49% predicted: Severe.</li> <li>■ &lt;35% predicted: Very severe.</li> </ul> <p><b>Step 3: Is it reversible or fixed?</b></p> <p>If FEV<sub>1</sub> or FVC ↑ by at least 12% and 200 mL after inhalation of a bronchodilator, it is reversible, so consider asthma!</p> <p><b>Step 4: Is it possibly consistent with emphysema?</b></p> <p>If TLC is &gt;120% predicted (indicative of hyperinflation) and DLCO is ↓ (indicative of loss of alveolocapillary membrane), consider emphysema.</p>	<p><b>Step 1: Is a restrictive process present?</b></p> <p>Look at TLC:</p> <ul style="list-style-type: none"> <li>■ &lt;80% or lower limit of normal: Restrictive process.</li> </ul> <p><b>Step 2: How severe is it?</b></p> <p>Look at TLC:</p> <ul style="list-style-type: none"> <li>■ 60% predicted but &lt; lower limit of normal: Mild.</li> <li>■ 40%-60% predicted: Moderate.</li> <li>■ &lt;40% predicted: Severe.</li> </ul> <p><b>Step 3: Is it a parenchymal process (Table 4.2)?</b></p> <p>Look at DLCO:</p> <ul style="list-style-type: none"> <li>■ ↓: Consider parenchymal process.</li> </ul> <p><b>Step 4: Is it an extraparenchymal process (Table 4.2)?</b></p> <p>DLCO is usually normal but have ↓ in maximal inspiratory and expiratory pressures.</p>

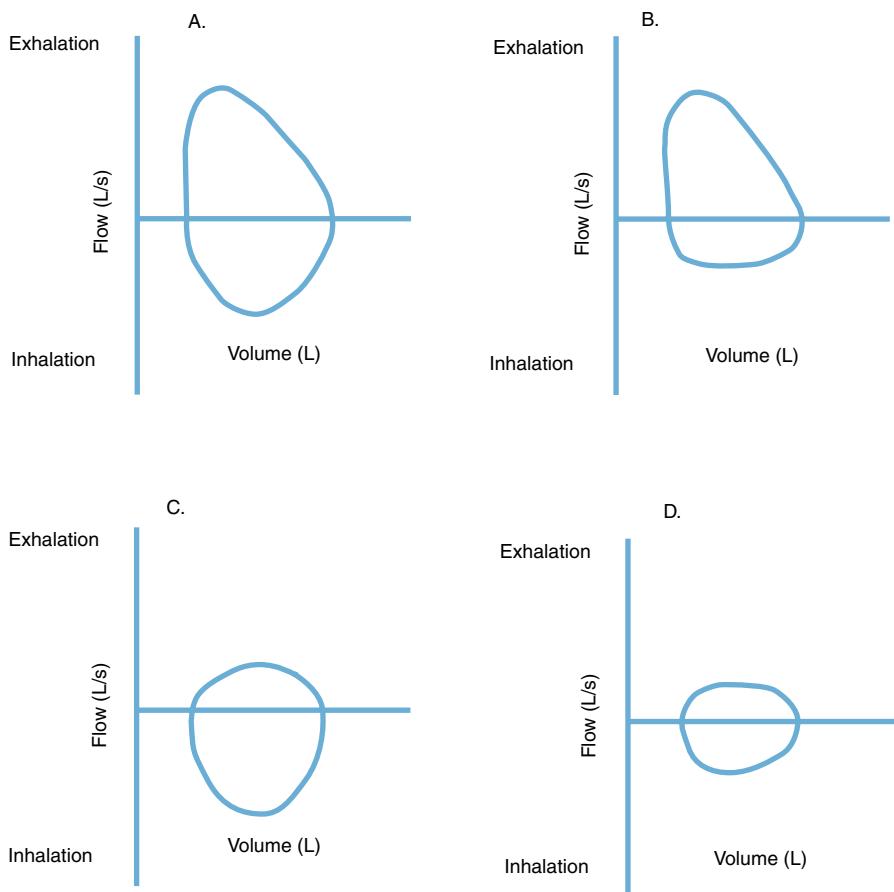
	FEV <sub>1</sub> /FVC	TLC	RV	VC		FEV <sub>1</sub> /FVC	TLC	RV	VC
<b>Obstructive</b>	↓	NI to ↑	↑	NI to ↓	<b>Restrictive</b>				
					Pulmonary parenchymal	NI to ↑	↓	↓	↓
					Extraparenchymal neuromuscular	NI	↓	↑	↓
					Extraparenchymal chest wall	NI	↓	↑	↓

**CT SCAN**

- Offers several advantages over routine CXRs:
  - Cross-sectional images allow for the comparison of different lesions that might be superimposed on CXR.
  - Better at characterizing lesions both by density and by size.
  - Particularly valuable in evaluating **mediastinal and hilar disease (use contrast)**.
- **CT angiography**, in which contrast is injected and images are rapidly acquired by helical scanning, can be used to detect **pulmonary embolism (PE)** in segmental or larger vessels.
- **High-resolution CT (HRCT)** provides individual cross-sectional images of 1 to 2 mm and allows for better recognition of **parenchymal lung processes**, such as **interstitial lung disease (ILD)**. Often done with prone and expiratory images to better assess for parenchymal lung disease.
- **Low-dose CT**: Noncontrast study that is best for looking for pulmonary nodules and is now being used for lung cancer screening.

**TABLE 4.2. Diagnostic Categories of Common Pulmonary Disorders by PFTs**

<b>Obstructive</b>
Asthma
COPD
Bronchiectasis
CF
<b>Restrictive—Parenchymal</b>
Idiopathic pulmonary fibrosis
Sarcoidosis
Drug- or radiation-related ILD
Collagen vascular disease-related ILD
<b>Restrictive—Extraparenchymal</b>
<b>Neuromuscular:</b>
■ Diaphragmatic weakness/paralysis
■ Myasthenia gravis
■ Guillain-Barré syndrome
■ Amyotrophic lateral sclerosis
■ Cervical spine injury
<b>Chest wall:</b>
■ Kyphoscoliosis
■ Obesity
■ Post-thoracoplasty



**FIGURE 4.2. Flow volume loops.** (A) Normal pattern. (B) Variable extrathoracic obstruction (eg, vocal cord paralysis or dysfunction). (C) Variable intrathoracic obstruction (eg, bronchogenic cysts). (D) Fixed obstruction (eg, tracheal stenosis resulting from prolonged intubation).

### PET SCAN

- A useful technique for the evaluation of pulmonary nodules >1 cm in size and for staging malignancy.
- Radiolabeled fluorodeoxyglucose is injected and rapidly transported into neoplastic cells, which then “light up” in hypermetabolic areas with PET imaging.

### KEY FACT

Helical or spiral CT with contrast is used for mediastinal and hilar disease. CT angiography is used for PE, but it can also be used to assess for mediastinal and hilar disease.

### KEY FACT

HRCT without contrast is used to detect specific lung diagnoses such as bronchiectasis, emphysema, and ILD.

### BRONCHOSCOPY

- Allows for the direct visualization of proximal portions of the endobronchial tree.
- **Bronchoalveolar lavage** is a technique used to sample cells and organisms from the alveolar space using aliquots of sterile saline. It is most helpful in diagnosing **infectious and neoplastic disease**, as well as in assessing for bleeding/capillaritis.
- **Transbronchial biopsy** is performed by passing a small forceps through the bronchoscope into the small airways to obtain parenchymal (alveolar) tissue. Transbronchial biopsy may be helpful in differentiating **infection, neoplasm, ILD, granulomatous disease, and organizing pneumonia**.
- **Transbronchial needle aspiration** involves the passing of a hollow-bore needle through the airway into a mass lesion or an enlarged lymph node. This is particularly useful in cases of mediastinal or hilar adenopathy, allowing for the differentiation of **neoplasm, sarcoidosis, fungal disease, and mycobacterial disease**. This is often done with endobronchial ultrasound.

## Evaluation of Common Pulmonary Symptoms

### DYSPNEA

Has four major causes: cardiac (eg, congestive heart failure [CHF]), pulmonary (eg, COPD, asthma, ILD, pulmonary embolism [PE]), psychogenic factors, and deconditioning.

Determine the time course (Table 4.3) and the extent of symptoms. Further distinctions include:

- **Orthopnea:** Dyspnea in the supine position; characteristic of CHF.
- **Platypnea:** Dyspnea while sitting upright.
- **Orthodeoxia:** Desaturation while sitting upright that improves when supine.
- **Diagnostic evaluation:** Review the history and physical (H&P) and obtain a CXR. Depending on the findings above, consider the following:
  - PFTs with spirometry and responsiveness to a bronchodilator; lung volumes; diffusion capacity; O<sub>2</sub> saturation at rest and with exercise; flow volume loops.
  - ECG and echocardiography ± stress testing
  - Chest CT: CT angiography to rule out PE in segmental or larger vessels. High-resolution computed tomography (HRCT) for ILD.



### KEY FACT

Platypnea-orthodeoxia syndrome is seen in lower lobe pulmonary AVMs or microvascular shunts due to hepatopulmonary syndrome.

### WHEEZING

- Expiratory wheezes suggest lower airway obstruction (eg, COPD or asthma) and inspiratory wheezes suggest upper airway obstruction. However, neither type of wheezing is sensitive or specific.
- Think of asthma if the patient has episodic wheezes, especially if they are often expiratory and monophonic (a single musical note) and respond to typical asthma medications (eg, bronchodilators).
- If wheezing does not respond to asthma medications, consider COPD, cardiac asthma/volume overload, vocal cord dysfunction, allergic bronchopulmonary aspergillosis (ABPA), and postnasal drip.
- ABPA is suggested by wheezing and cough with brown mucous plugs, peripheral eosinophilia, elevated serum IgE levels, immediate wheal-and-flare skin reactivity to *Aspergillus* antigens, and/or serum precipitants in a patient with asthma. Central bronchiectasis is also present.

**TABLE 4.3. Differential Diagnosis of Dyspnea Based on Rapidity of Onset**

	ACUTE DYSPNEA (MINUTES TO HOURS)	CHRONIC DYSPNEA (DAYS TO YEARS)
Pulmonary disorders	Pneumonia/bronchitis PE Pneumothorax Bronchospasm (asthma, COPD) Obstruction (anaphylaxis, aspiration)	COPD Asthma ILD Deconditioning Pulmonary hypertension
Cardiovascular disorders	Ischemia CHF Cardiac tamponade	Cardiomyopathy

**KEY FACT**

Remember that "all that wheezes is not asthma." Consider COPD, vocal cord dysfunction, PE, cardiac asthma/volume overload, foreign body aspiration, ABPA, postnasal drip, and even GERD.

**KEY FACT**

In a patient with worsening asthma, always think about concomitant GERD or ABPA.

**MNEMONIC*****To remember causes of hemoptysis***

For the most common causes, think of the **three B's**:

**B**ronchitis

**B**ronchiectasis

**B**ronchogenic carcinoma

For all causes, think of soldiers coughing up blood in a **BATTLECAMP**:

**B**ronchiectasis/**B**ronchitis

**A**spergilloma

**T**umor

**T**B

**L**ung abscess

**E**mboli

**CHF/Coagulopathy**

**AVM**

**M**itral stenosis

**P**neumonia

- Further distinguished as follows:

- **Polyphonic wheezes** (consisting of multiple notes): Suggest **dynamic compression of the large, more central airways**.

- **Monophonic wheezes**: Suggest disease of the smaller lower airways, **most typically asthma** (see Figure 4.2 for examples of flow volume loops in patients with upper airway obstruction).

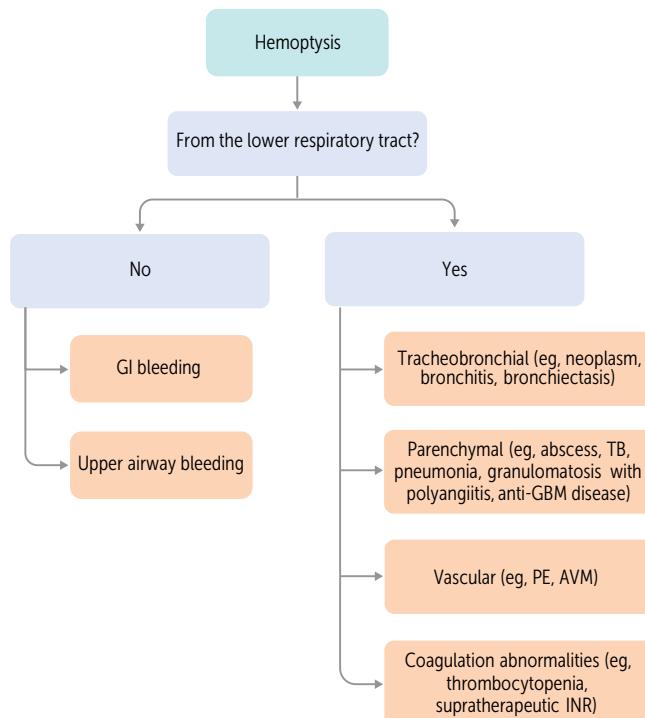
- **Diagnostic evaluation:** If the H&P does not point to the diagnosis, start empiric treatment for common causes such as asthma, especially with symptoms of wheezing combined with chronic cough. Lack of improvement following bronchodilator treatment for asthma suggests the need to either change therapy or investigate other potential etiologies with PFTs.

**HEMOPTYSIS**

The expectoration of blood from the lower respiratory tract, hemoptysis, can range from blood-streaked sputum to life-threatening bleeding. **Massive hemoptysis** is defined as the coughing up of >200 mL of blood in a 24-hour period. Figure 4.3 highlights an approach to hemoptysis.

**Symptoms/Exam**

- A history of TB or sarcoidosis may suggest aspergilloma. Frequent, multiple episodes of pneumonia could point to bronchiectasis. A diastolic heart murmur may suggest mitral stenosis (a frequently overlooked cause).
- A history of epistaxis, telangiectasia, and a bruit in the posterior aspect of the lungs may represent hereditary hemorrhagic telangiectasia with a ruptured pulmonary arteriovenous malformation (AVM).
- Renal insufficiency and hemoptysis may indicate granulomatosis with polyangiitis (formerly Wegener granulomatosis) or antiglomerular basement membrane (anti-GBM) disease (Goodpasture syndrome).
- Weight loss, tobacco abuse, and cachexia may suggest malignancy.



**FIGURE 4.3. Approach to hemoptysis.** (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

## Diagnosis

- Routine evaluation should include history and physical, CBC, ECG, CXR, UA, and coagulation studies. Consider **bronchoscopy** if there are risk factors for cancer (especially smoking) or to **localize source of bleeding**. Order a **chest CT** if **bronchiectasis or AVM** is higher on the differential.
- Additional studies, if indicated, include expectorated sputum for acid-fast bacilli and cytology, BUN/creatinine, ANA, ANCA, anti-GBM antibody, ABG, 100% O<sub>2</sub> to evaluate for shunt, and pulmonary arteriography.



### KEY FACT

To evaluate hemoptysis, do a bronchoscopy if you are concerned about cancer. Order a chest CT if you are considering bronchiectasis or AVM.

## Management

- Supportive care:** Bed rest with supplemental O<sub>2</sub> and blood products if needed. **Avoid antitussives, as an effective cough is needed to clear blood from the airways.** If gas exchange becomes compromised, consider early endotracheal intubation.
- Definitive treatment:**
  - Non-massive hemoptysis:** Treatment is directed at the specific underlying cause (eg, antibiotics for bronchitis).
  - Massive hemoptysis:** **Urgent bronchoscopy or bronchial artery angiography** may localize the site of bleeding. **Angiography plus embolization stops bleeding in >90% of cases.** Emergency surgery for massive hemoptysis is controversial and reserved for those who have failed embolization.



### KEY FACT

The majority of massive bleeds derive from high-pressure bronchial artery circulation rather than from low-pressure pulmonary arteries. Angiography plus embolization stops bleeding in >90% of cases.

## Obstructive Airway Disease

### PREOPERATIVE PULMONARY ASSESSMENT

- The type of surgery is a very important predictor of perioperative pulmonary complications with thoracic surgeries, upper abdominal surgery, emergency surgery, neck surgery, abdominal aortic aneurysm repairs, and vascular surgeries carrying the highest risk.
- Other risk factors include age >60 years, smoking, COPD, CHF, pulmonary hypertension, poor functional status, low serum albumin, and kidney disease (BUN >30 mg/dL).
- In patients with **known lung disease**, the goal is to **optimize treatment** of underlying lung disease.
- In patients without **known lung disease**, the goal is to **identify unexplained pulmonary symptoms and perform further workup**, which involves taking a history about exercise tolerance, chronic cough, and dyspnea. Consider PFTs, CXR, and ABG if undiagnosed symptoms are worrisome enough to change management or delay surgery.

### ASTHMA

See the Allergy and Immunology chapter.

### CHRONIC OBSTRUCTIVE LUNG DISEASE

Progressive chronic airflow limitation that is not fully reversible, resulting from chronic bronchitis and emphysema. Represents the fourth leading cause of death in the United States. Risk factors include cigarette smoking, a positive family history,  $\alpha_1$ -antitrypsin deficiency, and occupational or environmental exposure to smoke/dust/chemicals. Chronic bronchitis and emphysema can be distinguished as follows, although most patients have overlap:



### QUESTION

A 75-year-old man has worsening dyspnea on exertion and wheezing over the past two years. He has a heavy smoking history. PFTs yield the following results: FEV<sub>1</sub> = 60% predicted; FEV<sub>1</sub>/FVC = 55%; TLC by plethysmography = 55% predicted; DLCO = 50% predicted. What is your interpretation?

- **Chronic bronchitis:** Chronic productive cough for 3 months over 2 consecutive years.
- **Emphysema:** Abnormal enlargement of the air spaces distal to the terminal bronchioles with wall destruction.

### Symptoms/Exam

- Acute exacerbation is suggested by three features: **worsening dyspnea, ↑ cough, and a change in sputum volume or purulence.**
- Typically presents with chronic cough in the fourth or fifth decade of life. Dyspnea usually occurs only with moderate exercise. Chest wall hyperinflation, prolonged expiration, wheezing, and distant breath and heart sounds are also seen. Clubbing is **not** seen in COPD.
- Use of respiratory accessory muscles, cyanosis (“blue bloater” suggests **chronic bronchitis**), and pursed-lip breathing (“pink puffer” suggests **emphysema**) may be seen. Neck vein distention, a tender liver, and lower extremity edema could suggest cor pulmonale.

### KEY FACT

The cardinal symptoms of COPD exacerbation are ↑ dyspnea, ↑ cough, and change in ↑ sputum volume or purulence.

### KEY FACT

In acute exacerbations of COPD, inhaled corticosteroids are not beneficial but teaching proper use of them prior to discharge from the hospital is important. There is no advantage to IV over oral corticosteroids as long as the patient's GI absorption is not compromised.

### Differential

Acute bronchitis, asthma, bronchiectasis, cystic fibrosis (CF), and CHF.

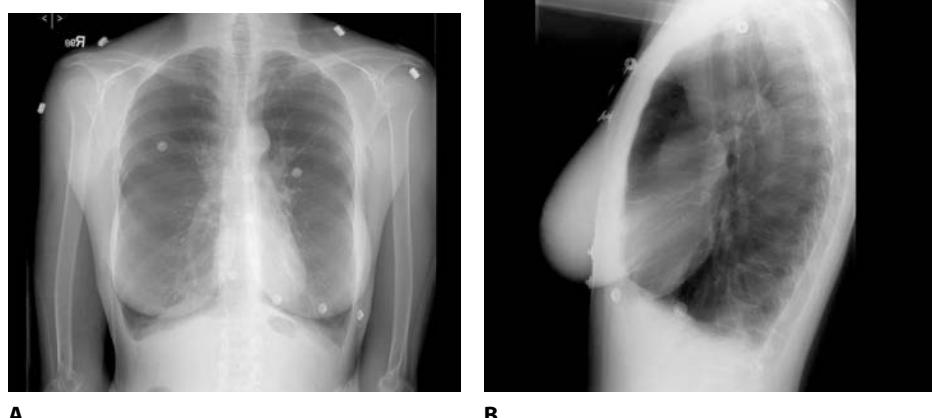
### Diagnosis

- Pulmonary function tests (PFTs), particularly FEV<sub>1</sub> (which indicates severity), are important for diagnostic confirmation and for predicting disease progression. Diagnosis is confirmed by post-bronchodilator PFTs showing an **FEV<sub>1</sub>/FVC of <0.7** and an **FEV<sub>1</sub> of <80% or lower limit of normal**. **Diffusing capacity is usually ↓.**
- CXR is not required for diagnosis but may show hyperinflation with ↓ lung markings, ↑ retro-sternal airspace, and flattened diaphragms (Figure 4.4).
- Obtain an O<sub>2</sub> saturation and check the ABG for evidence of hypoxemia, hypercarbia, or respiratory acidosis.
- Obtain an  $\alpha_1$ -antitrypsin level with **early-onset emphysema (fifth decade of life or earlier)** or in the setting of a suggestive family history. Associated with **basilar panlobular emphysema**.

A

### ANSWER

Mixed obstructive and restrictive ventilatory pattern.



**FIGURE 4.4. Chronic obstructive pulmonary disease (COPD).** Posteroanterior (A) and lateral (B) CXRs show the hallmarks of COPD: hyperinflation, hyperlucency of the lung fields, and diaphragmatic flattening in a 58-year-old woman with advanced disease. (Reproduced with permission from USMLE-Rx.com.)

## Management

- Treatment of acute COPD differs from that of acute asthma (Table 4.4).
- **Mild exacerbations:** Give **short-acting  $\beta_2$ -adrenergic** (albuterol) and **anticholinergic** (ipratropium) inhalers or nebulizers. Use as needed in all patients of all levels. These improve dyspnea and pulmonary function.
- **Moderate exacerbations:** Treat as described above. May require hospitalization. Also consider the following:
  - $O_2$  therapy if hypoxic.
  - Systemic oral or IV corticosteroids help  $\downarrow$  the length of exacerbations and improve  $FEV_1$ .
  - Antibiotics are indicated in the setting of worsening dyspnea, cough, or sputum production.
- Therapies for stable COPD (Table 4.5):
  - Smoking cessation.
  - Immunizations for influenza and pneumococcus.
  - **Supplemental oxygen therapy** if indicated (see Key Fact) is the only treatment besides smoking cessation with a proven mortality benefit.
  - **$\beta_2$ -adrenergic and anticholinergic agents** improve pulmonary function and  $\downarrow$  dyspnea. First-line maintenance therapy should include **long-acting  $\beta_2$ -agonists (LABA; salmeterol, formoterol)** and/or **long-acting muscarinic antagonists (LAMA; tiotropium)**, if short-acting agents do not control symptoms. LABAs  $\downarrow$  exacerbations and hospitalizations.
  - Inhaled corticosteroids can be added to LABA for maintenance therapy in more severe COPD ( $FEV_1 < 50\%$ , Global Initiative for COPD [GOLD] criteria 3-4). The combination of inhaled corticosteroids and LABA is more effective in  $\downarrow$  the frequency of exacerbations but may  $\uparrow$  the risk of pneumonia and other adverse effects. Their long-term safety is unknown.
  - **Pulmonary rehabilitation:** Associated with improved exercise tolerance and  $\downarrow$  pulmonary symptoms.
  - Azithromycin (macrolide antibiotic) or roflumilast (an oral phosphodiesterase-4 inhibitor) have been shown in patients with a history of frequent exacerbations to help with chronic control (not in acute exacerbations).
  - **Lung volume reduction surgery:**  $\downarrow$  hyperinflation to improve lung mechanics. Best for patients with severe COPD who (1) do not respond to pulmonary rehabilitation and other treatments, (2) have severe emphysema in the upper lobes, and (3) are at low risk for surgery.
  - Single- or double-lung transplantation may be indicated for some patients with a low  $FEV_1$ , hypercarbia, and cor pulmonale (right heart dilation and failure due to pulmonary hypertension).

TABLE 4.4. Treatment of Acute Exacerbations of Asthma and COPD

TREATMENT	ASTHMA	COPD
Peak expiratory flow useful	Yes	No
Systemic corticosteroids	Yes	Yes
Antibiotics	No	Yes
$O_2$	Yes	Yes
Combination bronchodilator therapy <sup>a</sup>	Yes	Yes
Noninvasive mechanical ventilation	Unclear	Yes

<sup>a</sup> $\beta_2$ -agonist and ipratropium bromide.

## MNEMONIC

**For the treatment of acute COPD exacerbations:**

**ABC-ON**

**A**ntibiotics

**B**ronchodilators

**C**orticosteroids

-

**O**xxygen

**N**oninvasive ventilation

## KEY FACT

For the majority of patients, 40 mg of oral prednisone daily for 5 days is equivalent to a traditional 2-week course.

## KEY FACT

General indications for long-term continuous  $O_2$  therapy (24 hours/day):

- $Pao_2 \leq 55$  mm Hg or  $O_2$  saturation  $\leq 88\%$  at rest.
- or
- $Pao_2 \leq 59$  mm Hg or  $O_2$  saturation  $\leq 89\%$  with cor pulmonale or erythrocytosis (hematocrit  $> 55\%$ ).

## KEY FACT

$O_2$  therapy and smoking cessation are the only interventions that  $\uparrow$  life expectancy in hypoxemic COPD patients. No medication has been shown to prevent the decline of  $FEV_1$ .



## QUESTION

A 45-year-old woman has had worsening asthma for 2 years despite treatment with albuterol and salmeterol/budesonide. Her cough is occasionally productive of bloody sputum. She has no fevers, chills, or night sweats. A recent CXR shows peribronchial thickening. What is the most likely etiology of her hemoptysis?

TABLE 4.5. Classification, Severity, and Treatment of Stable COPD<sup>a</sup>

STAGE	SPIROMETRY	TREATMENT FOR STABLE COPD
All stages	FEV <sub>1</sub> /FVC <0.7	Smoking cessation; annual influenza and pneumonia vaccinations
1 (mild)	FEV <sub>1</sub> ≥80% of predicted	Short-acting bronchodilator (albuterol, ipratropium) for relief
2 (moderate)	FEV <sub>1</sub> 50%-79% of predicted	Add long-acting $\beta_2$ -agonists and/or long-acting anticholinergic bronchodilators (ie, LABA or LABA + LAMA)
3 (severe)	FEV <sub>1</sub> 30%-49% of predicted	Combination of long-acting $\beta_2$ -agonists with inhaled corticosteroid
4 (very severe)	FEV <sub>1</sub> <30% of predicted or FEV <sub>1</sub> <50% of predicted plus chronic respiratory failure	Also add long-term O <sub>2</sub> PRN; consider surgery

<sup>a</sup>Classification is by the GOLD criteria.

## BRONCHIECTASIS

Irreversible dilatation and destruction of bronchi due to cycles of infection and inflammation, with mucopurulent sputum production. Characterized by dilated airways and focal constrictive areas.

### Symptoms/Exam

- Chronic bronchiectasis presents with **chronic productive cough** with purulent, often foul-smelling sputum. Sputum volume is correlated with decline in respiratory function and quality of life. Dyspnea, wheezing, pleuritic chest pain, and hemoptysis are all possible. Patients may have a history of recurrent respiratory tract infections.
- Acute exacerbations of bronchiectasis lead to a change in sputum production, dyspnea, cough, wheezing, low-grade fever, fatigue, and decline in exercise tolerance. Changes in chest exam, PFTs, and imaging may occur.

### Differential

Bronchiectasis is most commonly idiopathic, as most factors are conditions that are associated, rather than definitive. Associations include the following:

- Infections (recurrent, postinfectious), including *Pseudomonas*, *Haemophilus*, TB or other mycobacterial disease, pertussis, measles, influenza.
- Immunodeficiency, eg, common variable immune deficiency, immunoglobulin A (IgA) deficiency, HIV.
- Congenital conditions, eg, CF, 1° ciliary dyskinesia/Kartagener syndrome (autosomal recessive genetic disorder causing defects in the action of cilia in the respiratory tract).
- Autoimmune disease, eg, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren syndrome, relapsing polychondritis, inflammatory bowel disease (IBD).
- Hypersensitivity (ABPA).

A

### ANSWER

Bronchiectasis due to ABPA.

## Diagnosis

- CBC, including differential (may see neutrophilia; eosinophilia is seen in ABPA). CXR shows “tram lines” (airway dilation). Screen for common variable immune deficiency, IgA deficiency, and ABPA ( $\uparrow$  serum total IgE). Check HIV.
- HRCT is the best diagnostic tool for mapping airway abnormalities (Table 4.6). Findings include airway dilation, lack of tapering of bronchi with bronchial wall dilation, airways filled with mucous.
- Other tests to consider:
  - Spirometry quantifies the degree of airway obstruction pre- and post-bronchodilator (obstructive pattern due to mucous filling the airways,  $\downarrow$  FEV<sub>1</sub>/FVC ratio,  $\downarrow$  FEV<sub>1</sub>,  $\downarrow$  or normal FVC).
  - Sputum sample for bacterial, fungal, and mycobacterial cultures.
  - Sweat chloride test for CF.
  - ANA, RF, and anti-Ro/La if suspicious for connective tissue disease.

## Management

- Patients with acute exacerbations have high bacterial load and inflammation. Identify and treat acute exacerbations with antibiotics for 10 to 14 days (eg, if no sputum culture data is available, a fluoroquinolone is reasonable). Also consider antibiotics based on past sputum cultures and response to selected antibiotics.
- Treatment may also include: bronchodilators, airway clearance (chest physiotherapy, flutter devices, percussive vests, frequencers), mucolytic agents—hypertonic (7%) saline and DNase—helpful in stable CF but potentially harmful in patients with non-CF bronchiectasis, and outpatient pulmonary rehabilitation. For recurrent exacerbations, consider preventive therapy with a macrolide antibiotic (eg, azithromycin). Surgical resection for massive hemoptysis or unresolving infection.

## CYSTIC FIBROSIS

Caused by mutations in the CF transmembrane conductance regulator (CFTR), leading to chloride channel dysfunction. Consider especially in young adults with a history of bronchiectasis, sinus disease, infertility, or recurrent pancreatitis.

## Symptoms/Exam

- Look for a history of failure to thrive as a child, persistent respiratory infections (*Pseudomonas*), nasal polypsis, sinusitis, intestinal obstruction, malabsorption (steatorrhea, diarrhea), recurrent pancreatitis, hepatobiliary disease, and male infertility.
- Bronchiectasis and *Staphylococcus aureus* and *Pseudomonas aeruginosa* (mucoid variant) pneumonias are common. Exam reveals an  $\uparrow$  AP chest diameter, upper lung field crackles, nasal polyps, and clubbing.

## Differential

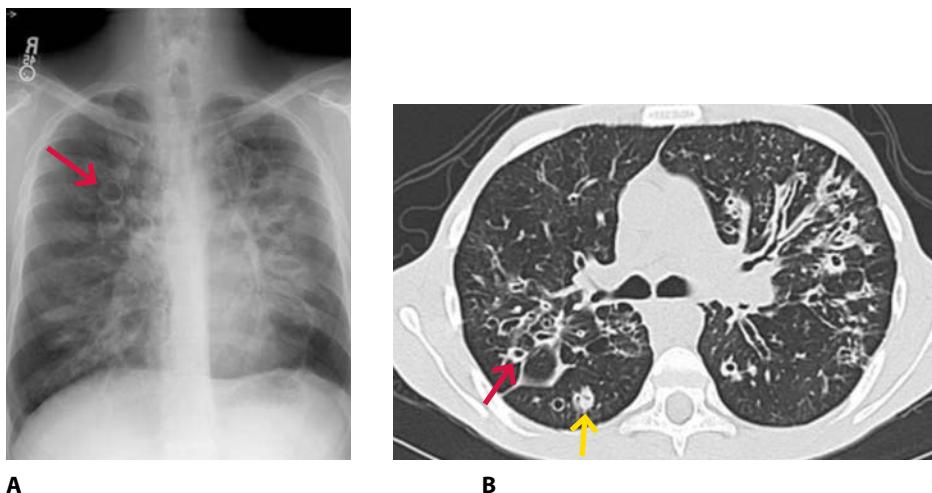
Immunodeficiency, asthma, ABPA, 1° ciliary dyskinesia/Kartagener,  $\alpha$ -1 antitrypsin deficiency, postinfectious bronchiectasis.

## Diagnosis

- A sweat chloride test shows an elevated sweat chloride concentration. Considered the screening test of choice, but a **normal test does not rule out CF**. If the sweat chloride test is inconclusive but there is **high clinical suspicion for CF**, do **genotyping** for CFTR mutations and a **nasal potential difference test** (measures ion transport in the nose).
- On CXR, early CF may present as hyperinflation. More advanced disease can manifest with peribronchial cuffing, interstitial markings, and bronchiectasis (Figure 4.5).

**TABLE 4.6. Distribution of Airway Abnormalities Aids in Diagnosis**

DISTRIBUTION	UNDERLYING CONDITION
Central (perihilar)	ABPA
Upper lobe	CF
Lower lobe	Idiopathic bronchiectasis



**FIGURE 4.5. Cystic fibrosis.** (A) Frontal CXR showing central cystic bronchiectasis (arrow) in a patient with CF. (B) Transaxial CT image showing cystic bronchiectasis (red arrow), with some bronchi containing impacted mucus (yellow arrow). (Reproduced with permission from USMLE-Rx.com.)

### Management

- **Acute pulmonary exacerbations:** Chest physical therapy to clear lower airway secretions. Also give bronchodilators and antibiotics based on culture and sensitivities. Inhaled recombinant DNase, given to cleave extracellular DNA in viscous sputum, will improve FEV<sub>1</sub> and ↓ exacerbations.
- **Chronic stable CF:**
  - Inhaled antibiotics (tobramycin/aztreonam), nebulized DNase, hypertonic (7%) saline.
  - Azithromycin three times per week.
  - Airway clearance: Aerobic exercise, flutter devices, external percussive vests or frequencers.
  - Pancreatic enzymes and vitamins A, D, E, and K.
  - Nutritional counseling.
  - Pneumococcal and influenza vaccines.
  - Also consider lung transplantation for severe progressive pulmonary disease. Genetic counseling and screening of family members. New targeted therapies for CF such as ivacaftor/lumacaftor improve outcomes in populations with certain mutations.

### SLEEP-DISORDERED BREATHING

An apneic period is ≥10 seconds in length. Patients with **obstructive sleep apnea (OSA)** have **episodic closure of the upper airway** during sleep with continued respiratory efforts. Patients with **central sleep apnea (CSA)** have **cessation of both airflow and respiratory efforts**. CSA is often associated with CNS disorders, respiratory muscle weakness, or cardiovascular disease (especially CHF), but it may also be idiopathic. See Table 4.7.

**Obesity hypoventilation syndrome (OHS)** is a condition that overlaps with OSA, and thus, often patients can have both OSA and OHS concomitantly. OHS is hypoventilation that occurs when **awake**; these patients have obesity and laboratory values consistent with hypoventilation when awake (ABG with PCO<sub>2</sub> >45 mm Hg, elevated HCO<sub>3</sub>, suggesting compensatory metabolic alkalosis for chronic respiratory acidosis).

**TABLE 4.7. Obstructive vs Central Sleep Apnea**

	OBSTRUCTIVE SLEEP APNEA	CENTRAL SLEEP APNEA
Definition	Apnea due to transient obstruction of the upper airway, but <b>ventilatory effort is present</b>	Apnea occurs, but there is <b>no compensatory ventilatory effort during apneic episode.</b> Tachypnea can occur after the apneic episode.
Risk factors	Obesity (large neck circumference), large tonsils, upper airway soft tissue abnormalities, hypothyroidism, craniofacial abnormalities	<b>CHF with reduced EF</b> is most common. <b>CNS disorders</b> , respiratory muscle weakness, opioids/sedatives, and renal/liver failure also ↑ risk.
Treatment	Weight loss (10%-20% of weight), nasal CPAP, avoidance of alcohol and sedatives, oral devices or upper airway surgery (uvulopalatopharyngoplasty) <b>O<sub>2</sub> supplementation is not recommended as initial treatment</b>	Treat underlying disease; O <sub>2</sub> if hypoxemic; consider BiPAP or CPAP; surgery has no role. Remove culprit medications (eg, sedatives).

### Symptoms/Exam

Patients may present with daytime hypersomnolence, morning headache, impaired cognition (due to small arousals during sleep), snoring, gasping or choking at night, and witnessed apneic episodes while sleeping. Patients with severe disease may have significant hypoxemia during sleep, pulmonary hypertension, systemic hypertension, heart failure, arrhythmias, and 2° erythrocytosis.

### Diagnosis

**Polysomnography** is needed to establish the diagnosis. The sum of apneas and hypopneas per hour of sleep, apnea-hypopnea index (AHI), is used to determine severity. AHI >5 per hour during a sleep study is abnormal:

- None/minimal AHI <5 per hour.
- Mild AHI ≥5, but <15 per hour.
- Moderate AHI ≥15, but <30 per hour.
- Severe AHI ≥30 per hour.

### KEY FACT

In CSA, apneic episodes are not accompanied by respiratory effort; patients may breathe faster after apneic episodes (periodic breathing = Cheyne-Stokes respiration). Polysomnography can distinguish between CSA and OSA.

### Management

CPAP (continuous positive airway pressure) for OSA, and occasionally CSA. BiPAP (bilevel positive airway pressure) for OHS (hypoventilation), and occasionally OSA and CSA if CPAP fails.

## Allergic Bronchopulmonary Aspergillosis

APBA is an immunologic reaction to antigens of *Aspergillus* present in the bronchial tree.

### Symptoms/Exam

**Asthma** (may be cough variant or exercise induced); expectoration of golden brown mucous plugs; fever with acute flare. Wheezing, rales, or bronchial breath sounds; digital clubbing and cyanosis (late-stage disease).

### Diagnosis

- Essential criteria for ABPA-S (seropositive ABPA) are as follows:
  - The presence of asthma.
  - ⊕ immediate skin tests to *Aspergillus*.
  - ↑ total serum IgE (>1000 ng/mL).
  - ↑ serum *Aspergillus*-specific IgE and/or IgG.

**KEY FACT**

ABPA should be considered in any patient with poorly controlled asthma or cystic fibrosis *and* elevated IgE, particularly in the presence of CXR infiltrates.

## ■ Other features include:

- The above plus central bronchiectasis = ABPA-CB (ABPA with central bronchiectasis).
- Precipitating antibodies to *Aspergillus*.
- Peripheral blood **eosinophilia** ( $>1000/\text{mm}^3$ ).
- CXR showing infiltrates—transient or fixed.
- A sputum culture that is  $\oplus$  for *Aspergillus* or that contains *Aspergillus* hyphae.

**Management**

- **Prednisone**; itraconazole may be used as an adjunctive medication.
- Chronic inhaled corticosteroids to control asthma.

**Complications**

Corticosteroid-dependent asthma, irreversible loss of pulmonary function, chronic bronchitis, pulmonary fibrosis, death due to respiratory failure or cor pulmonale.

**Pulmonary Vascular Disease****PULMONARY EMBOLISM**

See the Hospital Medicine chapter.

**PULMONARY HYPERTENSION**

Pulmonary hypertension is defined as a mean pulmonary artery pressure of  $>25$  mm Hg at rest (Table 4.8).

**Symptoms/Exam**

Presents with progressive dyspnea on exertion. In more advanced stages, patients may have exertional dizziness, atypical chest pain, or syncope. Raynaud phenomenon may suggest an underlying collagen vascular disease. Elevated pulmonary arterial pressure and right ventricular strain on exam are associated with JVD, right ventricular heave, a right-sided S4, a **fixed/split S2**, a **loud P2**, and tricuspid regurgitation. Hepatomegaly, a pulsatile liver, and ascites from progressive right ventricular overload are seen in advanced disease.

**TABLE 4.8. World Health Organization Classification of Pulmonary Hypertension**

GROUP 1: PULMONARY ARTERIAL HYPERTENSION (PAH)	GROUP 2: PULMONARY VENOUS HYPERTENSION	GROUP 3: LUNG DISEASE OR CHRONIC HYPOXIA	GROUP 4: THROMBOTIC OR EMBOLIC DISEASE	GROUP 5: DIRECTLY AFFECTING VESSELS
Idiopathic	Left heart disease (eg, mitral valve, atrial myxoma, (eg, scleroderma)	COPD	Chronic thromboembolic disease	Sarcoidosis, vasculitis, pulmonary Langerhans cell histiocytosis
Collagen vascular disease (eg, scleroderma)	mitral valve, atrial myxoma, systolic or diastolic dysfunction)	ILD		Gaucher disease, glycogen storage disease
HIV		Sleep apnea		Sickle cell disease, myeloproliferative disorders
Drugs/toxins (amphetamines, chemotherapy, cocaine)				
Portal hypertension				
Portopulmonary hypertension				

## Diagnosis

- ECG and transthoracic echocardiography (TTE) **with bubble study**. Echocardiogram estimates pulmonary arterial pressure and identifies left heart disease and congenital heart disease. Bubble study assesses for intracardiac shunt.
- CXR may demonstrate enlargement of pulmonary arteries with “pruning” of the peripheral vessels.
- PFTs can assess for underlying lung disease. Diffusing capacity may be ↓ due to pulmonary vascular disease.
- V/Q scan to evaluate for chronic thromboembolic disease. If positive, a pulmonary angiogram (CT) is needed.
- **Sleep study:** OSA is a potentially reversible cause of mild to moderate pulmonary hypertension.
- **Serologic testing** should be obtained for SLE, RA, scleroderma, and HIV. LFTs should also be performed as part of the evaluation.
- **Right heart catheterization:** To **confirm the diagnosis**, determine the severity of the disease, and evaluate for pulmonary venous hypertension (left heart failure). Can also assess the response to a vasodilator challenge trial (eg, inhaled nitric oxide, prostacyclin), which usually predicts response to long-term therapy with oral calcium channel blockers (CCBs).

## Management

1° treatment is therapy **directed at the underlying disease**, if possible. After treatment, reassess to determine whether advanced therapy is needed. For group 1 PAH, there is generally no effective treatment for underlying diseases; thus, therapy is aimed at treating the PAH itself. Treatment for groups 2 to 5 is focused on the underlying condition.

- **Vasodilator therapy**—PAH-specific drugs are intended for group 1 PAH:
  - Prostacyclin analogs (eg, epoprostenol, treprostinil).
  - Endothelin-1 antagonists (eg, bosentan).
  - Phosphodiesterase inhibitors (eg, sildenafil, tadalafil).
  - Oral CCBs: Use only if pulmonary arterial pressure ↓ during a vasodilator challenge.
- Other therapies may include:
  - Diuretics for right heart failure.
  - O<sub>2</sub>: Critical if O<sub>2</sub> saturation is <90% (hypoxemia worsens pulmonary vessel vasoconstriction).
  - **Anticoagulation** (↑ risk of thrombus formation): Warfarin for group 4 PAH (eg, CTEPH), and not typically for groups 2, 3, 5. Anticoagulation in group 1 PAH should be determined on a case-by-case basis.
  - Consider referral for **lung or heart-lung transplantation** if the disease progresses or fails to improve despite treatment.

## Pleural Disease

### PLEURAL EFFUSION

Abnormal accumulation of fluid in the pleural space. In the United States, the most common causes are CHF, pneumonia, and cancer. Distinguished as:

- **Transudative effusion:** Due to an imbalance between hydrostatic and oncotic pressures.
- **Exudative effusion:** Due to altered vascular permeability or impaired lymphatic drainage of fluid from pleural space.

### KEY FACT

Initial workup for etiology of pulmonary hypertension: CT chest, TTE with bubble study, PFTs, sleep study, V/Q scan, HIV, LFTs, RF, ANCA, and ANA. Definitive diagnosis is made with right heart catheterization.

### KEY FACT

The diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), which presents as progressive dyspnea and ↓ exercise tolerance, can be delayed since more common conditions are often suspected (eg, CAD, ILD, asthma) and worked up (ECG, echocardiogram, CXR, PFTs). In suspected CTEPH, a V/Q scan is the preferred test over the CT pulmonary angiogram because it is more sensitive in detecting abnormalities in CTEPH.



### QUESTION

A 46-year-old woman presents with 6 months of ↑ dyspnea on exertion. She also has dysphagia, heartburn, and Raynaud phenomenon. Notable findings include skin thickening of her hands, digital ulcers, and facial telangiectasia; normal pulmonary exam; and loud P2 on auscultation. What is the next diagnostic step?

### Symptoms/Exam

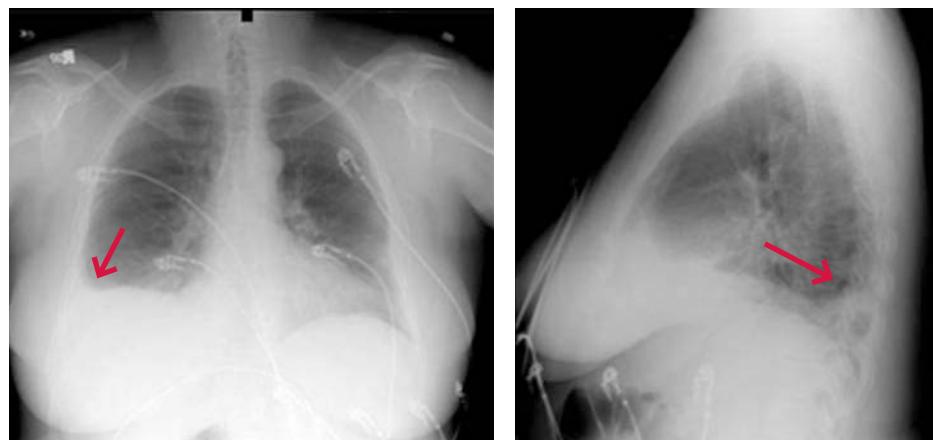
Presents with dyspnea. Dullness to percussion, ↓ or absent fremitus, and ↓ breath sounds on the affected side.

### Diagnosis

- **CXR** may demonstrate blunting of the costophrenic angle (Figure 4.6). Decubitus films and ultrasound help determine if fluid is free flowing or loculated. A finding of >1 cm of fluid on decubitus CXR suggests a significant amount of fluid.
- **Diagnostic thoracentesis:**
  - Should be performed on any clinically significant effusion (generally ≥1 cm in diameter on lateral decubitus film) for which the diagnosis is unknown.
  - Important to send pleural and serum protein and LDH to distinguish transudate from exudate using Light's criteria (see below and Table 4.9).
  - Send all pleural fluid for glucose, cell count, gram stain/cultures, and cytology.
  - Pleural fluid amylase, triglycerides, cholesterol, and hematocrit may be analyzed if appropriate (Table 4.10). Flow cytometry can also be obtained if suspicious for lymphoma.
- **Light's criteria**—pleural effusion is exudative if any of the following criteria are met:
  - Pleural fluid/serum protein ratio >0.5.
  - Pleural fluid/serum LDH ratio >0.6.
  - Pleural fluid LDH >2/3 the upper limit of normal for serum LDH.
- **If the etiology remains unclear**, consider (1) repeat thoracentesis, (2) evaluation for PE, or (3) pleural biopsy, which may aid in the diagnosis of cancer or TB.

### Management

- **Transudative pleural effusion:** Treatment is aimed at the underlying cause; therapeutic thoracentesis if the patient is symptomatic.
- **Malignant:** Indwelling pleural catheter placement or pleurodesis (in which an irritant is placed into the drained pleural space to obliterate the space) may be considered in symptomatic patients who are unresponsive to chemotherapy or radiation.
- **Parapneumonic:** Treat underlying pneumonia. Chest tube usually not required.
- **Empyema:** Chest tube insertion is indicated with evidence of empyema (pH <7.2, pus, glucose <40 mg/dL, gram stain +).
- **Hemothorax:** Requires drainage or fibrothorax will likely develop.



**FIGURE 4.6. Pleural effusion.** PA (A) and lateral (B) CXRs show blunting of the right costophrenic sulcus (arrows). (Reproduced with permission from USMLE-Rx.com.)

**A**

### ANSWER

For patients with pulmonary artery hypertension from systemic sclerosis, order echocardiogram with bubble study, stress test (rule out CAD), and rheumatologic serologic tests.

TABLE 4.9. Transudative vs Exudative Effusion

	TRANSUDATES ("OSIS")	EXUDATES
1° mechanisms	↑ Hydrostatic or ↓ oncotic pressures	↑ fluid production due to abnormal capillary permeability; impaired lymphatic drainage of fluid from the pleural space
Pleural effusion clues	If fluid is transudative by Light's criteria (0 of 3 criteria met), no further pleural labs are needed	↑ WBC count (>1000 indicates exudate, >100,000 points to empyema) ↓ glucose (<60 mg/dL) or ↑ LDH (>1000 IU/L): Cancer, empyema, TB, RA, lupus pleuritis, esophageal rupture ↓ pH <7.3 suggests cancer, infection (complicated parapneumonic), TB, lupus pleuritis, RA, esophageal rupture
Examples	<b>Cardiosis (CHF):</b> The most common cause; bilateral <b>Cirrhosis:</b> Generally bilateral but can be unilateral (hepatic hydrothorax, often on the right side) <b>Nephrosis</b> (nephrotic syndrome) <b>Thrombosis</b> (pulmonary embolus; either exudative or transudative)	<b>Parapneumonic</b> (viral, bacteria), <b>cancer</b> , TB, pancreatitis <b>Chylothorax:</b> Due to thoracic duct trauma or lymphoma <b>Other:</b> Collagen vascular disease, esophageal rupture, hemothorax, pulmonary embolus

## PNEUMOTHORAX

- **Spontaneous pneumothorax** (Figure 4.7): Can be primary (no known lung disease, seen in tall men who smoke cigarettes, Marfan syndrome, and cocaine use) or secondary (occurring with underlying lung disease, including COPD, CF, ILD, *Pneumocystis jiroveci* pneumonia, and lymphangioleiomyomatosis).
- **Iatrogenic pneumothorax:** A result of a procedure (thoracentesis, bronchoscopy, central venous catheter placement).
- **Traumatic pneumothorax:** Penetrating or blunt trauma, or barotrauma from mechanical ventilation, can cause air to enter the pleural space or with acute compression of the chest that results in alveolar rupture.

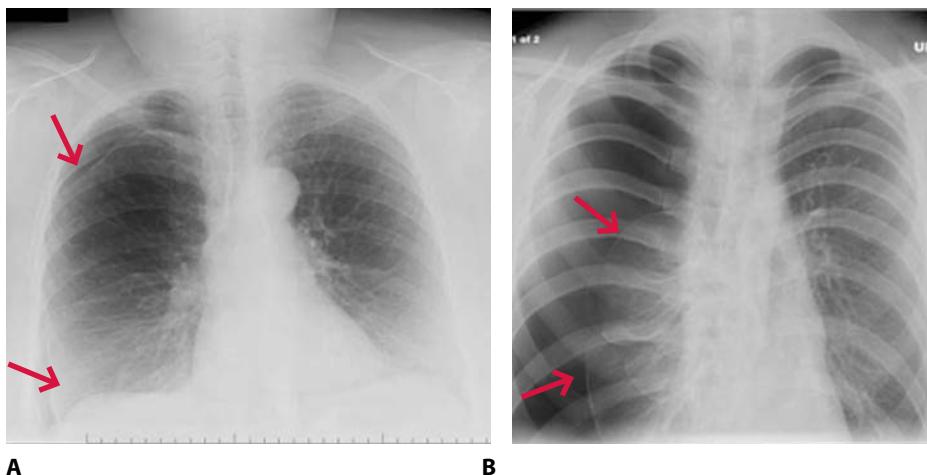
TABLE 4.10. Pleural Fluid Analysis and Interpretation

PLEURAL FLUID TEST	INTERPRETATION
pH	If pleural pH is <7.2 with parapneumonic effusion, drainage is required
Hematocrit	>50% of peripheral hematocrit suggests hemothorax
Glucose	<60 mg/dL suggests a complicated parapneumonic effusion or malignancy; if especially low (<30), think RA
Triglycerides	>110 mg/dL points to chylothorax (thoracic duct lymph disruption); milky white; due to lymphoma, cancer, trauma, or lymphangioleiomyomatosis
Lymphocytes	>50% lymphocytes is likely TB or malignancy
Eosinophils	>10% eosinophils is seen if air or blood is present, but <b>most commonly due to pneumothorax</b> ; also consider drug reaction, asbestos, paragonimiasis, Churg-Strauss syndrome, and pleural embolus
Amylase	↑ suggests acute pancreatitis, pancreaticopleural fistula or esophageal perforation



## QUESTION

A 34-year-old woman presents to the ED with chest pain and shortness of breath. A review of systems reveals several months of dyspnea and cough. CXR shows a right-sided pneumothorax. For what underlying disorder should she be evaluated?



**FIGURE 4.7. Pneumothorax.** (A) Small right pneumothorax. (B) Large right pneumothorax with collapse of the right lung and shifting of mediastinum to the left. Arrows denote pleural reflections. (Reproduced with permission from USMLE-Rx.com.)

### Symptoms/Exam

May present with unilateral chest pain (sharp or steady pressure) or acute shortness of breath. Examination may disclose distant heart sounds, and unilateral ↓ breath sounds, hyperresonance, and ↓ fremitus. In the setting of **tachycardia, hypotension, and tracheal deviation**, consider **tension pneumothorax**. Examination may be normal if the pneumothorax is small.

### Differential

Acute PE, myocardial infarction (MI), pleural effusion, aortic dissection, pneumonia, pericardial tamponade.

### Diagnosis

Obtain an **upright PA CXR**. Confirmed through the identification of a visceral pleural line away from the chest wall (see Figure 4.7).

### Management

- **Small pneumothoraces:** Observation and O<sub>2</sub> therapy. Supplemental O<sub>2</sub> accelerates the reabsorption of gas from the pleural space by ~8% to 9% per day.
- **Larger, more symptomatic pneumothoraces:** Drain with simple aspiration or a small-bore chest tube.
- Persistent air leaks and recurrences are more common with secondary than with 1° spontaneous pneumothoraces. Consider a **bronchopulmonary fistula** as the cause of a persistent air leak. For recurrent pneumothoraces, consider a preventive intervention, such as chemical pleurodesis.
- Smoking ↑ the risk of recurrence; counsel for smoking cessation.

### KEY FACT

Tension pneumothorax is a medical emergency that should be managed with immediate decompression of the pleural space. This can be done with a 14-gauge needle inserted into the chest in the second intercostal space at the midclavicular line.

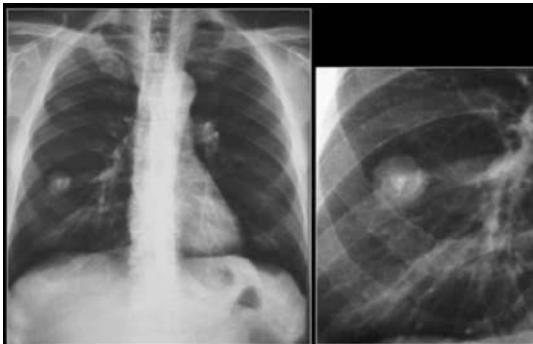
A

### ANSWER

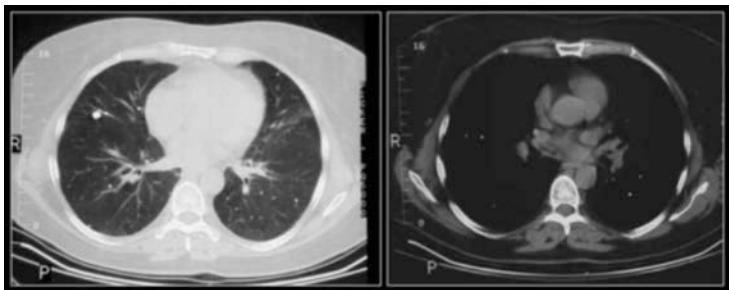
Consider lymphangioleiomyomatosis when a pneumothorax is diagnosed in a premenopausal woman. This is a cystic lung disease in childbearing women often presenting with pneumothorax and/or chylothorax.

### Solitary Pulmonary Nodule

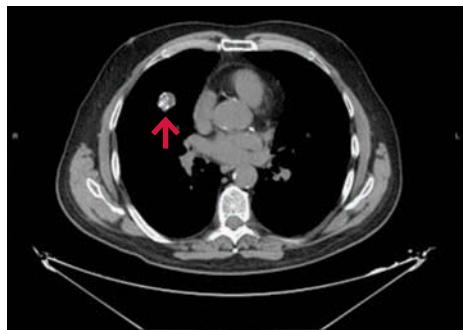
A solitary pulmonary nodule is an isolated lesion <3 cm in diameter surrounded by pulmonary parenchyma. Abnormalities ≥3 cm are considered lung masses and are much more likely to be malignant. (See Figure 4.8 and Table 4.11.)



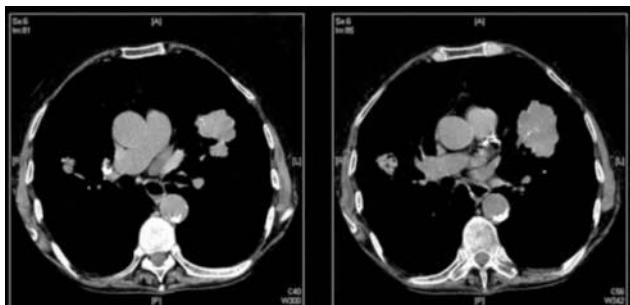
Central dense nidus



Diffuse solid calcification



Popcorn calcification

**BENIGN**

Eccentric calcification

**MALIGNANT****TABLE 4.11. Benign vs Malignant Solitary Pulmonary Nodules**

BENIGN FEATURES	
<b>Chest CT Patterns</b>	
Smooth border	
Central, diffuse, or "popcorn" calcification (see Figure 4.8)	
No growth of solid nodule over 2 years	
MALIGNANT FEATURES	
<b>Chest CT Patterns</b>	
Spiculated border or corona radiata sign (linear strands radiating from lesion); scalloped is intermediate risk	
No or minimal calcification, or eccentric or stippled	
Doubling time 1 month to 1 year	
Size >3 cm	
<b>Risk factors</b>	
Smoking history	
Weight loss, chronic cough, hemoptysis	
Exposure to asbestos, uranium, or radon	
Family history of lung cancer	

**QUESTION**

A 60-year-old nonsmoking man presents for follow-up of an incidental solid solitary lung nodule detected on noncontrast CT scan. The nodule is 7 mm in diameter with smooth borders. What is the most appropriate follow-up?

**FIGURE 4.8. Benign and malignant characteristics of nodule calcification.** (Images of central dense nidus, diffuse solid calcification, and eccentric calcification reproduced from Khan AN, et al. The calcified lung nodule: What does it mean? *Ann Thorac Med.* 2010;5(2):67-79. Image of popcorn calcification of a pulmonary hamartoma (arrow) reproduced with permission from USMLE-Rx.com.)

### Symptoms/Exam

Usually asymptomatic, but cough, hemoptysis, or dyspnea may be seen. Older age and a history of cigarette smoking raise the suspicion of cancer. Examination is often normal, but should include careful assessment for lymphadenopathy.

### Differential

- Neoplastic conditions (bronchogenic carcinoma, metastatic disease, pulmonary carcinoid, 1° sarcoma, and lymphoma).
- Infections (granuloma, old TB, histoplasmosis, coccidioides, cryptococcus, foreign body reaction).
- Inflammatory conditions (RA, vasculitis, sarcoidosis).
- Congenital conditions (hamartoma, bronchogenic cyst, lipoma).
- AVMs.
- Infarcts.

### Diagnosis

The goal of the workup is to **evaluate for malignancy without excess surgery or invasive testing**. Comparison of serial CXRs—if nodule can be visualized on CXR, then compare to prior CXRs for stability. **CT of the chest** identifies and characterizes nodules more effectively than CXR. IV contrast can better characterize nodules and demarcate lymphadenopathy. **PET scan** may suggest a lesion is more likely to be malignant and provide staging information for cancer.

### Management

Review prior imaging for growth or stability over time:

- **Stable:** The vast majority of solid solitary pulmonary nodules that are unchanged on serial CT scan over a 2-year period and sub-solid (ground glass or part-solid) solitary pulmonary nodules unchanged over a 3-year period are benign.
- **Growing:** A solid or sub-solid nodule that has clearly grown on serial imaging tests has a high likelihood of being malignant so perform workup for suspected cancer.

If no prior imaging or nodule does not have “definitely benign” characteristics (Table 4.11), then manage as described in Table 4.12.

**TABLE 4.12. Management of Solitary Pulmonary Nodules**

PURE GROUND GLASS NODULE	
SIZE	APPROACH
≤5 mm	No further imaging (unless multiple then serial CT)
>5 mm	Serial CTs at 12, 24, and 36 months if persistent at 3 months
SOLID OR PART-SOLID NODULE	
SIZE	APPROACH
<6 mm	Annual CT for 2 years and annually thereafter until patient is no longer eligible for definitive treatment
6-8 mm	Low-dose CT in 3 months and if no ↑ in size, low-dose CT at 6 months and then annual CT for 2 years and annually thereafter until patient is no longer eligible for definitive treatment
>8 mm	Consider PET/CT
Solid endobronchial nodule	CT in 1 month and if no resolution, then bronchoscopy



### KEY FACT

Lesions that ↑ in size or change in character are likely to be malignant and should be resected, assuming a low surgical risk and no evidence of metastatic disease.



### ANSWER

CT scan in 3 months.

## Interstitial Lung Disease

Represents >100 disorders; also known as diffuse parenchymal lung disease. The most common known causes are **occupational/exposure**, **connective tissue disease**, and **drugs** (Table 4.13).

TABLE 4.13. Categories of Interstitial Lung Disease

CATEGORY	PRESENTATION
<b>OCCUPATIONAL/EXPOSURE</b>	
Hypersensitivity pneumonitis (organic inhalations)	<p>Caused by an allergic reaction to inhaled organic agents</p> <p><b>Acute symptoms:</b> Fever, chills, cough, dyspnea 4-8 hours after exposure; inspiratory crackles; ground-glass opacities on CT</p> <p><b>Chronic symptoms:</b> Gradual cough and dyspnea, malaise, weight loss; diffuse fibrosis on biopsy</p> <p><b>Treatment:</b> Avoid common inciting agents such as mold, dust, bird droppings, aerosolized/humidified water (hot tubs), and pesticides; give corticosteroids if acute and severe</p>
Pneumoconioses	<p>Fibrotic lung diseases from inhalation of agents</p> <p><b>Asbestosis:</b> Construction and shipyard workers are at risk; presents decades after exposure with dyspnea and inspiratory crackles; CXR shows pleural calcifications and plaques; mesothelioma and pleural cancer are most often due to asbestos</p> <p><b>Silicosis:</b> Usually asymptomatic, but may see “eggshell calcification” (calcified periphery of hilar lymph nodes); associated with an ↑ incidence of TB, so check purified protein derivative (of tuberculin) and CXR</p> <p>Coal workers’ pneumoconiosis</p> <p>Berylliosis</p>
<b>DRUG AND RADIATION INDUCED</b>	
Drug reactions	<p>Symptoms improve 24-48 hours after the drug is stopped</p> <p>Crack cocaine inhalation presents with edema, pulmonary hemorrhage, and talc depositions</p> <p>Amiodarone-induced lung disease usually occurs within the first year; treat by stopping drug and giving 2-3 months of corticosteroids</p> <p>Other drugs: nitrofurantoin, chemotherapeutic agents (bleomycin, cyclophosphamide, methotrexate), amphotericin, busulfan, phenytoin, sulfasalazine, procainamide, gold salts</p>
Radiation exposure	<p>Radiation pneumonitis</p> <p><b>Occurs several months after radiotherapy</b> for cancer (eg, breast, lung, lymphoma); acute pneumonitis presents with fever, chest pain, cough, and dyspnea and is responsive to steroids</p> <p><b>Usually resolves in 6 months but may progress to pulmonary fibrosis (corticosteroids do not help)</b></p>

(continues)



### QUESTION

A 65-year-old man presents with gradual onset of dyspnea and nonproductive cough for the past year. Lung exam discloses bibasilar crackles and pulse oximetry on room air is 91%. The remainder of his examination is normal. What is the most likely diagnosis?

**KEY FACT**

When ILD is suspected, HRCT is essential for characterization of the type of disease. Surgical lung biopsy may also have an important role in diagnosis.

**KEY FACT**

IPF has a characteristic pattern of usual interstitial pneumonia (UIP) on HRCT and biopsy. Although HRCT is sufficient to diagnose IPF, a lung biopsy can help make a definitive diagnosis, and other causes such as connective tissue diseases and drugs must be excluded.

**A****ANSWER**

Idiopathic pulmonary fibrosis.

**TABLE 4.13. Categories of Interstitial Lung Disease (continued)**

CATEGORY	PRESENTATION
<b>CONNECTIVE TISSUE DISEASES</b>	
SLE	Pleural effusion or pleural thickening is common, but ILD is rare
RA	Pleural effusion is common; rheumatoid nodules may be seen; some treatments for RA (eg, methotrexate) can lead to ILD
Dermatomyositis/polymyositis	Presents with symmetric and proximal muscle weakness, elevated muscle enzymes, and ANA/anti-Jo-1 antibody ILD occurs in >10% of patients; diaphragmatic and chest wall weakness may also be seen
Scleroderma/Systemic sclerosis	ILD is often seen (especially with diffuse cutaneous disease), as is pulmonary hypertension
<b>GRANULOMATOUS DISEASE</b>	
Sarcoidosis	Stage I hilar adenopathy (spontaneous remission is common); progresses to stage IV: fibrosis and architectural distortion with no spontaneous remission
Langerhans cell histiocytosis	Also known as eosinophilic granuloma or histiocytosis X; young smokers are at risk
<b>VASCULITIS</b>	
Granulomatosis with polyangiitis	Presents with cough, hemoptysis, sinus symptoms, and glomerulonephritis; $\oplus$ c-ANCA, $\oplus$ anti-GBM antibodies; necrotizing granulomas
Eosinophilic granulomatosis with polyangiitis	Presents as <b>difficult-to-treat asthma with eosinophilia</b> ; flares with corticosteroid tapers
<b>OTHER</b>	
Eosinophilic pneumonias	<b>PIE syndrome:</b> "Pulmonary Infiltrates with peripheral blood Eosinophilia" Present with " <b>photographic negative</b> " (peripheral) pulmonary edema, weight loss, dyspnea, and cough Diagnosis: bronchoalveolar lavage with high eosinophils Treatment: corticosteroids
Lymphangioleiomyomatosis	Affects premenopausal women; associated with tuberous sclerosis Presents in childbearing years with dyspnea, cough, and chylous effusions Pneumothorax is common HRCT shows diffuse, thin-walled small cysts
Idiopathic interstitial pneumonias	See Table 4.14

TABLE 4.14. Categories of Idiopathic Interstitial Pneumonia

	SYMPTOMS/EXAM	DIAGNOSIS	TREATMENT
<b>Idiopathic pulmonary fibrosis (IPF)—the most common ILD</b>	Affects middle-age or older patients (>50 years); presents with chronic, nonproductive cough and gradually worsening dyspnea over many months  Not acutely ill and do not present with fever; very slow progression  Exam reveals bibasilar inspiratory crackles (Velcro-like), restrictive lung disease ( $\downarrow$ FVC, TLC, FRC), and $\downarrow$ gas exchange (DLco)	CXR with diffuse infiltrates (nonspecific)  Lung biopsy reveals <b>usual interstitial pneumonia</b> ; HRCT shows bibasilar, reticular patchiness with honeycombing and bronchiectasis in subpleural areas (Figure 4.9)	Has a poor prognosis despite immunosuppressive therapy; lung transplantation can improve survival and quality of life
Nonspecific interstitial pneumonia (NSIP)	<b>Similar to IPF, but patients are younger</b> , and inspiratory crackles are less common  Often associated with connective tissue disease		Consider corticosteroids and other immunosuppressive agents (eg, azathioprine, cyclophosphamide)
Cryptogenic organizing pneumonia	Acutely ill over days to weeks, and mimics community-acquired pneumonia symptoms and may have initial <b>flu-like</b> symptoms (eg, fever, fatigue, nonproductive cough); dyspnea on exertion and weight loss are also common  50% are idiopathic, 50% are associated with toxic fume inhalation, certain drug exposures, infections, connective tissue disorders, immunodeficiencies, radiation	CXR and CT show bilateral <b>patchy</b> opacities with normal lung volumes  Lung biopsy reveals organizing pneumonia but is not diagnostic	Responsive to corticosteroids
Acute interstitial pneumonia (also known as Hamman-Rich syndrome)	Presents with abrupt fever, cough, and dyspnea in previously healthy patients; progresses to acute <b>hypoxemic</b> respiratory failure over days to weeks  Clinically appears to be ARDS, including diffuse alveolar damage		Treatment is supportive; has a poor prognosis

Idiopathic interstitial pneumonia is a broad category of ILD of unknown etiology classified by histopathologic characteristics on lung biopsy (Table 4.14) and sometimes by radiographic appearance on HRCT.

#### Symptoms/Exam

The most common symptom is dyspnea. Ask about symptom onset, family history, and exposures (drugs, occupational/environmental, tobacco, radiation). **Pulmonary examination often reveals dry bibasilar crackles.**

### Diagnosis

- CXR shows a bibasilar interstitial pattern ± a nodular pattern or honeycombing. However, CXR can be normal in 20% of patients with early ILD. Also consider ILD in patients with crackles but no suspicion for CHF.
- HRCT characterizes and quantifies the extent of disease; directs further diagnostic workup, including biopsy. Patterns include inflammatory or traction bronchiectasis, honeycombing (Figure 4.9), reticulations, nodules, consolidation, ground-glass opacification, mosaic perfusion, and air trapping.
- PFTs most commonly show a restrictive pattern, consisting of a normal or ↑ FEV<sub>1</sub>/FVC, a ↓ TLC, and a ↓ DLCO. An obstructive pattern or mixed pattern may be observed in hypersensitivity pneumonitis and sarcoidosis.
- Lung biopsy for diagnosis/confirmation and activity. Almost always done by video-assisted thoracoscopic surgery. Serologies for connective tissue disease may be helpful.

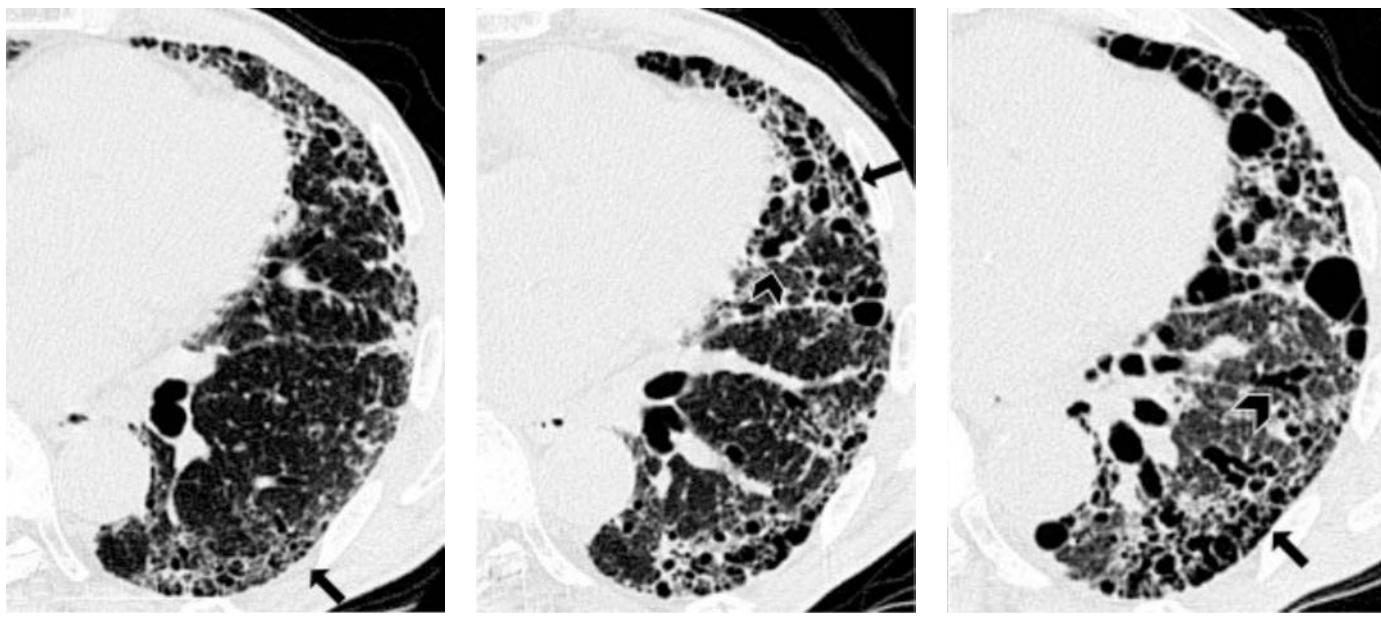
### KEY FACT

NSIP has a clinical presentation similar to that of IPF; however, NSIP may respond to corticosteroids/immunosuppressive agents and has a better prognosis.

### Management

Generally depends on the underlying diagnosis, but possible treatments include:

- Eliminating potential occupational/environmental exposures.
- Oxygen therapy for hypoxemia ( $\text{PaO}_2 < 55 \text{ mm Hg}$ ) at rest or with exercise.
- **Corticosteroids for NSIP, hypersensitivity pneumonitis, sarcoidosis. Do not use in IPF.**
- Immunosuppressive therapy for NSIP, hypersensitivity pneumonitis, and connective tissue disease-related ILD.
- New antifibrotic drugs such as pirfenidone and nintedanib have been approved for treatment of IPF.
- **Lung transplantation referral should be made for all patients with IPF and fibrotic NSIP.**



**FIGURE 4.9. Idiopathic pulmonary fibrosis (IPF).** HRCT findings of a 78-year-old man with IPF who died 20 months after initial diagnosis. Lower left lobe shows fibrosing changes at baseline (A), 6 months (B), and 12 months (C). Changes include subpleural predominant interstitial fibrosis, traction bronchiectasis (arrowheads), and honeycombing (arrows). The overall HRCT fibrosis score at the baseline, 6 months, and 12 months were 151.3, 162.5, and 185.8, respectively. (Reproduced with permission from USMLE-Rx.com.)

## HYPERSensitivity PNEUMONITIS

A complex immune-mediated lung disease resulting from repeated inhalational exposure to a wide variety of **organic dusts** (Table 4.15). Presents in acute, subacute, and chronic forms.

### Symptoms

- Acute: Nonproductive cough, shortness of breath, fever, diaphoresis, myalgias occurring 6-12 hours after intense antigen exposure.
- Chronic: Insidious onset of dyspnea, productive cough, fatigue, anorexia, weight loss.

### Exam

- Acute: Patients appear ill with fever, respiratory distress, and dry rales (wheezing is not a prominent symptom). Exam may be normal in asymptomatic patients between episodes of acute hypersensitivity pneumonitis.
- Chronic: Dry rales, ↓ breath sounds, digital clubbing.

### Differential

- Acute:
  - **Pneumonia:** Bacterial, viral, or atypical.
  - **Toxic fume bronchiolitis:** Sulfur dioxide, ammonia, chlorine.
  - **Organic dust toxic syndrome:** Inhalation of dusts contaminated with bacteria and fungi.
- Subacute or chronic: Chronic bronchitis, idiopathic pulmonary fibrosis, chronic eosinophilic pneumonia, collagen vascular disease, sarcoidosis, 1° pulmonary histiocytosis, alveolar proteinosis.



### KEY FACT

No single test is diagnostic for hypersensitivity pneumonitis. Suspect this diagnosis when symptoms develop after a patient moves to a new job or home. Moving away from the new environment may result in improvement of symptoms.

**T A B L E 4 . 1 5 . Selected Causes of Hypersensitivity Pneumonitis**

DISEASE	ANTIGEN	SOURCE
Farmer's lung	<i>Micropolyspora faeni</i> , <i>Thermoactinomyces vulgaris</i>	Moldy hay
"Humidifier lung" (Figure 4.10)	Thermophilic actinomycetes	Contaminated humidifiers, heating systems, or air conditioners
Bird fancier's lung ("pigeon breeder's disease")	Avian proteins	Bird serum and excreta
Bagassosis	<i>Thermoactinomyces sacchari</i> and <i>T vulgaris</i>	Moldy sugar-cane fiber (bagasse)
Sequoiosis	<i>Graphium</i> , <i>Aureobasidium</i> , and other fungi	Moldy redwood sawdust
Maple bark stripper's disease	<i>Cryptostroma</i> ( <i>Coniosporium</i> ) <i>corticale</i>	Rotting maple tree logs or bark
Mushroom picker's disease	Same as farmer's lung	Moldy compost
Suberosis	<i>Penicillium frequentans</i>	Moldy cork dust
Detergent worker's lung	<i>Bacillus subtilis</i> enzyme	Enzyme additives

(Reproduced with permission from Papadakis MA, et al. *Current Medical Diagnosis & Treatment 2016*. New York: McGraw-Hill, 2016, Table 9-20.)

**FIGURE 4.10. Bilateral interstitial infiltrates in humidifier lung disease.**

CXR of a 30-year-old printing plant worker shows patchy infiltrates predominantly in the lower and middle lung fields. (Reproduced from Baur X, et al.

Spotlight on the diagnosis of extrinsic allergic alveolitis (hypersensitivity pneumonitis). *J Occup Med Toxicol*. 2015;10:15.)

#### KEY FACT

Biopsy of erythema nodosum often shows only panniculitis rather than granulomas. It is more helpful to biopsy hilar lymphadenopathy, other skin findings, or pulmonary nodules.

#### KEY FACT

Bronchoscopic transbronchial biopsy of lung parenchyma or endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes are the procedures of choice for sarcoidosis diagnosis if peripheral lesions (eg, palpable lymph nodes, skin lesions) are not present.

**FIGURE 4.11. Bilateral hilar adenopathy.**

Frontal chest CXR findings may be seen in sarcoidosis, TB, or malignancy. (Reproduced with permission from USMLE-Rx.com.)

#### Diagnosis

- PFTs:
  - Acute: **Restrictive pattern** with ↓ TLC and ↓ FVC. ↓ DLCO is common.
  - Chronic: Combined obstructive and restrictive pattern.
- Imaging:
  - Acute: CXR shows transient patchy, peripheral, bilateral interstitial infiltrates (Figure 4.10). CT typically shows ground-glass opacifications and diffuse consolidation.
  - Subacute: CXR shows nodular, patchy infiltrates; CT reveals centrilobular nodules with areas of ground-glass opacity and air trapping.
  - Chronic: CXR shows fibrotic changes with honeycombing and areas of emphysema; CT shows honeycombing, fibrosis, traction bronchiectasis, ground-glass opacities, and small nodules.
- Labs:
  - Acute: ↑ WBC count; ↑ ESR. Eosinophils are not a feature in acute disease.
  - Acute or chronic: **High titers of precipitating IgG** against the offending antigen (indicates exposure, not necessarily disease).
- Bronchoalveolar lavage: Lymphocytosis with a predominance of CD8+ T cells.
- Lung biopsy: Interstitial and alveolar **noncaseating granulomas**; “foamy” macrophages; predominance of lymphocytes.
- Inhalational challenge: Not required or recommended for diagnosis; helpful when data are lacking or diagnosis is unclear. Performed only with careful medical monitoring.

#### Management

- Avoidance of the offending antigen.
- Oral corticosteroids at a dosage of 40-80 mg QD with tapering after clinical improvement has been achieved.

#### Complications

- Irreversible loss of lung function.
- Death is uncommon but has been reported.

#### SARCOIDOSIS

Sarcoidosis is a systemic disease of unknown etiology that primarily affects the lungs and lymphatics and is characterized by **noncaseating granulomas**. Commonly affects young and middle-aged adults. Often presents with **bilateral hilar adenopathy** (Figure 4.11), **pulmonary infiltrates**, and **skin lesions**. The eye, liver, lymphatics, salivary glands, heart, CNS, and bones may be involved as well.

#### Symptoms/Exam

Presents with nonspecific constitutional symptoms such as fever, fatigue, anorexia, weight loss, and arthralgias. **Löfgren syndrome** presents with fever, erythema nodosum, polyarthralgias, and hilar lymphadenopathy. **Heerfordt syndrome** presents with uveitis, parotid enlargement, fever, and facial palsy.

## Differential

Mycobacterial, fungal, bacterial (tularemia and brucellosis), and parasitic (toxoplasmosis) infection. Also includes berylliosis, malignancy, hypersensitivity pneumonitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

## Diagnosis

There is no one definitive diagnostic test, but transbronchial biopsy or endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes are the preferred procedures if a more accessible lesion (eg, palpable lymph nodes or rashes) is not present for biopsy. Diagnosis requires (1) **noncaseating granulomas on histopathology**, (2) **compatible clinical and radiographic findings**, and (3) **exclusion of other diseases that have a similar clinical picture**.

Baseline studies include:

- **Biopsy** to obtain **histologic confirmation of noncaseating granulomas**.
- **CXR** allows for **pulmonary staging** of sarcoidosis (Table 4.16).
- **HRCT** is often performed after CXR to elucidate findings, although chest CT is not a component of official staging.
- LFTs, calcium, BUN/creatinine.
- Angiotensin-converting enzyme level is not sensitive and its value for disease monitoring is unclear.
- Ophthalmologic exam to assess for eye involvement.
- ECG.

## Management

- Treatment remains controversial as clinical courses are variable, spontaneous remission is common, and it can be difficult to assess disease activity and severity. The goal is to ↓ inflammatory response and prevent fibrosis. **Systemic (oral) corticosteroids** are the mainstay of treatment in symptomatic patients.
- Indications for treatment of **pulmonary sarcoidosis** include **worsening pulmonary symptoms, declining PFTs, and worsening radiographic findings**. Indications for treatment of **extrapulmonary sarcoidosis** include **disabling symptoms, hypercalcemia, or ocular, neurologic, cardiac, or renal involvement** in view of the potential for end-organ damage.

**TABLE 4.16. Stages of Sarcoidosis**

	CXR FINDINGS	SPONTANEOUS RESOLUTION WITHOUT TREATMENT
<b>Stage 0</b>	Normal	—
<b>Stage 1</b>	Hilar lymphadenopathy (see Figure 4.11)	60%-80%
<b>Stage 2</b>	Hilar lymphadenopathy and reticulonodular opacities	50%-60%
<b>Stage 3</b>	Reticulonodular opacities (no lymphadenopathy)	<30%
<b>Stage 4</b>	Fibrotic changes	—

## KEY FACT

When considering a diagnosis of sarcoidosis, always rule out TB, endemic fungal infections, and malignancy. Beryllium exposure can cause a sarcoid-like clinical syndrome.

## KEY FACT

Although the CXR stages of sarcoidosis do not always predict severity of disease, in general, the higher the stage, the worse the patient's symptoms and PFTs.

## KEY FACT

PFTs in sarcoidosis often show a restrictive defect with ↓ lung volumes (low VC, low TLC), although PFTs may also be normal or demonstrate an obstructive pattern.

## KEY FACT

80% of cases of Löfgren syndrome (combination of bilateral hilar adenopathy, erythema nodosum, and joint symptoms) spontaneously remit.



## QUESTION 1

A 53-year-old man presents with acute onset of cough, shortness of breath, and fever. He has no significant past medical history and had been resting comfortably in his hot tub shortly before his symptoms developed. On exam, he has a fever, rales bilaterally, and mild respiratory distress. CXR shows patchy interstitial infiltrates, and CT reveals centrilobular nodules with ground-glass opacities. What is the likely diagnosis and treatment?



## QUESTION 2

A 27-year-old woman presents with 2 weeks of fevers and painful, erythematous nodules on her shins. Examination reveals bilateral ankle effusions. What is the most appropriate next step in diagnosis?

**KEY FACT**

Do not treat if patients are asymptomatic with stage 1 disease (bilateral hilar lymphadenopathy with or without erythema nodosum). May not need to treat stage 2 or 3 disease if patients don't have symptoms and have relatively preserved lung function.

**KEY FACT**

Consider immune reconstitution inflammatory syndrome if previously dormant or treated opportunistic infections such as TB, PJP, or *Cryptococcus* worsen with HAART initiation and a rapid ↑ in CD4 count.

**KEY FACT**

For PJP, the standard treatment is TMP-SMX (with corticosteroids if  $\text{Pao}_2 < 70 \text{ mm Hg}$ ).

**A****ANSWER 1**

"Hot tub lung" due to hypersensitivity to *Mycobacterium avium* complex (MAC). Treatment involves avoidance of further antigen exposure and empiric steroids with a taper.

**Pulmonary Complications of HIV**

Table 4.17 outlines both infectious and noninfectious pulmonary disorders associated with HIV. See the Infectious Diseases chapter for further details.

- **Symptoms/Exam:** Focus on extrapulmonary manifestations of a systemic disease. Skin, lymph node, and funduscopic examinations can narrow the differential to fungal, mycobacterial, or neoplastic etiologies.
- **Diagnosis:** Evaluate the following:
  - CXR.
  - CD4 count and viral load.
  - TB risk factors (eg, homelessness, imprisonment, international travel).
  - Adherence to TMP-SMX prophylaxis and antiretroviral medications.
  - Timing of the initiation of highly active antiretroviral therapy (HAART) to evaluate for immune reconstitution inflammatory syndrome.

***PNEUMOCYSTIS JIROVECII* PNEUMONIA**

- **Diagnosis:** Obtain a CXR in patients with suspected *Pneumocystis jirovecii* pneumonia (PJP), which may show **diffuse ground-glass opacities ± pneumatoceles** but can be normal. A chest CT is helpful if CXR is normal but suspicion for PJP remains high. ABGs, DLCO, and LDH may also be useful adjuncts when the diagnosis is still unclear.
  - In patients who are critically ill and those not responding to empiric therapy, fiberoptic bronchoscopy should be performed. Bronchoscopy is the diagnostic test of choice to rule out PJP; however, if patient is too unstable to tolerate the procedure, empiric PJP treatment should be started.
- **Management:** Unless a patient is critically ill, it is preferable to establish a diagnosis before empiric treatment is started. The standard therapy is TMP-SMX (with corticosteroids if  $\text{Pao}_2 < 70 \text{ mm Hg}$ ).

**A****ANSWER 2**

CXR for suspected Löfgren syndrome, an acute form of sarcoidosis characterized by fevers, lymphadenopathy, and erythema nodosum. Staging of sarcoidosis requires documentation of the extent of hilar lymphadenopathy and parenchymal involvement as well as an assessment of extrapulmonary/systemic involvement.

**High Altitude–Related Illness**

- **Acute mountain sickness:** Results from ascending to altitude above 6500 feet. Symptoms include **headache, insomnia, nausea/vomiting 6 to 12 hours after ascent**. Usually resolves within 24 hours if no further ascent is made. Prevent with acetazolamide.
- **High-altitude cerebral edema:** Similar to acute mountain sickness but additional symptoms include **ataxia and altered mental status**. Treatment includes evacuation to lower altitude, oxygen and/or hyperbaric oxygen, and dexamethasone.

**TABLE 4.17. Infectious and Noninfectious Pulmonary Manifestations of HIV**

INFECTIOUS	NONINFECTIONOUS
Bacterial pneumonia	Emphysema
TB	Lung carcinoma
<i>Nocardiosis</i>	Non-Hodgkin lymphoma
Fungal pneumonia (PJP)	Lymphocytic interstitial pneumonia
Cytomegalovirus infection	Kaposi sarcoma
Varicella-zoster virus infection	Pulmonary hypertension

- **High-altitude pulmonary edema:** Symptoms include **cough, shortness of breath, fatigue, and ↓ exercise tolerance 2 to 4 days after ascent.** Treatment includes evacuation to lower altitude, oxygen and/or hyperbaric oxygen, furosemide, and nifedipine or sildenafil.

## Carbon Monoxide Poisoning

- Commonly seen in burn victims due to smoke inhalation. However, also seen in the **winter among the indigent who use a gas range or oven to heat their homes.**
- Symptoms include unexplained flulike illness, frontal headache, nausea, shortness of breath, chest pain, lightheadedness, difficulty concentrating, confusion, delirium, coma.
- Diagnosis is carboxyhemoglobin  $\geq 25\%$  on an ABG.
- **Treat with normobaric oxygen.** However, if the patient is pregnant or there is loss of consciousness, persistent neurologic deficit, or evidence of cardiac ischemia, use hyperbaric oxygen.

## Critical Care

Mechanical ventilation can be divided into noninvasive and invasive mechanical ventilation.

### NONINVASIVE POSITIVE PRESSURE VENTILATION

- Noninvasive positive pressure ventilation refers to positive pressure ventilation delivered via a mask rather than by endotracheal or tracheostomy tube. Can deliver pressure support as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP).
- **Indications:** Hypercapnic COPD exacerbations, acute CHF, weaning from the ventilator. **Early use of NPPV in these patients ↓ intubation rates.**
- **Contraindications:** Severe acidemia, inability to protect the airway, altered mental status, impending cardiac or respiratory arrest, upper GI bleeding, recent facial/upper airway surgery, recent GI surgery.
- Common uses: CPAP is used for acute CHF or obstructive sleep apnea; BiPAP is used for COPD.

### INVASIVE MECHANICAL VENTILATION

Invasive ventilatory support is provided through an endotracheal tube or a tracheostomy tube. The main indications for mechanical ventilation are acute respiratory failure and airway protection.

#### Ventilator Mode

Full ventilatory support can be provided in a number of ways. Common ways include:

- **Assist control:** Delivers a **preset VT** with a minimum mandatory respiratory rate (RR). Spontaneous breaths above the minimum RR trigger the same VT as mandatory breaths. Is a good first choice in most clinical situations and **the most common ventilator mode used in the ICU and for ARDS.**



#### KEY FACT

Coma or impending cardiac or respiratory arrest warrants immediate intubation. Do not use NPPV to delay intubation if the patient is in severe respiratory distress.



#### KEY FACT

Use CPAP for OSA and CHF and BiPAP for COPD exacerbations. Check ABGs 30 to 60 minutes after NPPV is initiated. If no improvement is seen on ABG, intubate.



#### QUESTION

A 45-year-old man with a history of IV drug abuse presents with 3 to 4 days of severe progressive dyspnea and dry cough. He is cachectic and hypoxic with ambulation (82% on room air) and has bilateral crackles on auscultation. His CXR shows bilateral interstitial infiltrates, and a rapid HIV test is  $\oplus$ . What is the most likely diagnosis?

**KEY FACT**

The presence of ↑ peak inspiratory pressure and ↑ plateau pressure usually represents a problem with lung compliance.

**KEY FACT**

↑ peak inspiratory pressure without abnormal plateau pressures usually represents a problem with airway resistance.

**MNEMONIC****Causes of weaning difficulties: WHEANS NOT****Wheezes**

Heart disease (eg, left heart failure can make weaning in COPD more challenging; MI may occur during weaning due to oxygen consumption by respiratory muscles); hypertension

**E**lectrolyte imbalance (eg, acidosis; alkalemia can ↓ respiratory drive)

**A**nxiety, **A**irway abnormalities

**N**euromuscular disease, **N**euromuscular blockers (critical illness polyneuropathy is more common in patients with sepsis; it also should be considered in asthmatic patients who are more likely to receive corticosteroids and neuromuscular blockers, as these drugs ↑ the risk)

**S**edation, **S**ecretions

**N**utrition (under- and overfeeding)

**O**piates

**T**hyroid disease (hypothyroidism is an uncommon, but treatable, cause of failure to wean)

**A****ANSWER**

Community-acquired pneumonia, although must rule out *Pneumocystis jirovecii* pneumonia (PPJ).

- **Synchronized intermittent mandatory ventilation:** Delivers a preset VT with a minimum mandatory RR. Spontaneous breaths above the minimum rate trigger variable VT. The spontaneous breaths and mandatory breaths are synchronized to reduce breath stacking.
- **Pressure control:** Delivers a preset amount of pressure over a preset length of time. As a result, VT may vary depending on lung compliance.
- **Pressure support:** Provides inspiratory pressure support to ↓ the work of breathing for each breath. All breaths are spontaneous. The patient's lung mechanics determine VT and RR, so close monitoring is required. Used in **spontaneous breathing trials** during weaning from the ventilator.

**Settings and Measurements**

- The minute ventilation (MV) needs prior to intubation should be approximated. MV = RR × VT. Rates up to 35 are generally acceptable unless the patient cannot fully exhale at such rapid rates (eg, in status asthmaticus).
- Low VT (6 mL/kg) ↓ mortality in ARDS and may ↓ the risk of ventilator-induced lung injury.
- Fraction of inspired oxygen ( $\text{FiO}_2$ ): Titrate  $\text{FiO}_2$  down to achieve a goal  $\text{PaO}_2 \geq 60$  mm Hg or an arterial oxygen saturation of >90% (or 88% in ARDS).
- Positive end-expiratory pressure (PEEP): A small amount (5 cm H<sub>2</sub>O) is typically used ↑ in ARDS to improve oxygenation and possibly to prevent further lung injury, though higher pressures may be used depending on the situation. Additionally, higher levels of PEEP may be used in cardiogenic pulmonary edema to improve oxygenation and to ↓ preload and afterload.
- **Auto-PEEP:** Measured by covering the expiratory port on the ventilator at end-expiration. Caused by delayed emptying of the lungs and subsequent initiation of a new breath before the lungs have fully emptied. Common in mechanically ventilated patients with COPD and asthma. Can be treated by ↓ RR or VT or by ↑ expiratory time, or in severe cases, by momentarily disconnecting the patient from the ventilator and forcing full exhalation.

Table 4.18 outlines the differential for patients with ventilator crises.

**SEDATION MANAGEMENT AND WEANING**

- Administer both **anxiolytic** and **analgesic medications** while patients are receiving mechanical ventilation through an endotracheal tube. **Daily interruption of sedative infusions** ↓ the duration of mechanical ventilation and ICU stays.
- Once the patient is awake, attempt a **spontaneous breathing trial** to determine readiness for extubation. Also evaluate the strength of cough, secretions, and upper airway patency prior to extubation. Weigh the benefits of early extubation (preventing pneumonia, GI bleeding, venous thromboembolism) against the effects of premature extubation (reintubation, ↑ mortality).
- There are many causes that lead to failure to wean. The most common cause is persistence of the underlying disease process that initially led to the respiratory failure. Other causes of weaning difficulties are described by the mnemonic WHEANS NOT.

**HYPOTENSION**

Hypoxemia is defined as a ↓ in blood O<sub>2</sub> (in general, a  $\text{PaO}_2$  of <80 mm Hg). An age adjustment given by the formula  $80 - [(age - 20)/4]$  is used to define the lower limit of normal for  $\text{PaO}_2$ .

- **Symptoms/Exam:** Presents with dyspnea and tachypnea. Long-standing hypoxia results in fatigue, drowsiness, and delayed reaction time. Severe hypoxia

TABLE 4.18. Etiologies of Ventilator Crises

↑ PEAK AIRWAY PRESSURE/ NORMAL PLATEAU PRESSURE	↑ PEAK AIRWAY PRESSURE/ HIGH PLATEAU PRESSURE	↓ O <sub>2</sub> SATURATION	RISING P <sub>CO<sub>2</sub></sub>	PATIENT DISTRESS
Endotracheal tube obstruction, kink, or malposition	Right mainstem intubation <b>Reduced lung compliance:</b> Pulmonary edema, pneumonia	Ventilator/mixer malfunction Endotracheal tube malposition/leak	Ventilator malfunction Endotracheal tube malfunction/leak	Pain/discomfort unrelated to the ventilator or respiratory system (eg, MI)
<b>Airway obstruction:</b> Bronchospasm, mucous plug, secretions in airways	<b>Reduced chest wall/abdominal compliance:</b> Pneumothorax, abdominal distention	<b>New lung derangement:</b> Atelectasis, aspiration, edema	<b>New patient mechanical derangement:</b> Bronchospasm, edema	Endotracheal tube malposition
<b>Patient effort/agitation:</b> Coughing, biting, fighting (agitation with dysynchrony with ventilation)		<b>New cardiovascular derangement:</b> Shock, pulmonary embolism, ↓ in hemoglobin concentration ↑ oxygen consumption Changes in body position, ↑ shunt	↑ dead space ↑ CO <sub>2</sub> production	Increasing work of breathing Rising P <sub>CO<sub>2</sub></sub> Oxyhemoglobin desaturation Shock/PE Inadequate sedation Alcohol or drug withdrawal

(Adapted with permission from Hall JB, et al. *Principles of Critical Care*, 3rd ed. New York: McGraw-Hill, 2005, Table 36-4.)

may present with ↑ use of respiratory accessory muscles, cyanosis, and respiratory failure.

- The alveolar-arterial (A-a) oxygen gradient determines the differential diagnosis (Table 4.19):

$$\text{A-a gradient} = \text{PAO}_2 - \text{PAo}_2$$

where PAo<sub>2</sub> = 150 – Paco<sub>2</sub>/0.8 at sea level and room air.

- A normal gradient in a young, healthy patient is 5 to 10, but “normal” ↑ by about 1 mm Hg for every decade of life, so it is often estimated as (age /4) + 4. Figure 4.12 is a basic approach to interpretation of the A-a gradient.
- Management:** Treat underlying etiology. Give supplemental O<sub>2</sub>. Long-term O<sub>2</sub> therapy is indicated for a PAo<sub>2</sub> ≤ 55 mm Hg or an O<sub>2</sub> saturation ≤ 88%.

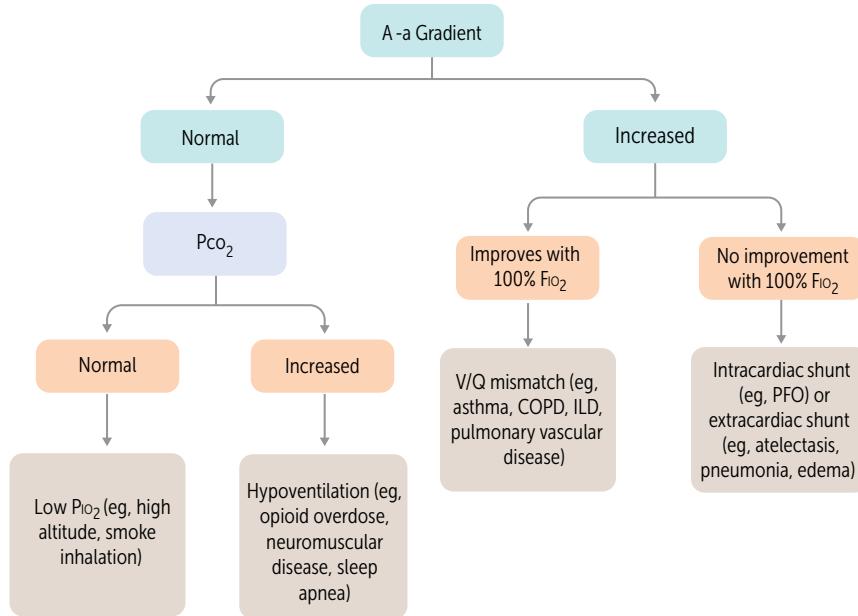


#### KEY FACT

Hypoxemia due to shunt does not correct with 100% O<sub>2</sub> therapy.

TABLE 4.19. Diagnosis of Hypoxemia by A-a Gradient and Response to Supplemental O<sub>2</sub>

ETIOLOGY	A-A GRADIENT	CORRECTS WITH SUPPLEMENTAL O <sub>2</sub> ?	CAUSES
↓ inspired Fio <sub>2</sub>	Normal	Yes	High altitude
Hypoventilation	Normal	Yes	See Table 4.20
Right-to-left shunt	↑	No	<b>Physiologic shunt:</b> Pneumonia, atelectasis, ARDS <b>Anatomic shunt:</b> Intracardiac shunt, pulmonary AVM, congenital heart disease, patent foramen ovale
Impaired diffusion capacity	↑	Yes; characterized by exercise-induced hypoxemia	Emphysema, ILD, pulmonary vascular disease, pulmonary alveolar proteinosis
V/Q mismatch	↑	Yes	PE, obstructive lung disease (COPD, asthma), pulmonary hypertension



**FIGURE 4.12. Interpretation of the A-a gradient.**  $\text{FIO}_2$  = fraction of inspired oxygen;  $\text{PCO}_2$  = partial pressure of carbon dioxide;  $\text{PIO}_2$  = inspired partial pressure of oxygen. (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

## HYPERCARBIA

↓ respiratory rate and somnolence = hypercarbia.

Table 4.20 lists the differential of hypercarbic respiratory failure.

Treatment depends on the etiology. Provide sufficient  $\text{O}_2$  through supplementation and adequate ventilation (noninvasive or invasive).

**TABLE 4.20. Etiologies of Hypercarbic Respiratory Failure**

CAUSE	MECHANISM	DISEASE STATES
Nervous system (CNS, peripheral nerve, neuromuscular junction) and muscle disorders	↓ minute ventilation leads to ↑ $\text{Paco}_2$	Drug overdose, CNS lesion/infarction, central sleep apnea, hypothyroidism, Guillain-Barré syndrome, amyotrophic lateral sclerosis, poliomyelitis, West Nile virus, ICU-acquired paresis, myasthenia gravis, botulism, muscular dystrophy, glycogen storage disease, ICU-acquired weakness
Lung disorders	↓ alveolar ventilation due to obstructive lung disease leads to ↑ $\text{Paco}_2$	COPD, asthma, CF
Chest wall disorders	Chest wall mechanics are altered, leading to ↓ alveolar ventilation and ↑ $\text{Paco}_2$	Kyphoscoliosis, massive obesity

## ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is an acute, inflammatory clinical syndrome that leads to diffuse lung damage in the form of alveolar and interstitial inflammation and edema. The pathological hallmark is diffuse alveolar damage. The **clinical hallmark of ARDS is acute hypoxic respiratory failure with bilateral pulmonary infiltrates that is not heart failure.** Commonly associated with pneumonia, aspiration, sepsis, trauma, acute pancreatitis, cardiopulmonary bypass, transfusion of blood products, inhalation injury, and reperfusion injury following lung transplantation.

- **Symptoms/Exam:** Presents with rapid onset of dyspnea, tachypnea, and diffuse crackles. Reduced single-breath DLCO is the most common pulmonary function abnormality in survivors.
- **Differential:** Cardiogenic pulmonary edema, pneumonia, diffuse alveolar hemorrhage, acute interstitial pneumonia, hypersensitivity pneumonitis, acute PE, cryptogenic organizing pneumonia.
- **Diagnosis:**
  - Look for **bilateral alveolar infiltrates on CXR with no evidence of left heart failure** (Figure 4.13); if measured, **pulmonary artery wedge pressure is <18 mm Hg.**
  - **ARDS = the above plus a  $\text{PaO}_2/\text{FiO}_2$  ratio of  $\leq 300 \text{ mm Hg}$ :**
    - Mild =  $200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2$  ratio of  $\leq 300 \text{ mm Hg}$ .
    - Moderate =  $100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2$  ratio of  $\leq 200 \text{ mm Hg}$ .
    - Severe =  $\text{PaO}_2/\text{FiO}_2$  ratio of  $\leq 100 \text{ mm Hg}$ .

### Management

Search for and treat the underlying cause. A bronchoalveolar lavage may narrow the etiology and help tailor antibiotic therapy in the event of pneumonia. There is no definitive evidence for corticosteroids in the prevention or treatment of ARDS. Most patients with ARDS require mechanical ventilation. **Note the following ventilation tips:**

- **Low VT (6 mL/kg of predicted body weight)  $\downarrow$  mortality.**
- **PEEP** can help improve oxygenation and  $\downarrow$  high levels of inspired  $\text{O}_2$ . Start with  $\text{FiO}_2$  at 100% and titrate down to avoid oxygen toxicity.
- **A conservative fluid management strategy** (aim for central venous pressure  $< 4 \text{ mm Hg}$ ) is associated with a shorter duration of mechanical ventilation and a  $\downarrow$  length of ICU stay.
- Consider ventilation in the prone position if ARDS is worsening despite the above treatments. Prone positioning alters the lung mechanics and gas exchange physiology so that oxygenation improves. There are many contraindications, such as spinal instability, shock or hemodynamic instability, recent tracheal surgery, and pregnancy.

## SHOCK

Shock is a physiologic state characterized by  $\downarrow$  tissue perfusion and subsequent tissue hypoxia. Prolonged tissue hypoxia often leads to cell death, organ damage, multorgan system failure, and eventual death.

### Symptoms/Exam

Vary depending on the underlying cause of shock (Table 4.21).

### Diagnosis

If the type of shock is still unclear after physical examination, additional information can be obtained through use of invasive monitoring devices:

- Echocardiography distinguishes poor cardiac function from hypovolemia; confirms pericardial tamponade or significant pulmonary hypertension.



**FIGURE 4.13. Acute respiratory distress syndrome (ARDS).** Diffuse bilateral consolidation in an intubated 21-year-old patient with a history of aspiration pneumonia. Echocardiogram had demonstrated normal left atrial pressures and good cardiac output, distinguishing this entity from cardiogenic pulmonary edema. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

To improve mortality in mechanically ventilated patients with ARDS, target a  $\text{Vt}$  of 6 mL/kg of predicted body weight.



### QUESTION

A 68-year-old woman is brought to the ED by family members for confusion. Notable findings: temperature,  $39.5^\circ\text{C}$  ( $103.1^\circ\text{F}$ ); BP,  $75/40 \text{ mm Hg}$ ; HR, 130 bpm; RR, 24 breaths per minute;  $\text{O}_2$  saturation 89% on room air; and warm skin. WBC count is  $15 \times 10^9/\text{L}$ , and UA is  $\oplus$  for nitrites and leukocyte esterase. After infusion of 3 L of normal saline, her BP is  $80/45 \text{ mm Hg}$ . What is the most appropriate initial vasopressor?

TABLE 4.21. Categories of Shock

	PHYSICAL FINDINGS	CARDIAC OUTPUT	SVR	PCWP ("WEDGE PRESSURE")	EXAMPLES
Distributive	Warm extremities; rapid capillary refill	↑	↓	↓	Sepsis, anaphylaxis
Cardiogenic	Cool, clammy extremities; delayed capillary refill; elevated JVP	↓	↑	↑ (except in RV infarct)	Acute MI, CHF
Hypovolemic	Cool extremities; flat JVP	↓	↑	↓	Trauma, bleeding
Obstructive	Cool extremities; variable JVP	↓	↑	↑ (tamponade) or ↓ (pulmonary embolism)	Tamponade, pulmonary embolism, tension pneumothorax

**KEY FACT**

Adrenal insufficiency and severe hypothyroidism may present clinically as shock. These diagnoses should be considered when patients fail to respond to fluid resuscitation.

- Central venous catheter estimates right heart filling.
- Pulmonary artery catheter measures cardiac output and pulmonary capillary occlusion pressure (PCWP, also known as “wedge pressure”) and calculates SVR to differentiate the type of shock. Has not been shown to improve patient outcomes compared to central venous catheters.

**Management**

Focus on resuscitation and improving end-organ perfusion. Aggressive IV fluid hydration (NS is first-line) should be given to patients with hypovolemic or distributive shock. Additionally, in anaphylaxis, give 1:1000 epinephrine intramuscularly, diphenhydramine, corticosteroids, albuterol and H<sub>2</sub> blockers. Blood products should be administered in cases of hemorrhagic shock. Broad-spectrum antibiotics should be given empirically if infection is suspected. If a patient remains in shock despite the restoration of intravascular volume, use vasopressors.

**SEPSIS**

Sepsis is a clinical syndrome associated with severe infection that arises from systemic inflammation and uncontrolled release of proinflammatory mediators, leading to extensive tissue injury. Associated with high mortality and morbidity. See Table 4.22 for details on the spectrum of disease.

TABLE 4.22. Conditions Associated With Sepsis

CONDITION	DEFINITION
Systemic inflammatory response syndrome (SIRS)	A clinical syndrome recognized by the presence of two or more of the following: <ul style="list-style-type: none"> <li>■ Temperature &gt;38°C (100.4°F) or &lt;36°C (96.8°F)</li> <li>■ HR &gt;90 bpm</li> <li>■ RR &gt;20 breaths per minute or a Paco<sub>2</sub> &lt;32 mm Hg</li> <li>■ WBC &gt;12,000 cells/mm<sup>3</sup>, &lt;4000 cells/mm<sup>3</sup>, or &gt;10% bands</li> </ul>
Sepsis	SIRS with known or suspected infection
Severe sepsis	Sepsis with organ dysfunction and hypoperfusion
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation combined with altered mental status, oliguria, and/or lactic acidosis

**ANSWER**

Norepinephrine for septic shock.

## Symptoms/Exam

Patients with systemic inflammatory response syndrome may have bounding pulses, warm extremities, and rapid capillary refill. Patients with severe sepsis and those with septic shock may have weak pulses, cool extremities, and slow capillary refill.

## Differential

Cardiogenic, obstructive, or hypovolemic shock, fulminant hepatic failure, drug overdose, adrenal insufficiency, pancreatitis.

## Diagnosis

Always obtain appropriate cultures, including blood cultures, before starting antibiotic therapy.

## Management

- **IV antibiotic therapy** geared toward suspected pathogens should be initiated within the **first hour of severe sepsis**.
- Early and aggressive volume resuscitation: Start first ( $\downarrow$  mortality) before vasopressors. The goal is a mean arterial pressure of  $>65$  mm Hg and a central venous pressure of 8 to 12 mm Hg.
- **Vasopressors:** Use in patients who are volume replete but still hypotensive. **Norepinephrine is the first-line agent for septic shock.** Vasopressin, epinephrine, and phenylephrine may be considered after failure of fluids and norepinephrine.
- Treatment should **not** include low-dose dopamine for renal protection.
- **Septic shock:** Empiric corticosteroids do **not** improve survival. In the setting of profound, refractory shock, perform a cosyntropin stimulation test (see the Endocrinology chapter), and then give corticosteroids while awaiting results.
- Consider the following interventions in all critically ill patients:
  - $\downarrow$  catheter-related bloodstream infections via handwashing, cleaning the skin with chlorhexidine, avoiding the femoral vein, using full-barrier precautions during catheter insertion, and removing unnecessary catheters.
  - Intensive insulin therapy targeting a blood glucose level of 80 to 110 mg/dL may  $\uparrow$  mortality in sepsis. Thus, the goal blood glucose level should be  $<150$  mg/dL.
  - Once hypoperfusion has resolved, blood transfusion should occur only at a **hemoglobin level of  $\leq 7$  g/dL** unless the patient is suffering from cardiac ischemia, lactic acidosis, or acute hemorrhage.
  - Sepsis is one of the most common causes of ARDS and low VT ventilation (**6 mL/kg of predicted body weight**) should be initiated if the patient requires mechanical ventilation.

## FEVER IN THE ICU

Defined as a temperature of  $\geq 38.3^{\circ}\text{C}$  ( $\geq 101^{\circ}\text{F}$ ), fever in the ICU may have an infectious (see the Mnemonic VW CARS) or noninfectious source. Noninfectious causes include pancreatitis, PE/DVT, adrenal insufficiency, ischemic bowel, drug reaction, withdrawal, acalculous cholecystitis, and neoplasm.

- Obtain blood cultures as well as other cultures (wound, urine, stool, endotracheal aspirate). CXR should be reviewed for any new infiltrates. If an obvious source of infection is identified, start antibiotics. If there is no obvious source of infection and fever is  $>39^{\circ}\text{C}$  ( $>102^{\circ}\text{F}$ ), evaluate for the noninfectious causes.
- If fever is  $>39^{\circ}\text{C}$  ( $>102^{\circ}\text{F}$ ), remove old central lines and culture the catheter tip at the same time as a peripheral blood culture or send cultures with direct time to positivity. Start empiric antibiotics if fever persists.



## MNEMONIC

**Infectious causes of fever in the ICU—**

### VW CARS

**V**entilator-associated pneumonia  
**W**ound infection  
**C**lostridium difficile colitis  
**A**bdominal abscess  
**R**elated to catheter  
**S**eptis/Sinusitis

### VENTILATOR-ASSOCIATED PNEUMONIA

Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops  $\geq 48$  hours after intubation. Up to 25% of mechanically ventilated patients develop VAP.

- **Symptoms/Exam:** Presents with fever, worsening hypoxia, and ↑ purulent secretions from the endotracheal tube. Chronic lung disease, ↑ length of mechanical ventilation, aspiration, low head-of-bed level, use of nasogastric tubes, and delayed extubation can all ↑ the risk of VAP.
- **Diagnosis:** VAP is suggested by:
  - **Clinical criteria:** fever  $\geq 48$  hours after intubation, leukocytosis, and ↑ secretions.
  - **Radiographic criteria:** New infiltrate on CXR.
  - **Airway sampling:** Via bronchoscopy, mini-BAL (of lower airways), or tracheal aspirate. There is no clear benefit to any method.
- **Management:** Patients should initially receive broad-spectrum antibiotics to cover *S aureus*, *Pseudomonas*, and *Enterobacteriaceae* such as vancomycin and piperacillin-tazobactam or vancomycin and ceftazidime. Antibiotics should be based on local resistance patterns and should be rapidly narrowed on the basis of respiratory cultures. An 8-day course of antibiotics is recommended.

Interventions that should be used to prevent VAP:

- Keep the head of the bed elevated to at least 30 degrees.
- Use universal and barrier precautions in the setting of multidrug-resistant organisms, including washing hands and wearing special gowns.
- ↓ the amount of mechanical ventilation time by interrupting sedation daily, using weaning protocols, and using noninvasive mechanical ventilation if applicable.

### NUTRITIONAL SUPPORT IN CRITICAL ILLNESS

- Early feeding is recommended though it may not need to be full nutritional support. Enteral feeding is preferred over parenteral routes, and most patients, even burn victims and those with airway injury, can tolerate nasogastric tube placement.
- Post-pyloric tube placement is not necessary as it has not been shown to ↓ the risk of pneumonia, aspiration, or reflux or the length of ICU stay and mortality.



#### KEY FACT

The most common etiologic agents of VAP are *S aureus*, *P aeruginosa*, and *Enterobacteriaceae* (eg, *E cloacae*), and initial treatment should cover these bacteria (eg, vancomycin and piperacillin-tazobactam or vancomycin and ceftazidime).

## CHAPTER 5

# Dermatology

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**KEY FACT**

Isotretinoin is teratogenic and is contraindicated in pregnancy. Side effects include dry skin, cheilitis, transaminase elevation, hypertriglyceridemia, and depression. It can also cause colitis, which may mimic inflammatory bowel disease (IBD), but the relationship between isotretinoin as a causative factor for IBD remains to be proven.

**KEY FACT**

In recalcitrant cases of acne, signs such as hirsutism and irregular menses may point to possible endocrine disorders (congenital adrenal hyperplasia, PCOS, Cushing disease).



**FIGURE 5.1. Severe acne.** Note the deep-seated nodules and pitted scarring on the cheek. (Reproduced with permission from Dr. Richard Usatine.)

**KEY FACT**

Think rosacea when the story is a chronic, waxing-and-waning facial rash that involves the cheeks and nose and is triggered by sun exposure, hot and spicy foods, or alcohol.

**KEY FACT**

If it looks like rosacea and the patient has been using topical corticosteroids, remember that rosacea can be steroid-induced and discontinue the topical steroids.

**Common Skin Disorders****ACNE**

Acne is due to excess sebum, abnormal follicular keratinization, and proliferation of *Propionibacterium acnes*. Medications that exacerbate acne include glucocorticoids, anabolic steroids, lithium, some antiepileptics, OCPs with androgenic potential, and iodides. **Dietary factors do not play a significant role.**

The therapeutic ladder is as follows:

- **Milder cases (comedonal acne with blackheads/whiteheads but no inflammatory lesions):** Topical retinoid + benzoyl peroxide or a topical antibiotic (such as clindamycin).
- **More severe/inflammatory cases (Figure 5.1): Systemic antibiotics (such as doxycycline/minocycline), oral isotretinoin, OCPs, or spironolactone.**
- In pregnancy, many of the usual treatment options are contraindicated. Common interventions include azelaic acid (category B), topical or systemic erythromycin (category B), topical clindamycin (category B), and topical benzoyl peroxide (category C).

**ROSACEA**

Rosacea is a chronic inflammatory **facial** disorder affecting middle-aged to older adults. The classic presentation of patchy **flushing** and facial erythema of rosacea mimics sunburn. **Triggers** include hot liquids, spicy food, alcohol, sun, and heat.

**Symptoms/Exam:**

- **Absence of comedones.** Exam reveals diffuse erythema and telangiectasia along with occasional erythematous papules and pustules (Figure 5.2).
- **Symmetric central facial involvement** (malar cheeks, nose, chin, forehead).
- **Rhinophyma**, bulbous, red nose, is a variant of this condition—also known as “Santa Claus nose”—most often seen in men with long-standing disease.
- **Management: Avoidance of triggers (sun, alcohol abuse, steroids); sun protection is key!** The therapeutic ladder is: topical antibiotic (eg, metronidazole gel) or azelaic acid → oral antibiotic (eg, tetracycline) → oral isotretinoin for severe, refractory disease. Consider laser treatment for telangiectasia and rhinophyma.



**FIGURE 5.2. Rosacea.** Papules, pustules, and telangiectasia are seen on the central face. Note the lack of comedones. (Reproduced with permission from Wolff K, Johnson RA. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill, 2009, Fig. 1-7.)

## HAND DERMATITIS

Hand dermatitis is a common disorder with lifetime prevalence of ~ 15%, but increased frequency in certain occupations (ie, hairdressers, food handlers). Often presents with complaints of burning, itching, stinging sensations. Multiple etiologies including dyshidrotic eczema, irritant contact dermatitis, nummular hand eczema, and chronic atopic hand dermatitis.

- **Symptoms/Exam:** Acutely presents with skin edema, erythema, and weeping. Chronically presents with thickening, scaling, and fissuring of skin (Figure 5.3).
- **Diagnosis:** Detailed history. Patch testing useful to determine if specific allergy.
- **Management:** Avoidance of triggers (eg, water, detergents, gloves). Protection of hands with gloves, moisturizers, and barrier creams. Topical high- to super-high-potency corticosteroids are first-line for mild-moderate disease. Severe or refractory disease may need phototherapy or systemic therapies such as oral corticosteroids, immunosuppressants (eg, methotrexate), or retinoids.

## SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a very common inflammatory reaction to *Malassezia globosa* (formerly *Pityrosporum ovale*) yeast.

- **Symptoms/Exam:** Reveals dry or “greasy,” yellow, sharply demarcated scales on an erythematous base (Figure 5.4). The greasy appearance and scalp involvement distinguish this condition from rosacea.
  - Generally localized to the **scalp, postauricular region, central facial area** (especially the eyebrows and nasolabial folds), and flexural areas.
  - Usually chronic and relapsing, improves during the summer and worsens in the fall and winter or with stress.



**FIGURE 5.4. Seborrheic dermatitis of HIV infection.** Extensive greasy scale-crust of the scalp, eyebrows, nasolabial folds and hair-bearing areas of the face. (Reproduced with permission from USMLE-Rx.com.)

## KEY FACT

Rosacea keratitis is uncommon but may lead to blindness.



**FIGURE 5.3. Hand dermatitis.** Note the skin thickening, fissures, dryness, scaling, and generalized redness.

(Reproduced with permission from Wolff K, Johnson RA. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 7th ed. New York: McGraw-Hill Education, 2013. Fig. 2-4A.)

## KEY FACT

Severe, recalcitrant or fulminant acute onset seborrheic dermatitis may be a clue pointing to underlying HIV infection or Parkinson disease.



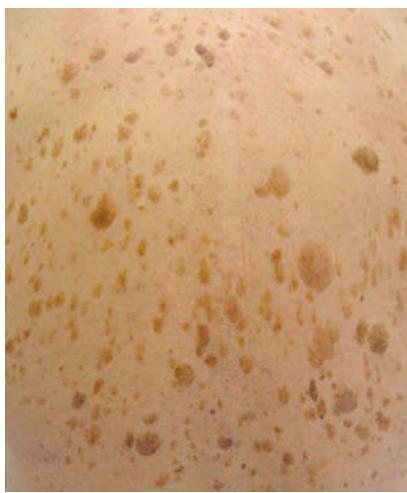
## QUESTION 1

A 40-year-old woman has had an erythematous rash with discrete papules and pustules and scattered telangiectasia limited to the cheeks, nasolabial folds, and nose for 2 months. She has no fatigue, ulcers, or joint pain. The rash worsens after she eats spicy food. CBC, chemistry, TSH, and ANA are normal. What is the most likely diagnosis?



## QUESTION 2

A 20-year-old woman presents with moderate to severe acne of 5 years' duration that has worsened over the past month. She has been using topical retinoids and antibiotics without improvement and takes oral contraceptives (OCPs) with regular menses. Exam reveals several tender papulonodular lesions, some of which have pustules. What is the most appropriate next step?

**FIGURE 5.5. Seborrheic keratoses.**

Abrupt appearance of many brown waxy “stuck-on” papules associated with colon cancer, also known as the Leser-Trélat sign. (Reproduced with permission from Dr. James Heilman.)

**KEY FACT**

Although seborrheic keratoses are benign, if many lesions appear suddenly, consider the presence of an internal malignancy (sign of Leser-Trélat).

**KEY FACT**

Consider HIV in a patient with severe psoriasis.

**ANSWER 1**

Rosacea affects the central face, including the nasolabial folds, and is associated with triggers (eg, spicy foods). In contrast, the malar rash of SLE spares facial areas that are anatomically protected from the sun.

**A****ANSWER 2**

Oral doxycycline for 4 to 6 weeks along with a topical retinoid for moderate to severe inflammatory acne (topical antibiotics are not usually used in conjunction with oral antibiotics).

**Management:**

- **Scalp:** Shampoos containing tar, zinc, selenium, or ketoconazole.
- **Facial:** Antifungal creams (such as ketoconazole 2% cream) ± mild topical corticosteroids.
- May require maintenance therapy.

**SEBORRHEIC KERATOSIS**

- Seborrheic keratosis is the **most common** benign epidermal growth; probable autosomal dominant inheritance.
- Asymptomatic; occasionally pruritic. Papules have a waxy “**stuck-on**” appearance (Figure 5.5).
- No treatment is necessary.

**ACTINIC KERATOSIS**

Actinic keratosis is a common lesion related to **extensive UV exposure** and history of sunburns. Up to 60% of SCC lesions develop from actinic keratosis, although each individual actinic keratosis has a low risk of transitioning into SCC (approximately 0.1% per year).

- **Symptoms/Exam:** Look for erythematous, rough, scaly papules or small plaques (Figure 5.6) most often on sun-exposed areas (ie, face, distal extremities).
- **Diagnosis:** Usually clinical but if uncertain or concern for SCC, perform shave or punch biopsy.
- **Management:** Cryotherapy if limited number of lesions. Topical agents (5-FU, imiquimod) or photodynamic therapy used for more widespread lesions.

**Psoriasis**

Psoriasis is a T-cell immune-mediated inflammatory disease with genetic predisposition characterized by bimodal peak incidences at 27 and 55 years of age. It has several distinct clinical presentations.

**Symptoms**

- Usually asymptomatic, although pruritus may be present.
- **Koebner phenomenon**—psoriatic lesions induced at sites of injury or irritation.



**FIGURE 5.6. Actinic keratosis.** Note the scaly ill-defined pink papule with adherent scale (arrow). One can often feel these lesions more easily than see them. (Reproduced with permission from Dr. Christopher Crosby.)

- Triggers include trauma, stress, and **medications** (lithium,  $\beta$ -blockers, prednisone taper, antimalarials, ACEIs, interferons).
- A severe form is seen in **HIV** infection.

### Exam

- Nail pitting (fine “ice-pick” stippling) is the most common nail manifestation of psoriasis, but a number of nail changes can occur.
- Psoriasis subtypes:
  - Localized plaque type** (Figure 5.7): Most common. Sharply demarcated, erythematous plaques with silvery-white scales, often symmetrically distributed on the elbows, knees, scalp, palms, and soles. **Gluteal pinking and umbilical skin involvement are pathognomonic.**
  - Guttate (“drop-like”):** Typically occurs in young adults following strep throat. Characterized by numerous small, discrete plaques that are widely distributed.
  - Generalized pustular or erythrodermic:** Rare, life-threatening variants.
  - Inverse psoriasis:** Involves the flexural surfaces (axillae, groin).

### Diagnosis

Diagnosed by clinical findings; biopsy is rarely performed. In **guttate psoriasis**, consider obtaining an ASO titer and/or a throat culture for group A  $\beta$ -hemolytic streptococcal infection. Consider 2° syphilis in the differential for guttate psoriasis.

### Management

See Table 5.1. In resistant cases, topical coal tar can be used as a corticosteroid-sparing drug and is highly effective when combined with UVB phototherapy. Phototherapy is generally used when the patient is resistant to topical therapy or when large areas of the body are involved and topical therapy is impractical.

### Complications

- Psoriatic arthritis** (affects <10% of psoriasis patients) can affect multiple joints (high-yield association with **DIP joints** of the hands) and may cause **sacroiliitis**. See the Rheumatology chapter for a more detailed discussion.
- Psoriasis is an independent risk factor for myocardial infarction, so patients should be followed by their 1° care physicians for cardiovascular risk factors.

TABLE 5.1. Management of Psoriasis

TYPE OF PSORIASIS	TREATMENT	EXAMPLES
<b>Limited plaque</b>	Topical therapies	Potent topical corticosteroids, vitamin D analogs (calcipotriene), topical calcineurin inhibitors, retinoids, anthralin, coal tar
<b>Generalized disease</b>	UV light and retinoids	UVB light, oral retinoids, PUVA (psoralen and UVA light), biologics
<b>Refractory disease or psoriatic arthritis</b>	Systemic immunosuppressants	Methotrexate, cyclosporine, anti-TNF agents, newer biologics such as apremilast, secukinumab, and ustekinumab
<b>Guttate psoriasis</b>	Oral antibiotics against strep, $\pm$ topical therapies or UVB	Penicillin VK or erythromycin

### KEY FACT

Nail pitting and distal finger (DIP) arthritis are manifestations of psoriasis. Nail changes are more frequent in patients with arthritis, so be sure to screen those with prominent nail changes for arthritis symptoms.



**FIGURE 5.7. Psoriasis.** Well-demarcated erythematous plaques with thick silvery scale and occasional punctate hemorrhagic scabs involving the elbows of a 50-year-old man with a 2-year history of psoriasis. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

Think of guttate psoriasis if you see widespread plaques after a sore throat.

### KEY FACT

Boards questions will focus on the recognition of psoriasis (classic plaques on the flexural surfaces and guttate variety); stepwise treatment based on the severity of disease; and associations with HIV, systemic corticosteroids, and psoriatic arthritis.



### QUESTION

A 45-year-old man presents with sharply demarcated, erythematous plaques with silvery-white scales on the outer elbows and anterior knees that have occurred episodically since he was a teenager. OTC topical hydrocortisone has provided no relief. The rash covers <3% of the total body area. CBC, chemistry, and UA results are normal. What is the most appropriate next step?

**KEY FACT**

Systemic corticosteroids are **contraindicated** in the treatment of psoriasis because of the risk of inducing pustular psoriasis and severe disease rebound on withdrawal of medication.

**KEY FACT**

**Bullous** impetigo is usually caused by *S aureus*.



**FIGURE 5.8. Impetigo.** Severe case of facial impetigo, with crusted erosions that may be due to *Streptococcus* or *S aureus*, including methicillin-resistant *S aureus*. (Reproduced with permission from James Heilman.)

**Cutaneous Infections****IMPETIGO**

Impetigo is a contagious, superficial epidermal infection caused by *Staphylococcus aureus*, group A *Streptococcus*, or both. Infection may occur as a 1° event or as a 2° superinfection of an underlying dermatitis.

- **Symptoms/Exam:** 1° lesions are vesicles or pustules that most often affect the face, often with an overlying **honey-colored crust** (Figure 5.8). Gram stain and culture useful in determining *Staphylococcus* versus *Streptococcus* as cause.
- **Management:** Mupirocin ointment for limited disease; systemic antibiotics with both *Staphylococcus* and *Streptococcus* coverage for more severe involvement. Systemic antibiotics should also be considered for localized disease in immunocompromised patients.

**DERMATOPHYTOSIS (TINEA)**

Dermatophytosis is a superficial fungal infection of the skin, hair follicles, and/or nails transmitted person-to-person via **fomites**. Scalp infection (tinea capitis) is usually seen in children. Predisposing factors include atopic dermatitis, immunosuppression, sweating, and occlusion.

**Symptoms/Exam**

- **Tinea pedis (feet):** Presents with dry scales, maceration, and/or fissuring of the web spaces and scaling in a “moccasin” or “ballet slipper” distribution; vesicles and bullae may occur.
- **Tinea cruris (groin):** Characterized by erythematous, well-demarcated annular plaques with **clear centers** and active, advancing, scaly, **sharp borders**. Usually begins unilaterally; more common in men. The differential includes intertrigo and erythrasma.
- **Tinea corporis (body):** Involves the face, trunk, and extremities. The size and degree of inflammation can vary, with scaly skin at the advancing border (Figure 5.9).

**A****ANSWER**

For typical psoriasis lesions, the next step involves high-potency topical corticosteroids for about 2 weeks, which can then be rotated with topical vitamin D analogs, retinoids, anthralin, or tar preparations.



**FIGURE 5.9. Tinea corporis.** A typical “ringworm-like” configuration can be seen. (Reproduced with permission from USMLE-Rx.com.)

- **Tinea barbae (beard):** Often accompanied by folliculitis and pseudofolliculitis (ingrown hairs).
- **Tinea capitis (hair):** Commonly affects the scalp, eyebrows, and eyelashes. Lesions generally show evidence of active infection with exudate, inflamed crusts, matted hair, and debris. Severe cases can develop into a patch with hair loss and scarring alopecia.
- **Tinea unguis/onychomycosis (nails):** Nail yellowing and thickening with subungual debris; frequently associated with chronic tinea pedis (Figure 5.10). Association between proximal subungual onychomycosis and HIV (the proximal nail plate is white and the distal plate is spared). Nail dystrophy is also seen in many other skin diseases and does not necessarily imply fungal infection.
- **Tinea cruris (groin):** Tinea tends to spare the scrotum while candida involves the scrotum—this can be a helpful diagnostic clue.

### Diagnosis

- KOH of skin scraping to identify hyphae ± fungal culture.
- Infected hairs in tinea capitis may fluoresce under UV light (Wood's light).

### Management

- Maintain good hygiene; keep affected areas dry.
- Topical antifungals; oral antifungals required for tinea capitis or refractory cases. Topical therapies require treatment twice daily for at least 2 weeks, with continuation of therapy at least 1 week after resolution of the lesions.
- **Topical therapy is usually ineffective for onychomycosis.** The risks and benefits of oral antifungal therapy should be discussed with patient; notable risk is rare hepatic failure. Oral terbinafine has the highest cure rate, followed by itraconazole and then griseofulvin. Recurrence is common, even with oral therapy.



**FIGURE 5.10. Tinea pedis with onychomycosis.** Severely pruritic desquamating scale of the plantar and dorsal feet with yellowing thickening and ridging of the toenails in a 55-year-old man with burning itchy feet. (Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

Tinea pedis affecting the web spaces is the most common inciting factor for cellulitis in otherwise healthy patients.

#### KEY FACT

If a patient with tinea pedis develops pruritic vesicles on the hands or body, it may represent an **id reaction**—a hypersensitivity reaction to a tinea infection on a distant body site.

#### KEY FACT

Tinea lesions that are painful suggest a 2<sup>o</sup> bacterial infection.

### PITYRIASIS (TINEA) VERSICOLOR

Pityriasis versicolor is a mild superficial infection caused by a fungus (***M. globosa*, formerly named *Pityrosporum ovale***) and facilitated by high humidity and sebum production. It commonly affects young and middle-aged adults. Patients usually notice the infection because involved areas do not tan, resulting in hypopigmentation.

- **Symptoms/Exam:** Reveals numerous round or oval, sharply demarcated macules that may be tan, brown, pink, or white (Figure 5.11) typically located on upper trunk, proximal extremities, face, or neck.
- **Diagnosis:** Can be confirmed with KOH preparation of skin scraping to identify hyphae and budding spores—“spaghetti and meatballs” appearance (Figure 5.12).



A



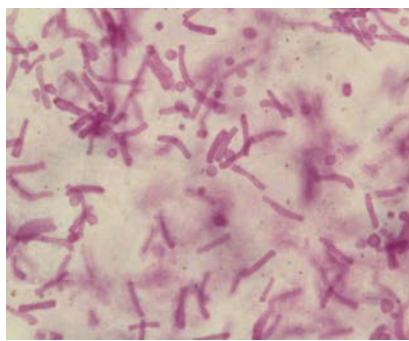
B

**FIGURE 5.11. Tinea versicolor caused by fungus *Malassezia globosa*.** (A) Note the multiple, well-demarcated hypopigmented macules. (B) Close-up view. (Source: CDC Public Health Image Library; content provider: Dr. Lucille K. Georg.)



#### QUESTION

A 40-year-old woman has had a nonpruritic, nonpainful rash for a month that is spreading despite application of an OTC corticosteroid cream. Exam shows hypopigmented macules on the chest, abdomen, and shoulders. Direct microscopic exam of a scale with 10% KOH shows large, blunt hyphae and thick-walled budding spores in a “spaghetti and meatballs” pattern. Her LFTs are normal. What is the most appropriate treatment?



**FIGURE 5.12. *Malassezia* on microscopy.** Note the “spaghetti and meatballs” appearance of hyphae and budding spores in a KOH smear of skin scraping. (Source: CDC Public Health Image Library; content provider: Dr. Lucille K. Georg.)



**FIGURE 5.13. Cutaneous candidiasis: intertrigo.** Confluent bright red papules with “satellite” pustules. (Source: CDC Public Health Image Library; content provider CDC/Dr. Hardin.)

### KEY FACT

Consider pityriasis rosea if you see a mildly itchy rash in a Christmas tree distribution with a herald patch.

### A

### ANSWER

Pityriasis (tinea) versicolor, a superficial mycotic infection, is effectively treated with ketoconazole or selenium shampoo. The infection commonly recurs, and prophylaxis and/or periodic courses of treatment may be necessary.

- **Management:** First-line treatment is topical ketoconazole or selenium shampoos. Second-line treatment is an oral azole antifungal (eg, fluconazole or itraconazole); **oral ketoconazole is no longer used** due to risk of toxicities (hepatic injury) and multiple medicine interactions.

### CANDIDIASIS

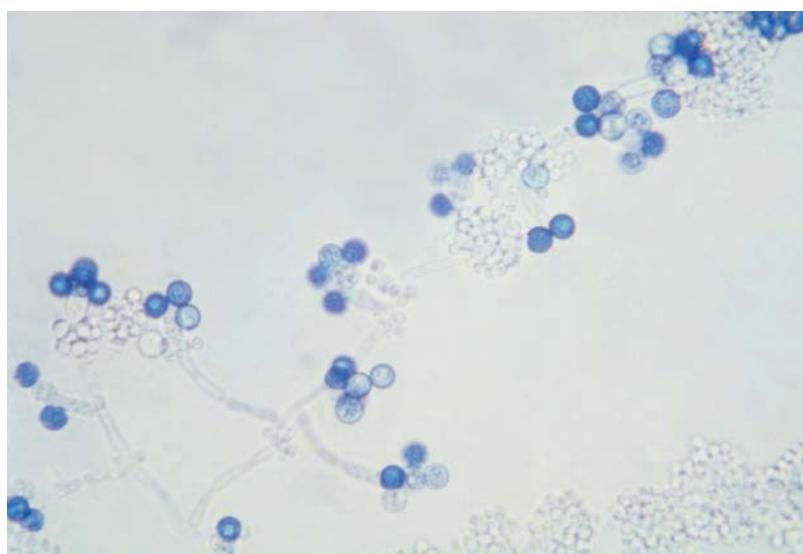
Risk factors for infection with *Candida* include DM, obesity, sweating, heat, maceration, systemic and topical corticosteroid use, and chronic debilitation. Antibiotic and OCP use may also be contributory.

- **Symptoms/Exam:** Look for brightly erythematous, sharply demarcated plaques with scalloped borders in moist intertriginous areas (Figure 5.13). **Satellite lesions** (scattered lesions at the periphery) may coalesce and extend into larger lesions. Usually a clinical diagnosis, supported by KOH stain of a skin scraping showing **pseudohyphae** and yeast forms (Figure 5.14).
- **Management:** First-line treatment is topical antifungals (eg, nystatin or clotrimazole). Terbinafine is ineffective for candidiasis. Skin care is key to preventing recurrences: may use topical drying agent like talc and encourage time with skin open to the air.

### PITYRIASIS ROSEA

Pityriasis rosea most often occurs in young adult **women**. Caused by human herpesviruses 6 and 7 (HHV-6 and -7).

- **Symptoms/Exam:**
  - Look for the larger “herald patch” which often precedes the generalized trunk eruption by 1 to 2 weeks. Mild pruritus is common.
  - Should also see dull pink “salmon-colored” plaques up to 2 cm in diameter with a “cigarette paper” (wrinkled) appearance, a silver **collarette of scale**, and a well-demarcated erythematous base (Figure 5.15).
  - Lesions are arranged in a “**Christmas tree**” distribution, with the long axis of lesions following lines of cleavage.



**FIGURE 5.14. *Candida albicans*.** This image shows pseudohyphae and chlamydospores—large, round structures that are dark in pigment; the smaller grape-like clusters are blastoconidia. (Source: CDC Public Health Image Library; content provider CDC/Dr. Gordon Roberstad.)



**FIGURE 5.15. Pityriasis rosea.** Plaques with an oval configuration with arrow pointing to a herald patch rimmed by a collarette of scale. (Source: CDC Public Health Image Library.)

- Involves the trunk and proximal extremities; **spares the face**.
- Consider syphilis as mimicker of pityriasis rosea.
- **Management:** Self-limited with spontaneous resolution within 2 months.

### HERPES SIMPLEX

Morbidity due to HSV infection results from recurrent outbreaks. Transmission occurs through direct contact with mucosal surfaces. **Asymptomatic viral shedding** occurs in 60% to 80% of infected patients.

- **Symptoms/Exam:**
  - Look for small, grouped vesicles/vesiculoulcerative lesions, and satellite vesicles, on an erythematous base that crust.
  - Most commonly affects the vermillion border of the lips, the genitals (often with enlarged inguinal lymph nodes), and the buttocks.
- **Diagnosis** can be confirmed with direct fluorescent antibody, viral culture, PCR (most sensitive, but costly), or evidence of viropathic changes on biopsy.
- **Management:**
  - Without treatment, lesions spontaneously heal within a week. Immediate treatment with oral antiviral agents may ↓ the duration of the outbreak by 12 to 24 hours. Parenteral acyclovir reserved for immunosuppressed patients. Acyclovir-resistant cases are treated with foscarnet or cidofovir.
  - Oral acyclovir, valacyclovir, and famciclovir are appropriate antiviral agents for genital HSV infection without systemic complications (meningitis, encephalitis, urinary retention).
- **Complications:** Eczema herpeticum, disseminated cutaneous disease in patients with underlying dermatitis (Figure 5.16). Immunosuppressed patients are at risk for potentially life-threatening **systemic disease** involving the lungs, liver, and CNS.

### HERPES ZOSTER

Varicella-zoster virus (VZV) causes both 1° infection **varicella** (chickenpox) and reactivation **herpes zoster** (shingles). The classic presentation of chickenpox is an acute itchy rash that starts on the face and trunk then spreads to the rest of body with rapid evolution into small vesicles (“**dewdrop on a rose petal**”) and the hallmark finding of lesions in **various stages of development**. There is a 10% to 20% lifetime incidence of herpes zoster following chickenpox. Incidence ↑ with age. Higher zoster risk in immunosuppressed adults (eg, HIV infection or malignancy).

#### KEY FACT

Tinea corporis (ringworm) is often mistaken for pityriasis rosea, but tinea corporis has scaly skin at the advancing border, whereas in pityriasis the scale is more central and well back from the advancing edge. KOH will be diagnostic for tinea corporis.

#### KEY FACT

For patients with frequent or severe HSV infection, consider suppressive treatment with low-dose antivirals as such treatment can ↓ outbreaks by 85% and viral shedding by 90%. Photo protection is key to the prevention of recurrence of orolabial herpes.

#### KEY FACT

HSV is the most common cause of recurrent erythema multiforme.

#### QUESTION 1

A 40-year-old woman with a history of herpes labialis infections since childhood presents with similar lesions on her face. Four months earlier, she underwent hematopoietic stem cell transplantation for acute myeloid leukemia and is currently on high-dose immunosuppressive medication. Exam reveals umbilicated vesicular lesions with raised, nonpustular, erythematous edges on her right cheek. Lab results show leukopenia and a creatinine level of 2.0 mg/dL. What is the most appropriate antiviral treatment?

#### QUESTION 2

Two months earlier, a 65-year-old woman had a painful rash on her left trunk that resolved after a week. She continues to feel sharp pains, especially at night, despite taking acetaminophen with codeine. Exam reveals scattered hypopigmentation in a dermatomal distribution with tingling and pain on light touch. What is the most appropriate treatment?



**FIGURE 5.16. Eczema herpeticum of the face in a patient with HSV infection.**

**infection.** Confluent and discrete crusted erosions associated with erythema and edema are seen in a patient with atopic dermatitis. (Reproduced with permission from Wolff K, et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 7th ed. New York: McGraw-Hill Education, 2013, Fig. 27-42.)

#### KEY FACT

Disseminated zoster or zoster in apparently healthy patients <40 years old should raise suspicion for HIV disease.

A

#### ANSWER 1

Formal cultures should be performed to confirm that HSV infection has recurred. If true recurrence but the lesions do not respond to acyclovir, consider resistance. Treatment options for resistant HSV include foscarnet and cidofovir.

#### KEY FACT

Disseminated zoster has ≥20 lesions outside of contiguous dermatomes.

A

#### ANSWER 2

Treat postherpetic neuralgia (PHN) with gabapentin, TCAs, or pregabalin. Spontaneous resolution is common during the first 6 months of a herpes zoster episode, but treatment may be indicated for pain that interferes with functioning or sleep. Capsaicin, amitriptyline, regional nerve blocks are other options.

#### Symptoms/Exam

- Presents with unilateral **dermatomal pain** followed by skin lesions.
- Exam reveals clustered vesicular lesions, most commonly on the trunk, that do not cross midline (Figure 5.17).
- Clinical variants:
  - **Herpes zoster ophthalmicus** comprises 7% to 10% of zoster cases. Lesions on the eye, eyelid, and forehead indicate CN V involvement. Look for **Hutchinson sign**: vesicles on either the tip or the side of the nose (Figure 5.18), which suggest involvement of the nasociliary branch of the ophthalmic nerve and thus imply possible infection in the deep structures of the eye—refer to ophthalmologist.
  - **Ramsay-Hunt syndrome** is the term used for herpes zoster that affects the external ear canal/auricle and is associated with facial palsy. Call ENT—treatment involves corticosteroids and antiviral therapy.

#### Diagnosis

Usually clinical diagnosis. Atypical presentations may warrant lab testing with direct fluorescent antibody, or PCR of a scraping from a skin lesion; VZV is very difficult to accurately culture, and thus **viral culture is not a recommended test**.

#### Management

- Antivirals (acyclovir, valacyclovir, famciclovir) are recommended to ↓ pain, vesicle formation, viral shedding, and ocular involvement in patients with HIV disease, those >50 years of age, and those presenting within 72 hours of symptom onset.
- No benefit to adjuvant therapy with corticosteroids, gabapentin, or TCAs for acute, uncomplicated zoster.



**FIGURE 5.17. Herpes zoster (shingles).** Unilateral crusted vesicles in the S2-S3 dermatomal distribution in 65-year-old man on methotrexate with a 4-day history of localized pruritus and erythema. (Reproduced with permission from USMLE-Rx.com.)

**A****B**

**FIGURE 5.18. Herpes zoster ophthalmicus with Hutchinson sign.** (A) Vesicles on either the tip or the side of the nose (Hutchinson sign) suggests possible infection in the deep structures of the eye. (B) Vesicular rash on an erythematous base in a V1 distribution on left side of face, ends at midline. (Courtesy of EyeRounds.org, The University of Iowa.)

- Complicated zoster (herpes zoster ophthalmicus, acute retinal necrosis, Ramsay-Hunt) may require IV antiviral therapy.

### Complications

**PHN:** ↑ risk in elderly patients and in those with severe rash. First-line treatment options are TCAs, gabapentin, and pregabalin.

### SMALLPOX

Case fatality rate of smallpox is 20% to 30%. Seen only in bioterrorism. Caused by variola, a double-stranded DNA poxvirus. Look for **sudden onset** of fever, headache, malaise, followed by centrifugally spreading rash. Lesions are synchronous (all in the same stage), occur after fever abates, and are more prominent on the face and extremities, whereas varicella lesions are in varying stages of development and healing, occur during fever, and are more prominent on the trunk.

### SCABIES

Skin infestation caused by the mite *Sarcoptes scabiei*. The female adult burrows and lays eggs in the stratum corneum. **Highly contagious;** spreads through prolonged contact with an infected host.

- Symptoms/Exam:**
  - Look for characteristic location (Figure 5.19) with **intense pruritus**, especially at night due to delayed type IV hypersensitivity reaction to the mites, their eggs, or their feces, resulting in a 2- to 4-week delay between infection and onset of symptoms. **Face is usually spared of both rash and itch.**
  - Exam reveals small pruritic vesicles, pustules, excoriations, and **burrows** (Figure 5.20).
- Diagnosis:** Made by skin scraping with light microscopy to identify mites, ova, or fecal pellets (Figure 5.21).
- Management:** First-line treatment is topical **permethrin 5%** cream below the neck; leave on for 8 hours and shower off. **Repeat treatment in 1 week.** Wash linens and clothing in hot water. **Ivermectin** may be needed to treat crusted scabies, conventional cases refractory to topical therapy, epidemics in institutions, or superinfected scabies.

### KEY FACT

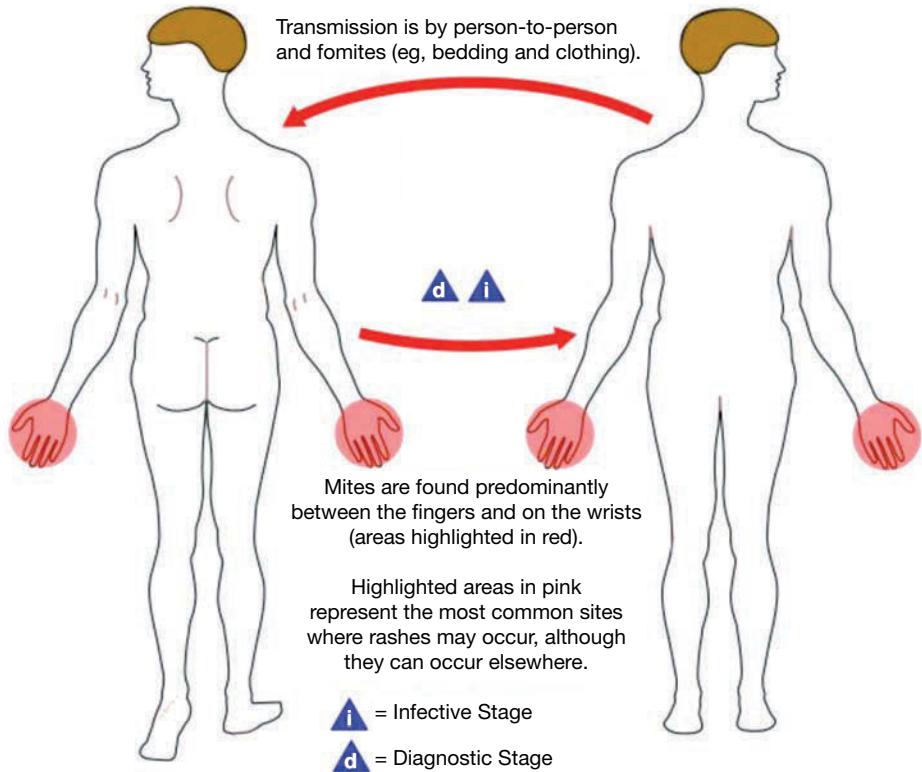
Zoster vaccine in patients age >60 years  
↓ risk of herpes zoster and incidence of PHN by 50% and 67%, respectively.

### KEY FACT

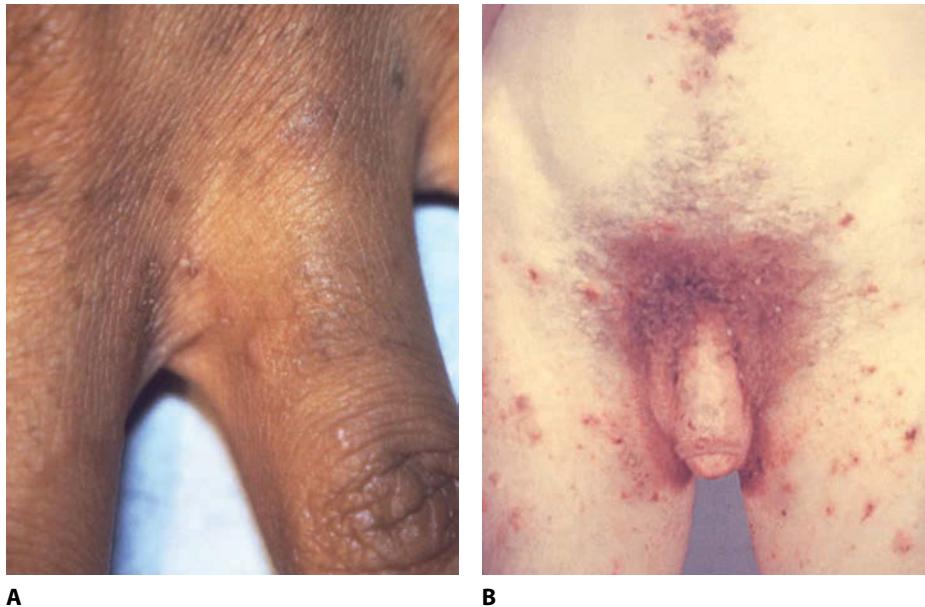
The pain of zoster may precede skin lesions by several days and may mimic that of angina, pleurisy, cholecystitis, appendicitis, or hepatitis.

### KEY FACT

Antiviral therapy within 72 hours may ↓ the duration and severity of PHN. This is especially important in elderly patients, a population that is at ↑ risk for this complication.



**FIGURE 5.19. Typical locations of scabies mites and lesions.** (Source: CDC Public Health Image Library; content provider CDC/Alexander J. da Silva, PhD/Melanie Moser.)

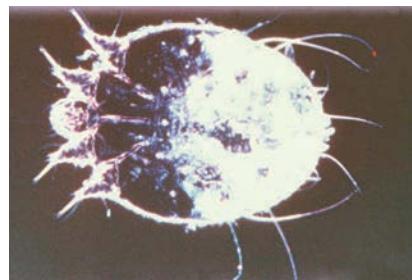


#### KEY FACT

Itching and rash secondary to hypersensitivity reactions may persist for weeks or months despite effectively treated scabies infection.

**FIGURE 5.20. Scabies.** (A) Dorsal surface of hand reveals papules and burrows in the interdigital web space between the index and middle fingers, due to an infestation of the human itch mite, *S scabiei*. (B) Pimple-like irritations and burrows in the skin around the groin and penis, characteristic of scabies. (Image A source: CDC Public Health Image Library. CDC/J. Pledger. Image B source: CDC Public Health Image Library; CDC/Susan Lindsley.)

- Complications:** Look for the variant **crusted scabies** (Norwegian scabies) in immunosuppressed patient (eg, HIV). Lesions are hyperkeratotic and crusted, covering large areas, and are associated with very high mite burden. Associated scalp lesions and nail dystrophy are also seen. Crusted scabies carries a high risk for superinfection with *S aureus*.



## Cutaneous Reaction Patterns

### ERYTHEMA NODOSUM

Erythema nodosum is an immunologic reaction in the panniculus (fat) triggered by infection, medications, and benign and malignant systemic diseases. The cause is often undetermined. Table 5.2 lists associated conditions.

- Symptoms/Exam:** Look for erythematous, tender nodules that are most commonly located on the anterior shins. May see fever, malaise, and arthralgias. Biopsy is **not indicated** for erythema nodosum.
- Management:** Spontaneous resolution is seen in 3 to 6 weeks without scarring. Anti-inflammatories may be used as adjuncts: NSAIDs, prednisone.

**FIGURE 5.21. Scabies mite on skin scraping.** Microscopic examination of a mineral oil preparation after scraping a burrow reveals *S scabiei* or “itch mite.” (Source: CDC Public Health Image Library; content provider Reed & Carnick Pharmaceuticals.)

### KEY FACT

Consider erythema nodosum in a patient with painful red nodules on the anterior shins and evaluate for the underlying cause.

TABLE 5.2. Cutaneous Reaction Patterns and Their Associated Conditions

REACTION PATTERN	DEFINITION	SIGNS AND SYMPTOMS	ASSOCIATED CONDITIONS
Erythema nodosum	Inflammatory/immunologic reaction pattern of the subcutaneous fat	<b>Tender bumps on the anterior shins</b> Appear as red, ill-defined erythematous lesions, but palpated as deep-seated nodules Fever, malaise, arthralgias (50%)	<b>Infection:</b> <ul style="list-style-type: none"><li>Streptococcal</li><li>TB</li><li>Coccidioidomycosis</li><li>Other bacteria, fungi, viruses</li></ul> <b>Medication use:</b> <ul style="list-style-type: none"><li>Sulfonamides</li><li>OCPs</li></ul> <b>Other:</b> <ul style="list-style-type: none"><li>Sarcoidosis (Löfgren syndrome)</li><li>Ulcerative colitis &gt; Crohn disease</li><li>Leukemia</li><li>Behçet disease</li></ul>
Erythema multiforme	Reaction pattern of dermal blood vessels and 2° epidermal changes	<b>Target lesion</b> (Figure 5.22): <ul style="list-style-type: none"><li>Palms and soles, face, genitals</li><li>Bilateral, symmetric</li></ul> <b>EM minor:</b> <ul style="list-style-type: none"><li>Little or no mucous membrane involvement</li><li>No systemic symptoms</li></ul> <b>EM major:</b> <ul style="list-style-type: none"><li>⊕ Nikolsky sign</li><li>Systemic (pulmonary, eyes and other mucous membranes prominently involved)</li></ul>	<b>Recurrent EM minor:</b> <ul style="list-style-type: none"><li>HSV (the cause in 90% of cases)</li></ul> <b>EM major:</b> <ul style="list-style-type: none"><li>Medication use (sulfonamides, NSAIDs, anticonvulsants [phenytoin])</li><li>Mycoplasma pneumoniae</li></ul> <b>Idiopathic: 50%</b>

## ERYTHEMA MULTIFORME

### KEY FACT

Infections are responsible for >90% of EM. HSV is the most common infectious cause.



**FIGURE 5.22. Erythema multiforme.**

Target lesions on the palms. (Reproduced with permission from Goldsmith LA, et al. *Fitzpatrick's Dermatology in General Medicine*, 8th ed. New York: McGraw-Hill Education, 2012, Fig. 38-2.)

### KEY FACT

Consider EM in a patient with target lesions on the palms or soles, and examine the patient for bullae, eye involvement, and mucous membrane involvement, all of which would indicate EM major.

### Symptoms/Exam

- Target lesions present with a dusky-purple central zone (or, later, with a crust, blister, or erosion) with an outer concentric red zone (Figure 5.22).
- Symmetric and bilateral involvement of the **palms**, **soles**, face, and genitalia is seen.
- Subtypes can be further distinguished as follows:
  - **EM minor:** No mucosal involvement; no systemic symptoms.
  - **EM major:** May have bullae; involves mucosal surfaces; may involve eyes and lungs. May have systemic symptoms (fever, malaise, myalgias), especially with increasing mucosal involvement.

### Management

- **EM minor:** Self-limited; consider acyclovir prophylaxis for recurrent episodes.
- **EM major:** Patient may require hospitalization if unable to tolerate oral intake secondary to pain from mucosal involvement.

## URTICARIAL VASCULITIS

**Urticarial vasculitis** is a form of leukocytoclastic vasculitis often limited to the skin. Most cases are idiopathic, but the condition can also be medication induced, related to rheumatic diseases such as SLE, or caused by viral infection.

Individual lesions that persist for >24 hours suggest urticarial vasculitis and require a biopsy.

Treatment is dictated by the underlying cause; if no cause can be identified, a trial of anti-inflammatory or immunomodulating medications is indicated.

See the Allergy and Immunology chapter for more on urticaria.

## BLISTERING DISORDERS

### KEY FACT

Think of bullous pemphigoid in an elderly, hospitalized patient who has an itchy rash, as bullous pemphigoid can present with intense itch or urticarial rash before bullae develop.

**Bullous pemphigoid** and **pemphigus vulgaris** are **autoimmune blistering disorders** of the skin and mucous membranes resulting from the loss of cell-to-cell adhesion (Figures 5.23 and 5.24).

The differential of blistering disorders is quite large and includes hereditary disorders, such as epidermolysis bullosa. **Bullous pemphigoid** and **pemphigus vulgaris** are diagnosed by skin biopsy and direct immunofluorescence. Table 5.3 distinguishes these disorders in terms of their clinical presentation.

Treatment is with topical high-potency corticosteroids for localized disease; prednisone ± other immunosuppressants for diffuse disease.



A



B

**FIGURE 5.23. Bullous pemphigoid.** (A) Bullae with serous fluid are seen in a 91-year-old woman with a 6-month history of lesions on the extensor surfaces of the extremities. Findings on skin biopsy and direct immunofluorescence consistent with bullous pemphigoid. (B) Tense bullae and urticarial plaques in a 77-year-old woman with a 1-month history of pruritic urticarial lesions. (Images reproduced with permission from USMLE-Rx.com.)



**FIGURE 5.24. Pemphigus vulgaris.** Patient with pemphigus vulgaris has extensive blistering on trunk and mouth. Because of the fragility of the blisters, pemphigus vulgaris presents as erosions. (Used with permission from Deyanira Pacheco-Tovar, et al. Image copyright © 2011.)

## Cutaneous Drug Reactions

In the hospital, two-thirds of all cutaneous reactions are due to penicillins/β-lactams, sulfonamides, and blood products. In ambulatory settings, antibiotics, NSAIDs,

**TABLE 5.3. Bullous Pemphigoid Versus Pemphigus Vulgaris**

	BULLOUS PEMPHIGOID (BP)	PEMPHIGUS VULGARIS
Site of blistering	Subepidermal	Intraepidermal
Epidemiology	Age >60 The most common autoimmune blistering disease	Age 40-60
Pruritus	Severe	Not prominent
Nikolsky sign (superficial separation of skin with pressure)	⊖	⊕
Oral mucosal lesions	Minority (<30%)	Majority (>50%)
Blisters and bullae	Intact, tense (see Figure 5.23)	Rupture easily; flaccid (see Figure 5.24)—often so fragile that you do not find intact vesicles, only erosions/crusting/mouth sores
Subtypes	None	Drug induced (penicillamine and ACEIs), paraneoplastic
Ancillary diagnostic tests	BP antigen 1, BP antigen 2	Look for serum <b>anti-desmosomal antibodies</b>



### QUESTION

A 20-year-old woman has episodes of large, raised red welts and intense itching all over her body that last for 48 hours and then disappear. She has had about three such episodes a week for the past 2 months with no obvious trigger and has derived no relief from hydroxyzine and fexofenadine. Her temperature is 37.9°C (100.3°F), and exam reveals discrete, dark wheal-and-flare lesions consistent with urticaria on both arms and legs and on her trunk and back. Some lesions look like purpura. UA shows erythrocytes and erythrocyte casts. What measure will most likely establish the diagnosis?

**KEY FACT**

There are multiple causes of **photosensitivity rashes** including SLE, dermatomyositis, medications (ie, retinoids), and porphyrias.

**MNEMONIC**

**SANTA** (*medications that cause SJS*)

**S**ulfa drugs

**A**llopurinol

**N**SAIDs

**T**etracyclines

**A**nticonvulsants (eg, carbamazepine)

**ANSWER**

Urticaria that does not respond to usual treatment should prompt a workup for urticarial vasculitis, with ESR, CBC, ANA, complement, and skin biopsy from the edge of a wheal. Histopathologic evidence of vascular damage, nuclear debris, or erythrocyte extravasation is diagnostic.

and **anticonvulsants** are the most common culprits. The most frequent drug eruptions are:

- **Morbilliform** (30%-50% of cases).
- **Fixed.**
- **Urticaria ± angioedema.**

See Tables 5.4 and 5.5 and Figures 5.25 and 5.26 for the pathophysiology and clinical patterns of various drug eruptions.

**Diagnosis**

- Clinical features favoring medication as a cause of skin reactions include the following:
  - Previous experience with a given drug.
  - Lack of alternative explanations (eg, worsening of preexisting disease, infection).
  - **Timing:** Most typical morbilliform drug reactions occur **within 2 weeks**. **Drug reaction with eosinophilia and systemic symptoms (DRESS)** may be delayed up to 8 weeks.
  - **Discontinuation:** Reaction should abate within 3 weeks.
  - **Rechallenge:** Allows for a definitive diagnosis, although usually impractical and contraindicated if there is a severe reaction like DRESS, SJS, TEN.
- Consider drug levels for dose-dependent reactions. Skin biopsy is occasionally helpful in determining the reaction pattern but cannot identify the specific agent. **Peripheral eosinophilia** is suggestive of drug sensitivity.

**TABLE 5.4. Nonimmunologic Drug Reactions**

PREDICTABLE	
Side effect	Sedation with antihistamines, chemotherapy-induced alopecia
2° pharmacologic effect	Orthostatic hypotension with a phenothiazine
Drug-drug interaction	Seizure from theophylline while taking erythromycin
Excessive dosing	Headache with antihypertensives, hypoglycemia with sulfonylurea
UNPREDICTABLE	
Drug intolerance	Tinnitus with aspirin
Pseudoallergic reaction	Direct release of mast cell mediators by opiates, vancomycin, radiocontrast media
Idiosyncratic reaction	Anemia (hemolysis) by antioxidant drugs (G6PD deficiency)
CHRONIC REACTIONS	
Drug overdose	Unconsciousness and respiratory depression from opioids, alcohol, barbiturates
Drug toxicity	Hepatotoxicity from methotrexate

TABLE 5.5. Clinical Features of Severe Cutaneous Reactions Often Induced by Drugs

DIAGNOSIS	TYPICAL SKIN LESIONS	COMMON SIGNS AND SYMPTOMS	OTHER CAUSES NOT RELATED TO MEDICATIONS	DRUGS MOST OFTEN IMPLICATED
Stevens-Johnson syndrome	Small blisters on dusky purpuric macules or atypical targets (see Figure 5.25)  Rare areas of confluence. Detachment of $\leq 10\%$ of body surface area $>90\%$ have mucous membrane involvement	Some 10% to 30% present with fever	<i>Mycoplasma</i> or HSV (rare)	NSAIDs, sulfa drugs, antiepileptics (phenytoin, carbamazepine), penicillin, allopurinol
Toxic epidermal necrolysis	Individual lesions are like those seen in SJS (see Figure 5.26)	Fever is nearly universal. "Acute skin failure"; leukopenia.  Confluent erythema The outer layer of the epidermis readily separates from the basal layer with lateral pressure <b>(Nikolsky sign)</b>  Large sheets of necrotic epidermis  Detachment of $>30\%$ of body surface area	Viral infections, immunization, chemicals, <i>Mycoplasma</i> pneumonia	Same as above
Drug reaction with eosinophilia and systemic symptoms	Severe exanthem (may become purpuric)  Exfoliative dermatitis	Fever, lymphadenopathy, <b>hepatitis, nephritis, and eosinophilia</b>	Viral reactivation (HHV-6/HHV-7, CMV, EBV)	Aromatic anticonvulsants, allopurinol, sulfonamides, abacavir, antibiotics
Acute generalized pustulosis	Rapid development of many pinpoint nonfollicular pustules on a background of erythema	Fever is a near constant feature, neutrophilia	Drug is the cause in 90%, others = viral infection, mercury ingestion	Antibiotics (macrolides, penicillins, cephalosporins)
Anticoagulant-induced necrosis	Purpura and necrosis	Pain in affected areas	DIC	Warfarin, especially in the setting of low protein C or S
Angioedema	Urticaria or swelling of the central part of the face	Respiratory distress, cardiovascular collapse	Insect stings, foods	NSAIDs, ACE inhibitors, penicillin

(Adapted with permission from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 323.)



**FIGURE 5.25.** **Stevens-Johnson syndrome.** Ulcers and hemorrhagic erosions on the trunk and face; they begin as a generalized eruption of target-like lesions that becomes confluent, erythematous, and bullous. (Source: Balasundaram S, et al. Oral lesions associated with nevirapine-related Stevens Johnson syndrome: A report of four cases. *J Oral Maxillofac Pathol*. 2011;15(1):39-45.)

### MNEMONIC

**MMRISK (malignant melanoma risk)**

- Moles: atypical
- Moles: total number >50
- Red hair and freckling
- Inability to tan: skin phototypes I and II
- Severe sunburn, especially in childhood or history of tanning bed use
- Kindred: first-degree relative

### MNEMONIC

**ABCDEs of Melanoma**

- Asymmetry
- Borders: irregular
- Color: variegated
- Diameter >6 mm
- Evolution: lesion changes over time

### KEY FACT

Patients with numerous atypical nevi (**atypical nevus syndrome or dysplastic nevus syndrome**) and with two first-degree relatives with a history of melanoma have a lifetime risk of melanoma approaching 100%.

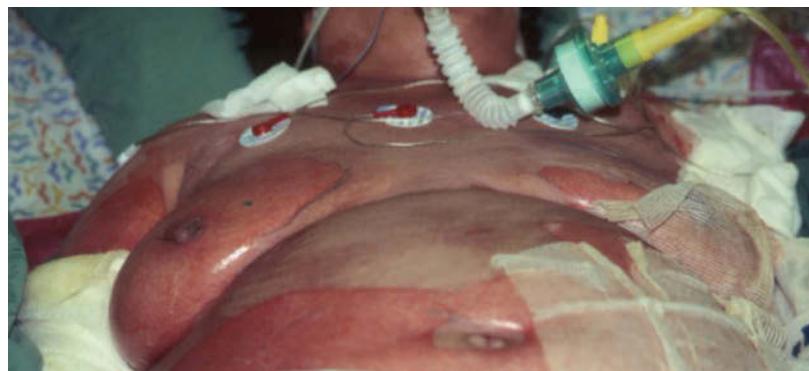
## Cutaneous Oncology

### MELANOMA

Melanoma is a malignancy of melanocytes that may occur on any skin or mucosal surface. It is the **sixth most common cancer** in the United States. Risk factors are expressed in the mnemonic **MMRISK**.

### Symptoms

- Look for a **changing mole** or new evolving pigmented lesion. Use the “**ABCDEs**” mnemonic to help you remember the five characteristics of melanoma (Figure 5.27).
- **Superficial spreading** malignant melanomas are most common (responsible for 70% of all melanomas in white patients), arising on sun-exposed regions of older patients.
- Acral melanoma is the most common type of melanoma in darker-skinned individuals—always check the hands and feet.



**FIGURE 5.26.** **Toxic epidermal necrolysis.** Bulla formation with rapid desquamation affecting bilateral breasts, lower abdomen, and anteromedial aspect of the right arm. The central anterior trunk is not affected. (Source: Cohen S, et al. Ceftriaxone-induced toxic epidermal necrolysis mimicking burn injury: a case report. *J Med Case Rep*. 2009;3:9323.)

## Exam

Physical findings are expressed in the ABCDEs mnemonic.

## Diagnosis

- Lesions suspicious for melanoma may need an **excisional biopsy** depending on size. Tumor thickness and lymph node status are the most important prognostic factors. Melanomas <1.0 mm in thickness are considered **lower risk**, and **staging workup is typically not indicated in these cases**. Regional spread is stage III and metastasis is stage IV.
- Additional significant prognostic indicators include site, specific histologic features, gender (men are at higher risk than women).

## Management

- Wide excision with appropriate margins. **Sentinel lymph node biopsy** is recommended for malignant melanomas >0.75- to 1.0-mm thick and is also essential in medical decision making with regard to adjuvant therapy.
- Adjuvant options include chemotherapy, immunotherapy (interferon- $\alpha$ , ipilimumab, PD-1 inhibitors), and targeted therapies.
- Benefit of targeted therapies depends on mitogen-activated protein mutation status: BRAF V600E and BRAF V600K mutants responsive to BRAF inhibitors (dabrafenib and vemurafenib) and MEK inhibitor (trametinib).

## Complications

Metastasis usually occurs in the following sequence: local recurrence, regional lymph nodes, distant metastasis (liver, lung, bone, brain). Five-year survival rates with lymph node involvement and distant metastasis are 30% and 10%, respectively.

## BASAL CELL CARCINOMA

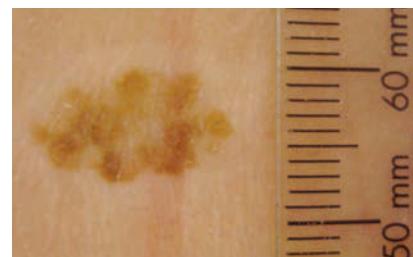
Basal cell carcinoma represents 80% of all skin cancers. The mean age at diagnosis is 62 years.

- Symptoms/Exam:** Lesions occur in sun-exposed areas:
  - Head and neck:** Presents with papules or nodules with **telangiectasia** and a “pearly” or translucent quality. A central erosion or crust (noduloulcerative type) is often seen (Figure 5.28).
  - Chest, back, and extremities:** A scaly erythematous plaque (superficial type) is seen that may resemble a plaque of eczema.
- Diagnosis:** Via shave biopsy.
- Management:** Surgical removal; type of surgery depends on the individual tumor and on patient characteristics. Sun avoidance and patient education are key components of management.
- Complications:** Metastatic spread is uncommon (<0.1%) but may be **locally invasive** and destructive.

## SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma represents 20% of all skin cancers; typically affects patients >55 years of age. SCC in situ, also known as Bowen disease, is confined to the epidermis (Figure 5.29); invasive SCC invades into the dermis.

- Symptoms/Exam:** SCCs may arise within **actinic keratoses**, scars/chronic wounds, or within HPV-induced lesions. Keratoacanthomas are considered by many to be low-grade SCCs—these rapidly appear and then involute and have a distinctive crater-like appearance.
- Diagnosis:** Skin biopsy.



**FIGURE 5.27. Melanoma.** This asymptomatic 7- × 10-mm irregularly brown-pigmented asymmetrical patch with scalloped borders, central hypopigmentation, and a hypopigmented halo was noted on the lower back of an 83-year-old man during a routine physical exam. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

Advanced cutaneous melanomas should be tested for **BRAF V600 mutation** status. Tumors containing this mutation may be treated with targeted therapy using dabrafenib or vemurafenib.



**FIGURE 5.28. Basal cell carcinoma.** Typically presents as shiny or “pearly” nodule with umbilicated center and telangiectasia. BCC grows slowly in contrast to rapid, more aggressive growth of SCC. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 5.29. Squamous cell carcinoma.** Ulcerative lesion on the tip of the nose in a patient with sun-damaged skin. More common in immunosuppressed or transplant patients. (Source: National Cancer Institute.)

**KEY FACT**

Avoiding direct sunlight, especially during peak hours, is associated with a ↓ risk of non-melanoma skin cancers and malignant melanoma.



**FIGURE 5.30. Cutaneous T-cell lymphoma.** Multiple pruritic erythematous plaques with fine scale ranging in size from 1 cm to 10 cm and involving the sacral region, left lateral thigh, abdomen, and axillary vaults. Skin biopsy demonstrated a lymphocytic infiltrate with atypical cells supporting a diagnosis of CTCL. (Reproduced with permission from USMLE-Rx.com.)

- **Management:** For invasive disease, primarily **surgical**. Prevention with sun avoidance and patient education are key components of disease management.
- **Complications:** Overall 5-year recurrence and metastatic rates are 8% and 5%, respectively.

**CUTANEOUS T-CELL LYMPHOMA**

Also known as **mycosis fungoides**, CTCL is an indolent malignancy of mature CD4 helper T lymphocytes. Average age of onset is 50 years (range 5-70); men are affected twice as often as women. CTCL is divided into patch, plaque, and tumor stages (Figure 5.30).

- **Symptoms/Exam:** Presents with scaly, **pruritic**, erythematous patches and plaques most commonly located in a “bathing trunk” distribution.
- **Management:** Treat patch/plaque stages with topical corticosteroids, UV light, MTX, or nitrogen mustard; systemic therapy is used for nonresponsive or more advanced disease.
- **Complications:** Look for **Sézary syndrome**—rare leukemic form of CTCL characterized by erythroderma, lymphadenopathy, and circulating **Sézary cells**. Without therapy, its course is progressive, and patients succumb to opportunistic infections.

**Dermatologic Manifestations of Systemic Disease****CARDIOVASCULAR****Infective Endocarditis**

Classic dermatologic findings associated with infective endocarditis are outlined in Table 5.6. Other extracardiac manifestations include Roth spots (oval retinal hemorrhages with a clear, pale center) and peripheral emboli.

**Livedo Reticularis**

Livedo reticularis is the obstruction of arteriolar flow from vasospasm, obstruction, hyperviscosity, or obstruction of venous outflow. May be idiopathic, but key significance of this skin finding is to consider underlying 2° etiologies:

- Atheroemboli (postangiography/post-cardiac catheterization) and cholesterol emboli syndrome (see the Nephrology and Rheumatology chapters).
- Antiphospholipid antibody syndrome
- SLE
- Cryoglobulins

**KEY FACT**

Livedo reticularis is a clinical reaction pattern resulting from vascular obstruction or hyperviscosity. Look for associated cholesterol emboli, cryoglobulinemia, or antiphospholipid antibody syndrome.

**KEY FACT**

A + test for RF is often seen in cryoglobulinemia.

**TABLE 5.6. Classic Dermatologic Manifestations of Infective Endocarditis**

CLINICAL FINDINGS	CHARACTERISTICS
Clubbing	Sign of long-standing disease
Janeway lesions	Small, slightly papular red/violaceous hemorrhages on the palmar and plantar surfaces (Figure 5.31A) Most commonly seen in acute endocarditis
Osler nodes	Small, <b>tender</b> violaceous papules on the pads of the digits due to immune complex deposition ( <b>Osler = Ouch</b> ) (Figure 5.31B)
Petechiae or purpura	Emolic or vasculitic
Splinter hemorrhages	Subungual, dark red linear macules (Figure 5.32)



A



B

**FIGURE 5.31. Cutaneous manifestations of infective endocarditis.** (A) Janeway lesions.

Note the hemorrhagic, infarcted papules on the volar fingers in a patient with *S aureus* endocarditis. (B) Osler nodes (arrows). (Image A reproduced with permission from Wolff K, Johnson RA.

*Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill, 2009, Fig. 24-46. Image B reproduced with permission from Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill, 2008, Fig. 151-11.)

- Medications (eg, prednisone, amantadine, epinephrine)
- Other hypercoagulable states and vasculitides
- **Symptoms/Exam:** Look for livedo in the extremities, especially after cold exposure. Presents with a mottled or **netlike reddish-blue to purple** (livid) discoloredation of the skin (Figure 5.33).
- **Diagnosis:** Test for underlying disease with coagulation studies, ANA, RF, antiphospholipid antibodies, and cryoglobulins.
- **Management:** Treat the underlying disease. Pentoxifylline 400 mg PO TID and low-dose ASA may be helpful.

### GASTROINTESTINAL

Table 5.7 outlines the dermatologic manifestations of common GI disorders.

**FIGURE 5.33. Livedo reticularis.** Reaction pattern resulting from vascular obstruction or hyperviscosity. (Reproduced with permission from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 19th ed. New York: McGraw-Hill Education, 2015, Fig. 302-3C.)**FIGURE 5.32. Splinter hemorrhage.**

A subungual hemorrhage in the midportion of the fingernail bed is seen in a woman with endocarditis. These may also be seen in cholesterol emboli or following nail trauma. (Reproduced with permission from USMLE-Rx.com.)



### QUESTION 1

A 65-year-old woman presents with abdominal pain, myalgias, nausea, generalized weakness, and acute kidney injury; creatinine level, 5 mg/dL (baseline, 1.2 mg/dL). A week earlier, she was hospitalized for chest pain and had cardiac catheterization with stent placement. Exam reveals low-grade fever (37.8°C [100°F]), left carotid bruit, nonpalpable distal pulses with left great toe cool and cyanotic, pretibial edema, and netlike violaceous rash over her legs. Leukocyte count is 7000/µL with 60% neutrophils, 30% lymphocytes, and 10% eosinophils; low C3 and normal C4 level; UA shows 1+ blood, 5 to 10 erythrocytes/hpf, 1+ protein, and 3 to 5 leukocytes/hpf. What is the most likely diagnosis?



### QUESTION 2

A 45-year-old man, former IV drug user, has had palpable purpura on his lower extremities for several months. Lab results are: AST, 70 U/L; ALT, 90 U/L; alkaline phosphatase, 80 U/L;  $\oplus$  anti-HCV antibody;  $\oplus$  anti-HBs antibody; and  $\ominus$  HBsAg. What diagnostic test should be done next?

TABLE 5.7. Dermatologic Manifestations of GI Disorders

DISORDER	ETIOLOGY	SKIN MANIFESTATIONS	MOST COMMON DISEASE ASSOCIATIONS
Porphyria cutanea tarda	↓ activity of uroporphyrinogen decarboxylase, an enzyme in the heme biosynthetic pathway May be inherited or acquired	<b>Painless</b> vesicles and bullae on the face and dorsa of the hands ( <b>light-exposed areas</b> ) Facial hypertrichosis	HCV (85%) <b>Medications:</b> NSAIDs, estrogens, tetracyclines
Cryoglobulinemia	Cryoglobulins are immunoglobulins that precipitate on cold exposure, causing vessel occlusion or immune complex vasculitis	Palpable purpura, livedo reticularis	HCV; lymphoproliferative disorders (lymphoma, myeloma)
Lichen planus	Idiopathic	Flat-topped purple, polygonal, pruritic papules (Figure 5.34). Affect the flexor wrist, lumbar region, shins, and penis. Mucous membrane lesions are found in 40% to 50% of cases	<b>Chronic HBV and HCV;</b> 1° biliary cirrhosis <b>Medications:</b> Streptomycin, tetracycline, NSAIDs, HCTZ, antimalarials
Dermatitis herpetiformis	Likely immune complexes of IgA and epidermal tissue transglutaminase The cutaneous manifestation of gluten sensitivity	<b>Extremely pruritic</b> , grouped vesicles symmetrically distributed over the elbows, forearms, back, buttocks, and knees (Figure 5.35)	<b>Gluten-sensitive enteropathy; celiac disease</b> ↑ risk of GI lymphoma, always treat with a gluten-free diet even in the absence of symptoms to reduce risk
Pyoderma gangrenosum	Unknown; an underlying immunologic abnormality is favored	Painful, rapidly advancing deep ulcer (Figure 5.36)	<b>Ulcerative colitis &gt; Crohn disease</b>

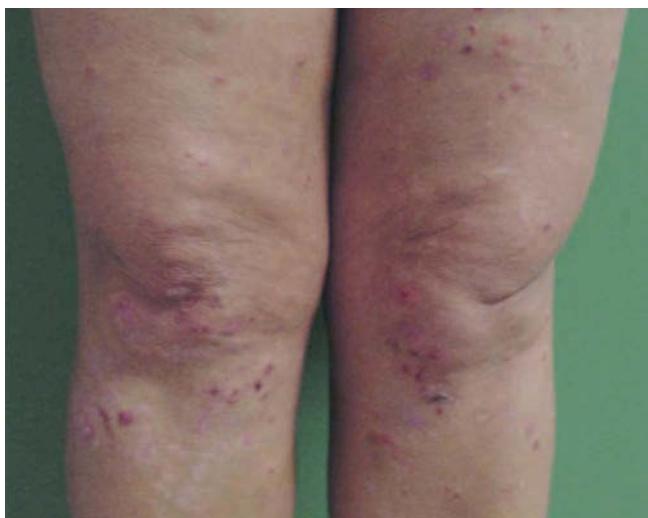
**A****ANSWER 1**

**Cholesterol emboli syndrome** is a rare sequela of recent cardiac catheterization and can mimic vasculitis. It results in acute renal failure, lower extremity livedo reticularis, cyanotic toes, low C3 levels, and peripheral **eosinophilia**.

**A****ANSWER 2**

Serum cryoglobulins to test for cryoglobulinemia associated with HCV. Palpable purpura is characteristic of vasculitis. Although porphyria cutanea tarda is also associated with HCV, its lesions are characterized by plaques in sun-exposed areas (eg, dorsa of hands).

**FIGURE 5.34.** **Lichen planus.** Numerous pruritic, polygonal, purple flat-topped papules with reticulate white lacy lines (Wickham striae) on the extremities of a 42-year-old African American woman with HIV and HCV infection. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 5.35. Dermatitis herpetiformis.** The classic early lesions include papules, urticarial plaques, small grouped vesicles, and crusts over the extensor surfaces. (Source: Rocha Mendes FB, et al. Review: dermatitis herpetiformis. *An Bras Dermatol*. 2013;88(4):594-599. Image copyright ©2013 by Anais Brasileiros de Dermatologia.)

#### ENDOCRINE AND METABOLIC

Common dermatologic manifestations of endocrine and metabolic disorders include the following:

- Acanthosis nigricans affects the axillae, groin, and neck (Figure 5.37):
  - Insulin resistance: DM, obesity, Cushing disease.
  - Medications: Nicotinic acid, glucocorticoid therapy, OCPs, growth hormone therapy.
  - Paraneoplastic: Gastric adenocarcinoma.
- Necrobiosis lipoidica affects the lower legs, >80% pretibial (Figure 5.38): DM.



**FIGURE 5.38. Necrobiosis lipoidica diabetorum.** (A) A large, symmetric plaque with active tan-pink, well-demarcated, raised, firm border and a yellow center in the pretibial region of a 28-year-old diabetic woman. The central parts of the lesion are depressed with atrophic changes of epidermal thinning and telangiectasia against a yellow background. (B) Same lesion several months later showing progression with a granulomatous, more elevated and reddish border. (Image A reproduced with permission from Wolff K, et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill Education, 2009, Fig. 15-6. Image B reproduced with permission from Wolff K, et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 7th ed. New York: McGraw-Hill Education, 2013, Fig. 15-7.)



**FIGURE 5.36. Pyoderma gangrenosum.** Foul-smelling, nonhealing, punched-out ulceration with rolled borders and 1 to 3 cm of peripheral erythema involving the left medial malleolar region of a 43-year-old man with rheumatoid arthritis. The base of the ulcer is 50% covered with beefy red tissue and a yellow fibrinous exudate with exposed tendon, but there is no frank purulent discharge. Skin biopsy demonstrated diffuse neutrophilic infiltrate consistent with pyoderma gangrenosum. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 5.37. Acanthosis nigricans.** Note the velvety, dark brown hyperpigmentation on the posterior neck of this 40-year-old man with type 2 DM. (Reproduced with permission from USMLE-Rx.com.)



#### QUESTION

A 40-year-old woman has 2-year history of progressive fatigue but no other symptoms. Exam reveals xanthomas on extensor surfaces and mild hepatomegaly. Lab results include normal CBC, AST, and ALT; alkaline phosphatase, 600 U/L; and total bilirubin, 3.2 mg/dL. What study would help establish the diagnosis?

- Xanthoma (crops of small, discrete, dome-shaped, yellow-orange papules) affects the eyelids and tendons—classically involving the Achilles tendon: Hyperlipidemia; familial combined hypertriglyceridemia (triglyceride level  $>1000 \text{ mg/dL}$ ); 1° biliary cirrhosis.
- Hyperpigmentation (generalized with predominance on sun-exposed areas, palmar creases, and areas with chronic pressure): Addison disease.

### KEY FACT

Calciphylaxis should be considered in a poorly compliant hemodialysis patient who has an elevated calcium-phosphorus product and presents with skin ulcerations.



**FIGURE 5.39. Calciphylaxis.** This peritoneal dialysis patient was on chronic warfarin therapy for atrial fibrillation. She noticed a small painful nodule on the abdomen that was followed by progressive skin necrosis and ulceration of the anterior abdominal wall. She was treated with hyperbaric oxygen, intravenous thiosulfate, and discontinuation of warfarin, with slow resolution of the ulceration. (Reproduced with permission from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 19th ed. New York: McGraw-Hill Education, 2015, Fig. 335-5.)

### RENAL

Cutaneous signs associated with end-stage renal disease (ESRD) are:

- **Nephrogenic systemic fibrosis:** A complication usually seen 2 to 4 weeks after exposure to gadolinium contrast (eg, from MRI) in patients with ESRD. Presents as a scleroderma-like, progressive skin hardening that leads to marked reduction in quality of life and mobility and occasionally causes fibrosis of visceral organs.
- **Calcinosis cutis:** Calcified subcutaneous nodules or masses that are painless and do not ulcerate.
- **Calciphylaxis:** Calcific uremic arteriolopathy. Progressive calcification of vessels leads to ischemic necrosis of surrounding skin and soft tissues. Lesions present as painful violaceous nodules on the trunk, proximal extremities, and buttocks (Figure 5.39). Risk factors include use of **warfarin**, vitamin D analogs, or calcium-based phosphate binders; an elevated calcium-phosphorus product ( $>55 \text{ mg}^2/\text{dL}^2$  increases risk); protein S or C deficiency; obesity; and female gender. Treatment includes sodium thiosulfate.

### HEMATOLOGIC

Table 5.8 outlines the dermatologic manifestations of hematologic disorders.

#### Sweet Syndrome

Sweet syndrome is a **neutrophilic dermatosis** that can be divided into five subgroups based on etiology/association: paraneoplastic (most commonly associated with **acute myeloid leukemia** and lymphomas), drug induced, pregnancy related, associated with inflammatory or autoimmune disorders (eg, IBD), and idiopathic.

**TABLE 5.8. Dermatologic Manifestations of Hematologic Disease**

DISORDER	SKIN MANIFESTATIONS	MOST COMMON DISEASE ASSOCIATIONS
1° Immunoglobulin light chain (AL) amyloidosis	Blood vessel fragility leads to "raccoon eyes" and "pinch purpura" (purpura due to mild trauma) Macroglossia	Multiple myeloma, Waldenström macroglobulinemia
Mastocytosis	Solitary mastocytoma or generalized urticaria A $\oplus$ Darier sign (pruritus and wheal) is elicited by stroking	Lymphoma, leukemia

### A

### ANSWER

Antimitochondrial antibody titer. Titers of  $>1:40$  occur in  $>90\%$  of patients with 1° biliary cirrhosis. Up to 80% of patients report fatigue. Xanthomas and an elevated serum alkaline phosphatase level are also characteristic.

Differential diagnosis includes leukemia cutis and infection.

- **Diagnosis:** Requires two major and two minor criteria:

- **Major:**

1. Abrupt onset of tender, erythematous plaques. Lesions are often described as “pseudovesicular” in that they look like vesicles or bullae but are firm on palpation.
2. Histopathology consistent with Sweet syndrome (dense neutrophilic infiltrate).

- **Minor:**

1. Fever and constitutional symptoms.
2. Leukocytosis.
3. Preceded by associated infection (eg, streptococcal or yersiniosis) or associated with malignancy, inflammatory disorders, or pregnancy.
4. Excellent response to corticosteroids.

- **Management:** First-line is systemic corticosteroids. Alternative treatments are dapsone, colchicine, and potassium iodide.


**KEY FACT**

If a patient with acute myeloid leukemia or an autoimmune disorder (eg, RA) abruptly develops tender red plaques associated with fevers and an ↑ WBC count, consider Sweet syndrome. Biopsy demonstrates an abundance of polymorphonuclear leukocytes, and the condition responds well to corticosteroids.

**ONCOLOGIC**

### Post-transplant Skin Malignancy

SCCs are more common than BCCs in post-transplant patients.


**KEY FACT**

Transplant recipients should be regularly examined for skin cancers because they are at higher risk.

### Paraneoplastic Disease

Table 5.9 outlines the dermatologic manifestations of common paraneoplastic disorders.

**TABLE 5.9. Dermatologic Manifestations of Neoplastic Disease**

DISORDER	SKIN MANIFESTATIONS	COMMONLY ASSOCIATED MALIGNANCY
Glucagonoma	Necrolytic migratory erythema, glossitis, angular cheilitis	Glucagon-secreting tumors of the pancreas
Dermatomyositis	Heliotrope rash, Gottron papules (violaceous papules overlying the finger joints), photodistributed eruption	<b>Ovarian cancer;</b> other solid tumors
Extramammary Paget disease	Erythematous plaques with scales, erosion, and exudate Affects the anogenital region	Underlying vulvar or penile adenocarcinomas and regional internal malignancies
Leukocytoclastic vasculitis	Small vessel vasculitis; palpable purpura	Lymphoproliferative neoplasms; solid tumors; of note, there are many nonparaneoplastic causes
Sign of Leser-Trélat	Abrupt eruption of numerous pruritic seborrheic keratoses	<b>Adenocarcinomas (60%), especially gastric</b>
Acanthosis nigricans (see Figure 5.37)	Thickened, velvety, hyperpigmented plaques; may occur extensively and in unusual areas (ie, palms) in contrast to its manifestation in type 2 DM (eg, axilla and neck)	<b>Gastric</b>
Tripe palm	Variant of acanthosis nigricans with velvety thickening of palms and ridged appearance; named after ruminant gut lining	<b>Gastric or lung</b>
Sweet syndrome	Tender, erythematous, well-demarcated papules and plaques typically appearing on face, neck, upper extremities	<b>Myelogenous leukemia;</b> 20% of Sweet syndrome is malignancy-related

**HIV DISEASE**

In HIV-infected patients, **seborrheic dermatitis** is one of the **most common** cutaneous conditions (see Figure 5.4), usually developing early and increasing in severity with decreasing CD4 counts. Common mucocutaneous findings and skin disorders associated with HIV are outlined in Tables 5.10 and Figures 5.40, 5.41, and 5.42.

**KEY FACT**

More than 90% of patients with pulmonary KS will have mucocutaneous KS. Inspect the skin and hard palate carefully!

**KEY FACT**

A new violaceous skin lesion in a patient with HIV is either KS or bacillary angiomatosis.

**KEY FACT**

Cutaneous signs of HIV-associated lipodystrophy should alert the physician to possible associated hyperlipidemia, insulin resistance, type 2 DM, and an ↑ risk of CAD.

**Kaposi Sarcoma**

Kaposi sarcoma is a **vascular** neoplasm linked to infection with **HHV-8**. Often confused with **bacillary angiomatosis**, the skin lesions of *Bartonella* infection. KS almost exclusively affects men who have sex with men.

- **Symptoms/Exam:** Presents with asymptomatic mucocutaneous lesions that may bleed easily or ulcerate and cause pain. Less commonly involves the respiratory tract (nodules or hemoptysis) or the GI tract (GI bleed).
- **Diagnosis:** Skin biopsy of characteristic lesions (Figure 5.43).
- **Management:** First-line treatment is highly active antiretroviral therapy (HAART). KS frequently regresses and sometimes resolves completely when HAART proves successful. Local measures include intralesional chemotherapy, irradiation, laser surgery, and excision.

**HIV-Associated Lipodystrophy**

Lipodystrophy in HIV infection is part of a metabolic syndrome that includes hyperlipidemia, insulin resistance, and type 2 DM. Protease inhibitors are frequently implicated, most commonly **ritonavir/saquinavir**, followed by indinavir, nelfinavir, and the nucleoside analog stavudine. However, lipodystrophy can also occur in HIV-infected patients who are not on protease inhibitors.

- **Symptoms/Exam:** Look for facial and peripheral fat wasting; dorsothoracic fat pad hypertrophy; ↑ abdominal girth (**central adiposity**) secondary to accumulation of intra-abdominal fat.
- **Management:** Treated by modification of HAART regimen. Injection of filler or surgical correction for severe lesions.



**FIGURE 5.40. Oral hairy leukoplakia.** White plaques with vertical corrugations are seen on the inferolateral aspect of the tongue. The lesions are fixed, unlike those of thrush, which can be brushed off with a gauze pad. (Source: CDC Public Health Image Library; content provider CDC/J.S. Greenspan, BDS, University of California, San Francisco; Sol Silverman, Jr., DDS.)

**TABLE 5.10. Correlation Between HIV-Associated Dermatoses and CD4 Cell Counts**

CD4 >200	CD4 <200	CD4 <50
Seborrheic dermatitis	<b>Infection:</b>	<b>Unusual opportunistic infections:</b>
Psoriasis	■ Chronic HSV	■ Chronic HSV
Reactive arthritis	■ Molluscum contagiosum	■ Refractory molluscum contagiosum
Atopic dermatitis	■ Bacillary angiomatosis	■ Chronic VZV
Herpes zoster	■ Systemic fungal infection	■ Atypical mycobacteria
Rosacea	■ Mycobacterial infection	■ Crusted scabies
Oral hairy leukoplakia	■ KS	■ KS
Warts	<b>Inflammatory:</b>	
<i>S. aureus</i> folliculitis	■ Eosinophilic folliculitis	
Mucocutaneous candidiasis	■ Drug reactions	
KS	■ Photodermatitis	
	■ Prurigo nodularis	



**A**                    **B**

**FIGURE 5.41. *Molluscum contagiosum*.** (A) Recurrent crops of umbilicated papules developed on the arms and trunk of a 40-year-old man with AIDS. (B) Close-up view of typical molluscum bumps depicts the classic umbilicated center. (Image A reproduced with permission from USMLE-Rx.com; image B source: Centers for Disease Control and Prevention.)



**FIGURE 5.42. Major aphthous ulcers.** Painful lesions, resembling many other oral ulcerative conditions, are also known as periadenitis mucosa necrotica recurrens and canker sores; their cause remains unknown. (Source: CDC Public Health Image Library; content provider CDC/Robert E. Sumpter.)



**FIGURE 5.43. HIV-associated KS.** Characteristic violaceous plaques on the alar and tip of the nose in an HIV-positive female patient. (Source: Sand M, et al. Cutaneous lesions of the nose. *Head Face Med*. 2010;6:7.)

## Autoimmune Diseases With Prominent Cutaneous Features

Table 5.11 lists the dermatologic manifestations of common autoimmune disorders, including SLE, dermatomyositis, and scleroderma.

## Miscellaneous

### PIGMENTARY DISORDERS

Table 5.12 outlines hyper- and hypopigmentation disorders and their associated conditions.

### VERRUCA AND CONDYLOMA

HPV infection, the most common STI, causes clinical lesions that vary by subtype. More than 150 types of HPV have been identified. Skin manifestations include:

- **Verruca vulgaris**, the common wart (70% of all warts), occurs primarily on the extremities.
- Verruca planae (flat warts) are smoother and flatter than common warts and more often appear on the face.



### QUESTION

A 40-year-old man with HIV (last CD4 count 400/ $\mu$ L; HIV RNA viral load 20,000–30,000 copies/mL) noticed a small, raised, nontender, violaceous lesion on his left arm a month ago. He has never received antiretroviral therapy and has been asymptomatic until now. Labs show no significant change in CD4 count and HIV RNA; normal CBC, chemistry, LFTs, and CXR. Excisional biopsy of lesion shows spindle cells and other features consistent with KS. What is the most appropriate treatment?

TABLE 5.11. Cutaneous Manifestations of Autoimmune Diseases

DISORDER	CUTANEOUS MANIFESTATIONS	SYSTEMIC ASSOCIATIONS
SLE	<b>Acute cutaneous:</b> Malar ("butterfly") rash (Figure 5.44); photodistribution <b>Other:</b> Discoid plaques, periungual telangiectasia, alopecia, lupus panniculitis, painless oral ulcers	See the Rheumatology chapter for details on the diagnosis and management of SLE
Dermatomyositis	Heliotrope rash (a violaceous rash over the eyelids) is nearly pathognomonic Gottron papules (flat-topped violaceous papules) over bony prominences, especially the metacarpophalangeal joints "Shawl sign" (erythema over the upper back and chest)	↑ risk of malignancy (ovary > other solid tumors [breast, lung, stomach, colon, uterus])
Scleroderma	<b>Extremities:</b> Raynaud phenomenon (Figure 5.45), sclerodactyly, periungual telangiectasia, sclerosis, calcinosis <b>Face:</b> Telangiectasia; masklike facies <b>Other:</b> Cutaneous calcification, nailfold capillary changes	See the Rheumatology chapter for a discussion of the systemic manifestations of scleroderma
Morphea (localized scleroderma of unknown etiology)	Asymptomatic depressed very firm plaques, often violaceous and then ivory-colored	Associated with <i>Borrelia burgdorferi</i> infection in Europe only; also occurs post-radiation therapy

- Verruca plantaris (plantar foot warts) can be painful and difficult to treat.
- **Condyloma acuminata**, warts in the genital region (Figure 5.48).
- **Management:** In immunocompetent patients, lesions usually resolve spontaneously over 1 to 2 years. Treatment modalities include mechanical destruction (cryotherapy,

TABLE 5.12. Pigmentary Disorders

HYPERTIGMENTATION	ASSOCIATED CONDITIONS
Pigmented nevi, freckles, lentigines	Peutz-Jeghers syndrome (intestinal polyps with oral mucosa and cutaneous hyperpigmented freckles)
Melasma	Estrogen effect; often seen in pregnancy (mask of pregnancy) and with OCP use
Café-au-lait spots (Figure 5.46), axillary freckling	Neurofibromatosis
HYPOPIGMENTATION	ASSOCIATED CONDITIONS
Vitiligo (melanocytes destroyed) (Figure 5.47)	Hypothyroidism, hyperthyroidism, pernicious anemia, DM, Addison disease
Albinism	The eye and vision are often affected



## ANSWER

Start HAART immediately for KS, an AIDS-related complication. The patient does not have extensive cutaneous or mucosal disease or visceral (lung or GI tract) involvement, so systemic chemotherapy is not needed at this time.



A



B



C



D

**FIGURE 5.44. Skin lesions in SLE.** (A) Typical “malar rash” with red, sharply defined erythema in a “butterfly” pattern on the face; (B) malar rash with interface dermatitis; (C) crusting and interface changes affecting the ear; and (D) generalized lupus rash at both knees. (Source: Chiewchengchol D, et al. Mucocutaneous manifestations in juvenile-onset systemic lupus erythematosus: a review of literature. *Pediatr Rheumatol Online J*. 2015;13:1.)

laser therapy) or stimulation of the immune system (topical imiquimod; application of sensitizing agents).

- **Complications:** Malignant transformation to SCC may occur in certain subtypes. Genital HPV types (types 16 and 18) play an important role in the malignant transformation of benign verrucae into **cervical and anogenital cancer** (see the Oncology chapter). In **immunocompromised** patients, you see ↑ incidence and more widespread disease.

## ERYthroderMA

Erythroderma is a rare, severe, potentially life-threatening disorder presenting with diffuse scaling and erythema involving >90% of body surface area (Figure 5.49). Etiologies include worsening of preexisting condition (ie, psoriasis), drug hypersensitivity reactions, infections (eg, staphylococcal scalded skin syndrome), and malignancies (ie, CTCL). Treatment includes supportive care and addressing underlying cause.



**FIGURE 5.45. Raynaud phenomenon.** Fingertips of a man whose job involved activities in a subzero walk-in freezer. He had episodic fingertip pain with associated discoloration triggered by cold exposure for 3 years until ischemic ulceration and necrosis of left middle finger developed that required surgical intervention. This photo taken 2 months postoperatively shows healing of the digit. (Source: Shah J, et al. Raynaud's Phenomenon. *Eplasty*. 2013;13:e58.)



**FIGURE 5.46. Café-au-lait spot of neurofibromatosis.** Large 7-cm flat café-au-lait macule among many fleshy papulonodules. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 5.47. Vitiligo.** Note the cutaneous depigmentation as a result of loss of melanocytes. (Reproduced with permission from Dr. Richard Usatine.)

**FIGURE 5.48. Condyloma**

**acuminata.** Soft wart-like growths on the penis caused by HPV infection—the most common STI. (Source: CDC Public Health Image Library; content provider CDC/Robert E. Sumpfer.)

**FIGURE 5.49. Erythroderma.**

Papulosquamous plaques with bright red confluent erythema on the arms and trunk of a 64-year-old man developed two weeks after oral intake of an unknown amount of aloe vera leaves taken to enhance well-being. (Source: Okoduwa C, et al. Erythroderma: review of a potentially life-threatening dermatosis. *Indian J Dermatol.* 2009;54(1):1-6.)

## VASCULAR LEG ULCERS

Venous stasis and arterial insufficiency ulcers typically appear in the lower extremities. Table 5.13 contrasts both types of ulcers. See the Geriatric Medicine chapter for further discussion of these lesions.

## NUTRIENT DEFICIENCIES

Nutrient deficiencies are less common in industrialized nations. Specific manifestations of nutrient deficiencies are listed in Table 5.14.

## ALOPECIA

Alopecia is a very common problem with a broad spectrum of causes from age-related to pathologic. Alopecia causes are divided into scarring and nonscarring; can also conceptualize them clinically as focal or diffuse (Table 5.15).

■ **Nonscarring:**

- Androgenetic alopecia (male and female pattern hair loss).
- Alopecia areata: Circular areas of complete alopecia that can be localized or diffuse (Figure 5.50).
- Telogen effluvium: Rapid onset of diffuse hair loss ~ 2 to 3 months after illness, injury, childbirth, stress.
- Anagen effluvium: Toxin-mediated rapid onset of diffuse hair loss ~ 2 weeks after chemotherapy or antimetabolite treatment.
- Trichotillomania due to hair pulling behavior.
- Traction alopecia due to chronic traction of hair from hairstyle.

■ **Scarring:** Neutrophilic versus lymphocytic scarring alopecias—some examples include lupus, lichen planopilaris (redness and scaling around hair shafts with diffuse patches of scarring hair loss), frontal fibrosing alopecia (scarring hair loss of the frontal hairline).

**TABLE 5.13. Key Distinguishing Features of Leg Ulcers Due to Venous Stasis Versus Arterial Insufficiency**

	VENOUS	ARTERIAL
<b>Location</b>	Between ankle and knee	At terminal branches of arteries
<b>Appearance</b>	Ulcer, often among background of hyperpigmentation, edema, and stasis dermatitis	Sharply demarcated ulcer edges
<b>Pain</b>	Mild	Moderate to severe
<b>Other features</b>	Often associated with chronic lower leg edema	May see claudication or absence of posterior tibial and dorsalis pedis pulses Typical CV risk factors present
<b>Management</b>	Elevate legs to reduce edema Compression Wound care	Wound care Measure ankle-brachial index Consider referral to vascular surgery

TABLE 5.14. Key Features of Nutrient Deficiencies

NUTRIENT DEFICIENCY	DERMATOLOGIC MANIFESTATIONS
B <sub>3</sub> (Niacin)—Pellagra	D's: Diarrhea, dementia, and <b>dermatitis</b> ; lesions typically symmetric and in sun-exposed areas
B <sub>6</sub> (pyridoxine)	Look for recent exposure to medications such as <b>isoniazid</b> ; skin manifestations include seborrheic dermatitis-like lesions, intertrigo, angular chelitis, and atrophic glossitis
Vitamin B <sub>12</sub>	Pallor due to accompanying macrocytic (?) anemia plus grey-brown nail discoloration, glossitis, generalized hyperpigmentation
Vitamin A	Hyperkeratosis and xerosis (dry skin); poor night vision
Vitamin C (scurvy)	Perifollicular and gingival hemorrhages and coiled "corkscrew" hairs
Iron	Hair loss, brittle nails, koilonychia (spoon-shaped nails)
Zinc	Dermatitis, xerosis, seborrhea



TABLE 5.15. Causes of Alopecia by Focal Versus Diffuse Distribution

FOCAL ALOPECIA	DIFFUSE ALOPECIA
Nonscarring:	Androgenetic pattern hair loss
Focal alopecia areata (Figure 5.50)	Diffuse alopecia areata (can progress to full loss of hair, alopecia totalis)
Tinea capitis	Telogen effluvium (associated with illness, injury, childbirth, stress)
Trichotillomania	Anagen effluvium (associated with chemotherapy, antimetabolite treatment)
Traction alopecia	
Scarring:	Syphilitic alopecia ("moth-eaten" appearance)
Discoid lupus	

**FIGURE 5.50. Alopecia areata.** Well-demarcated hair loss of the scalp in a 30-year-old woman with generalized anxiety disorder occurred over 2 months. Note the lack of inflammation including no redness or scale. (Reproduced with permission from USMLE-Rx.com.)

## NOTES

## CHAPTER 6

# Endocrinology

Talia R. Kahn, MD, MPH  
Diana Alba, MD

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Disorders of Lipid and Carbohydrate Metabolism	196		
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## Pituitary Disorders

Under hypothalamic regulation, the anterior pituitary produces and releases adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), and prolactin. The posterior pituitary stores and releases antidiuretic hormone (ADH) and oxytocin.

### PITUITARY TUMORS

Microadenomas are <1 cm; macroadenomas are >1 cm. The risk of panhypopituitarism and visual loss ↑ with tumor size.

#### Symptoms/Exam

- Neurologic symptoms: **Headache**; **visual field cuts**, especially “tunnel vision”; **diplopia**. If the cavernous sinus is invaded by tumor, **cranial nerve palsies** may develop.
- Hormonal excess or deficiency: See Tables 6.1 and 6.2.
- Asymptomatic: Pituitary “incidentalomas” are sellar masses (Table 6.3) found in patients who undergo imaging for reasons other than pituitary-related symptoms. Compared to masses <1 cm (microincidentalomas), masses >1 cm (macroincidentalomas) are more likely to cause symptoms at time of discovery, and more likely to grow and cause visual and hormonal disturbances over time.

#### Differential

When found incidentally on imaging studies, the differential for a sellar lesion is broad (Table 6.3).

#### Diagnosis

- Labs: If the history and physical or imaging is suggestive of tumor, check TSH, free T<sub>4</sub>, prolactin, LH, FSH, IGF-1, and testosterone (in men) or estradiol (in women with amenorrhea) to assess for hormonal excess or deficiency based on the patient’s clinical signs and symptoms. To check for adrenal insufficiency (AI), perform an

### KEY FACT

When given LH and FSH levels, make sure they are appropriate for reproductive age of the woman (ie, in postmenopausal woman, LH and FSH should be high).

TABLE 6.1. Pituitary Hormone Excess

HORMONE	INCREASED BY	EXCESS	INITIAL TEST(S)	CONFIRMATORY TEST
ACTH	CRH, stress	Cushing syndrome	24-hour urine free cortisol <i>OR</i> nocturnal salivary cortisol <i>OR</i> overnight low dose dexamethasone test	
TSH	TRH	Hyperthyroidism	TSH, free (or total) thyroxine	
LH/FSH	GnRH		LH/FSH	
GH	GHRH, hypoglycemia, dopamine	Acromegaly	IGF-1	Glucose tolerance test
Prolactin	Pregnancy, nursing, TRH, stress	Galactorrhea, hypogonadism	Prolactin	
ADH	↑ osmolality; hypovolemia	SIADH		Simultaneous serum sodium, urine sodium, and urine osmolality

**TABLE 6.2. Pituitary Hormone Deficiency**

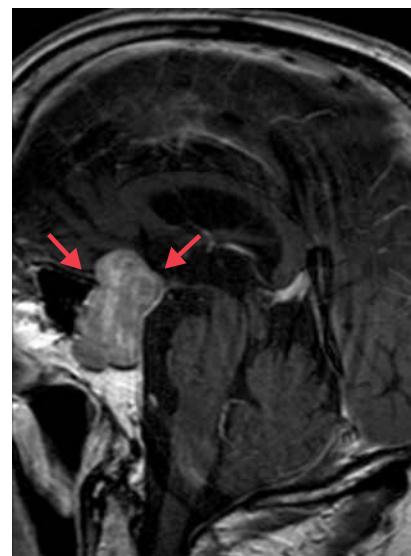
HORMONE	DECREASED BY	DEFICIENCY	INITIAL TEST(S)	CONFIRMATORY TEST
ACTH	High cortisol	Adrenal insufficiency	Simultaneous ACTH, cortisol	Cosyntropin stimulation test
TSH	High $T_4$ and/or $T_3$	Hypothyroidism	Free $T_4$	
LH/FSH	Gonadal sex steroids	Hypogonadism	Simultaneous LH, FSH, testosterone (male), estradiol (female)	
GH	Somatostatin	Multiple	IGF-1	GH stimulation testing (rarely necessary)
Prolactin	Dopamine	Inability to lactate	Serum prolactin	
ADH	↓ Osmolality	Diabetes insipidus	Simultaneous serum sodium, urine and serum osmolality	Water deprivation test and desmopressin challenge test

early-morning cortisol or ACTH (cosyntropin) stimulation test. To check for cortisol excess, perform a dexamethasone suppression test.

- Pituitary imaging: Order a sellar-specific MRI (Figure 6.1). A standard brain MRI may miss these small tumors!
- Formal visual field testing: For macroadenomas or tumors compressing the optic chiasm.

**TABLE 6.3. Differential Diagnosis of Sellar Lesions**

LESION	EXAMPLES
Pituitary adenoma	Prolactinoma: The most common pituitary microadenoma GH secreting: Often very large Nonfunctioning: One-third of all pituitary tumors; the most common macroadenoma ACTH secreting: The most common cause of Cushing syndrome TSH secreting: Rare
Physiologic enlargement of the pituitary gland	Hyperplasia due to pregnancy, 1° hypothyroidism, or 1° hypogonadism
Primary malignancies	Germ cell tumor, sarcoma, lymphoma, pituitary carcinoma
Metastases	Breast cancer, lung cancer
Cysts	Rathke cleft, arachnoid, dermoid
Infections in immunocompromised patients	Abscess, tuberculoma
Other	Craniopharyngioma, meningioma, lymphocytic hypophysitis (autoimmune disorder that often occurs during pregnancy or postpartum, or secondary to cancer immunotherapy, mainly ipilimumab)



**FIGURE 6.1. Pituitary macroadenoma.** Sagittal post-contrast MRI of a 42-year-old woman with loss of peripheral vision shows a large, heterogeneously enhancing mass in the midline expanding the sella and extending into the anterior cranial fossa. (Reproduced with permission from USMLE-Rx.com.)



### QUESTION

A 63-year-old man on warfarin for atrial fibrillation presents with an excruciating headache, nausea, vomiting, vertigo, and altered mental status. He has a known pituitary adenoma. His BP is 65/35 mm Hg, and he has meningismus. What is the most appropriate treatment?

**KEY FACT**

Suspect pituitary adenoma when patient presents with multiple hormone abnormalities such as hypothyroidism + AI.

**KEY FACT**

Damage to the hypothalamus or pituitary stalk by tumors in the sellar region cause DI. Pituitary adenomas rarely cause DI.

**KEY FACT**

Women typically present with prolactinomas earlier than men because they develop amenorrhea and galactorrhea. Thus, women often have microprolactinomas ( $<1$  cm) at diagnosis, whereas men have macroprolactinomas.

**KEY FACT**

The prolactin level will be  $<150$  ng/mL if the hyperprolactinemia is caused by drugs or if due to "stalk effect." Prolactin levels  $>200$  ng/mL are almost always due to a prolactinoma.

**KEY FACT**

Always check urine pregnancy test in a woman presenting with amenorrhea and hyperprolactinemia!

**Management**

- Surgery: If the tumor is causing mass effect, visual field deficits, or hypopituitarism or there is evidence of GH, ACTH, TSH excess.
- Surveillance: If the lesion does not meet criteria for surgical removal, then the patient should be followed with neuroimaging (MRI at 6 months for macroincidentalomas, 1 year for a microincidentaloma), visual field examinations if lesion abuts the optic nerve or chiasm, and hormonal testing for macroincidentalomas (6 months and yearly).

**Prolactinoma**

The **most common type of pituitary tumor** is prolactinoma. The majority are microadenomas ( $<1$  cm).

**Symptoms/Exam**

- Women: Galactorrhea; amenorrhea; oligomenorrhea with anovulation and infertility in 90% of cases (due to inhibition of GnRH from  $\uparrow$  prolactin).
- Men: Impotence,  $\downarrow$  libido, galactorrhea (very rare).
- Both: Headache, visual field cuts, hypopituitarism.

**Differential**

There are many causes of elevated prolactin outside the pituitary (Table 6.4).

**Diagnosis**

- Labs:  $\uparrow$  prolactin with normal TFTs and a  $\ominus$  pregnancy test.
- Imaging: Obtain an MRI if prolactin is  $\uparrow$  in the absence of pregnancy or the medications listed in Table 6.4.

**TABLE 6.4. Etiologies of Hyperprolactinemia**

PHYSIOLOGIC	PATHOLOGIC		
	ADENOMA/HYPERPLASIA	DRUGS	OTHER DISORDERS
Pregnancy	Lactotroph adenoma:	Psychiatric medications	1° hypothyroidism (TRH)
Nipple stimulation	Micro- or macroprolactinoma	(antipsychotics, SSRIs, TCAs)	stimulates release of prolactin)
Stress	Lactotroph hyperplasia:	Verapamil	CKD ( $\downarrow$ urinary clearance of prolactin)
Exercise	Usually due to disruption of normal dopamine inhibition	Protease inhibitors	Cirrhosis
Chest wall trauma	of prolactin	Gastric motility agents (metoclopramide, domperidone)	Hypothalamic or pituitary stalk lesions which compress the pituitary stalk and disrupt dopamine flow ("stalk effect")
		Opioids	Macroprolactinemia ( $\uparrow$ circulating level of a high-molecular-weight prolactin that is biologically inactive)
		Cocaine	
		Methyldopa	
		Estrogens	

(Modified with permission from Gardner DG, Shoback D. *Greenspan's Basic & Clinical Endocrinology*, 8th ed. New York: McGraw-Hill, 2007: 119.)

**ANSWER**

Pituitary apoplexy, a hemorrhagic pituitary infarction, is a neurosurgical emergency. Treat with corticosteroids  $\pm$  transphenoidal decompression. Note that pituitary apoplexy may present suddenly and similarly to a ruptured aneurysm or subarachnoid hemorrhage.

## Management

- Observation for women with **microadenoma** who are **asymptomatic and have normal menses**. In pregnancy, women with prolactinomas should be monitored every 3 months. If symptoms develop (eg, headache, visual field deficits), then medical therapy should be pursued.
- If symptomatic, do the following:
  - Medical: **Dopamine agonists** such as bromocriptine or cabergoline. Cabergoline has fewer side effects and is better tolerated. Once prolactin is normalized, repeat pituitary MRI to ensure tumor shrinkage.
  - Surgery: Transsphenoidal resection is curative and is generally used if medical therapy is ineffective.
  - Radiation: Conventional radiotherapy or gamma-knife radiosurgery is reserved for patients with macroadenomas that are growing despite treatment with dopamine agonists or if tumor recurs after surgery (rare).



### KEY FACT

Prolactinoma is the most common functional pituitary tumor and can usually be treated medically with dopamine agonists (bromocriptine, cabergoline). If <1 cm in size and the woman has normal menses, observation is the preferred treatment.

## GROWTH HORMONE EXCESS

Growth hormone excess leads to acromegaly when it occurs in adulthood. Etiologies are as follows:

- Benign pituitary adenoma: GH-secreting pituitary adenomas are responsible for nearly all cases of acromegaly.
- Iatrogenic: Associated with treatment with human GH.
- Ectopic GH or GHRH: Extremely rare; seen with lung carcinoma, carcinoid tumors, and pancreatic islet cell tumors.

## Symptoms/Exam

- Almost all patients have soft tissue proliferation (hand/foot/jaw enlargement) and **coarsening of facial features with frontal bossing, and prognathism** (Figure 6.2). An ↑ in shoe, ring, hat, or glove size is common. Macroglossia and hypertrophy of pharyngeal and laryngeal tissue occurs causing a **coarse, deepening voice**. Headache and visual loss are direct effects of tumor.
- Additional symptoms include:
  - Cardiac: Hypertension, cardiomyopathy (order an echocardiogram).
  - Endocrine: ↑ insulin resistance with glucose intolerance or overt **diabetes**; hypogonadism.
  - Constitutional: Heat intolerance, weight gain, excessive sweating, fatigue.



**FIGURE 6.2. Growth hormone excess.** Facial aspect of acromegaly. (Source: Chanson P, et al. Acromegaly. *Orphanet Journal of Rare Diseases*. 2008;3:17.)



### QUESTION

A 60-year-old woman with DM presents with complaints of headaches, arthralgias, and hand, feet, and jaw enlargement. She has hypertension and coarsened facial features. What is the most likely diagnosis?

**KEY FACT**

In a patient with coarse facial features and new diabetes mellitus, check IGF-1 (not GH) to rule out acromegaly.

**KEY FACT**

Do an oral glucose load after screening for IGF-1. If GH levels do not drop after an oral glucose load of 75 g, acromegaly is diagnosed.

**KEY FACT**

Treat GH-secreting pituitary adenomas with transsphenoidal surgery. If refractory, try medical therapy such as somatostatin analogs. This is in contrast to prolactinomas, where medical therapy is usually first-line.

**KEY FACT**

ACTH deficiency is the most life-threatening aspect of panhypopituitarism. Fortunately, ACTH function is generally preserved the longest and since the pituitary does not control aldosterone, you don't see cardiovascular collapse.

**ANSWER**

Acromegaly from a benign pituitary adenoma.

- GI: ↑ incidence of colonic polyps and colon cancer (**order a colonoscopy**).
- Musculoskeletal: Carpal tunnel syndrome, arthropathy, malalignment of the teeth.
- Pulmonary: Obstructive sleep apnea.

**Diagnosis**

- Labs:
  - IGF-1 level: ↑ IGF-1 level is **the best initial test**.
  - Glucose tolerance test: Normally, GH levels should drop after an oral glucose load. However, in GH-secreting pituitary adenomas, GH secretion is autonomous, does not suppress, and may paradoxically rise with hyperglycemia; therefore, **a lack of suppression or rise in GH levels after a 75-g oral glucose load is diagnostic of excess GH secretion**.
- Radiology: Pituitary MRI.

**Management**

- Surgical: **Transsphenoidal resection** is **first-line therapy**, even if asymptomatic, and is usually curative.
- Medical: If GH excess persists after surgery, long-acting somatostatin analogs (octreotide and lanreotide) or GH-receptor antagonists (pegvisomant) may be added.
- Radiotherapy: For patients with inadequate responses to surgical and medical therapy or postsurgical recurrence. Requires several years to be effective.

**HYPOPITUITARISM**

↓ or absent secretion of one or more pituitary hormones. Etiologies of hypopituitarism are outlined below.

**Symptoms/Exam**

Presentation depends on the particular hormone deficiency. **In panhypopituitarism, hormones are lost in the following order:**

- GH deficiency: May be asymptomatic in adults or symptoms may be overshadowed by other manifestations of hypopituitarism. Has been associated with ↑ fat mass, bone loss, ↓ muscle mass, and cardiovascular disease (CVD) risk factors.
- LH/FSH deficiency: Hypogonadism. Manifested in adult men as lack of libido/impotence and in adult women as irregular menses/amenorrhea. In prepubertal boys and girls, hypogonadism manifest as failure to develop 2° sex characteristics.
- TSH deficiency: Hypothyroidism.
- ACTH deficiency: AI (weakness, nausea, vomiting, anorexia, weight loss, fever, hypotension). **Hyperkalemia is generally present only in 1° AI**.
- ADH deficiency (DI): Seen only if the posterior pituitary is also involved.

**Differential**

Remember the “**eight I’s**”: Invasive, Infiltrative, Infarction, Injury, Immunologic, Iatrogenic, Infectious, Idiopathic:

- **Invasive:** Pituitary adenomas (most common), craniopharyngioma, 1° CNS tumors, metastatic tumors, anatomic malformations (eg, encephalocele and parasellar aneurysms).
- **Infiltrative:** Sarcoidosis, hemochromatosis, histiocytosis X.
- **Infarction:**
  - Sheehan syndrome: Pituitary infarction associated with postpartum hemorrhage and vascular collapse. Typically presents with difficulty in lactation and failure to resume menses postpartum.

- **Pituitary apoplexy:** Spontaneous hemorrhagic infarction of a preexisting pituitary tumor. Symptoms include severe headache, nausea and vomiting, meningismus, vertigo, visual defects and fluctuating consciousness.
- **Injury:** Severe head trauma can lead to anterior pituitary dysfunction and DI.
- **Immunologic:** **Lymphocytic hypophysitis**—destructive lymphocytic infiltration causing hypopituitarism often during pregnancy and postpartum or secondary to cancer immunotherapy (mainly ipilimumab). May cause symptoms of mass lesion and ACTH insufficiency.
- **Iatrogenic:** Most likely after **pituitary surgery or radiation therapy**.
- **Infectious:** Rare; includes TB, syphilis, and fungi.
- **Idiopathic:** **Empty sella syndrome**—an enlarged sella turcica that is not entirely filled with pituitary tissue; the pituitary gland may be flattened by CSF pressure. If there is no sellar mass or clinical evidence of hormonal excess or deficiency, no additional workup is necessary though some recommend measuring  $T_4$  and morning cortisol.

### Diagnosis

Generally, test for deficiency in the target-organ hormone and the pituitary hormone (Table 6.2):

- ACTH/adrenal axis: Abnormal ACTH and cortisol. See the discussion of AI below for details on the **cosyntropin test**. Note that **the test may be normal in acute pituitary dysfunction** because for some period, the adrenals can still respond to pharmacologic doses of ACTH.
- Thyroid axis: Low free  $T_4$  in  $2^\circ$  hypothyroidism (**TSH levels are not reliable for this diagnosis**, as levels may be low or normal).
- Gonadotropins: Low FSH/LH (unnecessary to check in women with normal menstrual cycles), testosterone, or estradiol.
- GH: Low IGF-1; abnormal GH stimulation testing (rarely necessary but is the most accurate diagnostic test and measures GH before and after IV insulin or arginine).
- ADH: If DI is suspected, test as described in the Diabetes Insipidus section (Figure 6.3).

### Management

**Treat the underlying cause.** Medical treatment consists of correcting hormone deficiencies:

- ACTH: Hydrocortisone 10 to 30 mg/day, two-thirds in the morning and one-third in the afternoon/evening.
- TSH: Replace with levothyroxine (adjust to a goal of normal free  $T_4$ , not TSH). **Must assess for and treat AI before replacement with levothyroxine**, because treatment of central hypothyroidism can precipitate an adrenal crisis, since thyroid hormones accelerate cortisol catabolism.
- LH/FSH:
  - Men: Replace testosterone by injection, patch, or gel.
  - Women: If premenopausal, OCPs or hormone replacement therapy (HRT).
- GH: In the past, treatment of GH deficiency in adults was not treated, however, Human GH is available and should be considered to improve quality of life, bone density, and muscle mass.
- ADH: Intranasal DDAVP 10  $\mu\text{g}$  daily or twice daily.

### DIABETES INSIPIDUS

Antidiuretic hormone, as the name suggests, prevents the production of dilute urine. Deficient ADH action resulting in copious amounts of **extremely dilute urine and possibly hypernatremia**. Subtypes are as follows:

- **Central DI:** Deficient ADH secretion by the posterior pituitary. Caused by hypothalamic masses, recent neurosurgery, traumatic brain injury,  $1^\circ$  or  $2^\circ$  brain can-

### KEY FACT

The most common causes of panhypopituitarism are pituitary tumors and their treatments (cranial irradiation and surgery).

### KEY FACT

In a man with hypopituitarism and skin bronzing, think hemochromatosis.

### KEY FACT

In acute  $2^\circ$  AI, a cosyntropin stimulation test result is likely to be inappropriately “normal” because the adrenal glands have not had time to atrophy. So if suspicion for AI is high, treat with steroids!

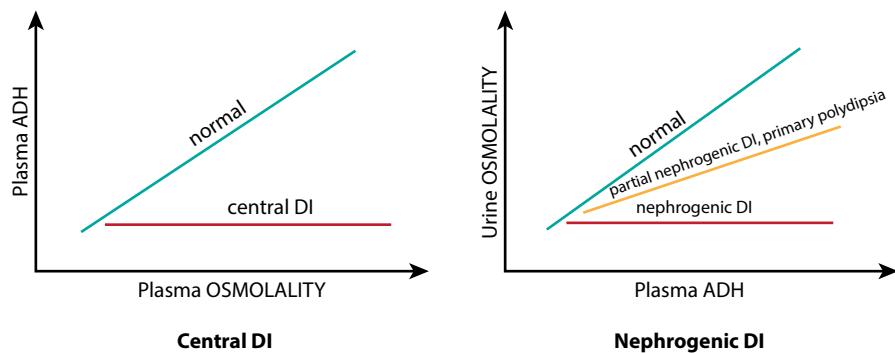
### KEY FACT

Seventy-five percent or more of the pituitary must be destroyed before there is clinical evidence of hypopituitarism.



### QUESTION

A man presents with a large skull contusion after being hit in the head with a wood plank. He has confusion and ↑ urinary volume. Labs include sodium, 168 mEq/L; serum osmolality, 305 mOsm/L; and urine osmolality, 105 mOsm/L. What is the most appropriate treatment?



**FIGURE 6.3. Central and nephrogenic DI.** In central DI, as plasma osmolality increases, plasma ADH does not appropriately increase. In nephrogenic DI, as plasma ADH increases, urine osmolality does not appropriately increase. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

The most common cause of acquired nephrogenic DI is lithium use.

### KEY FACT

Patients with DI have large volumes of extremely dilute urine, and urine output does not ↓ as it should if fluid intake is ↓, such as with a water deprivation test. If urine osmolality is low in a hypernatremic patient, consider DI.

### KEY FACT

To establish the diagnosis of DI, perform a water deprivation test. Water restriction should not influence urine output or osmolality in DI, since ADH production or action is impaired.

A

### ANSWER

DDAVP (central DI from head trauma).

cers, infiltrative diseases (eg, Langerhans cell histiocytosis, sarcoidosis), and vascular conditions (eg, Sheehan syndrome, stroke). May also be iatrogenic (eg, radiation, surgery) or idiopathic.

- **Nephrogenic DI (“ADH resistant”):** Normal ADH secretion, but impaired ability to act on the kidneys. Caused by congenital/inherited defects, CKD, hypercalcemia ( $\text{Ca}^{2+} > 11 \text{ mg/dL}$ ), persistent hypokalemia (potassium  $< 3 \text{ mEq/L}$ ), sickle cell disease, amyloidosis, myeloma, and drugs (eg, lithium).

### Symptoms/Exam

Characterized by polyuria and polydipsia. The hallmark is **inappropriately dilute urine** in the setting of ↑ serum osmolality (urine osmolality  $<$  serum osmolality). **Hypernatremia** occurs if the patient lacks access to free water or does not have an intact thirst mechanism (Figure 6.3).

### Differential

Psychogenic polydipsia (polyuria due to ↑ drinking, usually  $> 5 \text{ L}$  of water per day, leading to dilution of extracellular fluid and water diuresis), nephrogenic DI, central DI, and diabetes.

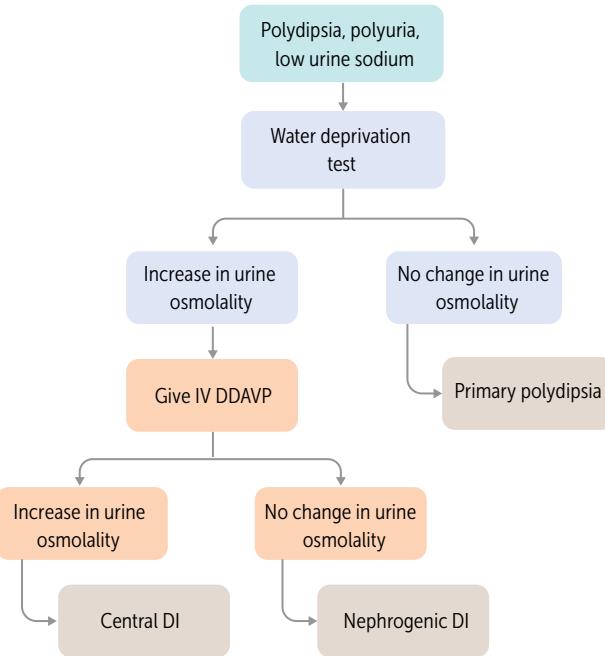
### Diagnosis

Order a plasma and urine osmolality test (see also Table 6.5 and Figure 6.4).

- **Water deprivation test** to establish the diagnosis of DI:
  - Normal response: Urine osmolality ↑ in response to water deprivation.

**TABLE 6.5. Diagnosis of Central DI, Nephrogenic DI, and Psychogenic Polydipsia**

TEST	CENTRAL DI	NEPHROGENIC DI	PSYCHOGENIC POLYDIPSIA
Random plasma osmolality	↑	↑	↓
Random urine osmolality	↓	↓	↓
Urine osmolality during water deprivation	No change	No change	↑
Urine osmolality after IV DDAVP	↑	No change	↑
Plasma ADH	↓	Normal to ↑	↓



**FIGURE 6.4. Diagnosis of diabetes insipidus.** (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

- DI: Urine osmolality is low ( $\leq 300$  mOsm/L, usually around 50 mOsm/L) despite water restriction.
- Psychogenic polydipsia: Urine osmolality  $\uparrow$  more than plasma osmolality.
- Desmopressin challenge test (DDAVP; comparable to synthetic ADH) to distinguish central or nephrogenic DI: Urine osmolality  $\uparrow$  in central DI, but not in nephrogenic DI.
- If central DI is diagnosed, obtain a pituitary MRI to determine the etiology.

### Management

- Central DI: DDAVP administration (IV, SQ, PO, or intranasal).
- Nephrogenic DI: Remove the offending agent and treat the underlying disorder if possible. A low-solute diet and thiazide diuretics. Use amiloride for lithium-induced nephrogenic DI that does not improve after lithium is stopped.

## Thyroid Disorders

### TESTS AND IMAGING

#### Thyroid Function Tests

Table 6.6 outlines the role of TFTs in diagnosing thyroid disorders. Figure 6.5 illustrates the hypothalamic-pituitary-thyroid axis.

- Thyrotropin (TSH) is the best screening test and the most sensitive indicator of thyroid dysfunction. If there is 2° (pituitary) thyroid dysfunction, TSH is unreliable, and  $FT_4$  is used instead.
- If TSH is abnormal, then check  $FT_4$ .
- If TSH is low and  $FT_4$  is normal, then check a total or free  $T_3$  to rule out “ $T_3$  thyrotoxicosis” (a predominance of  $T_3$  production over  $T_4$  production; usually seen

#### KEY FACT

If urine osmolality  $\uparrow$  and urine output  $\downarrow$  after DDAVP administration, you have diagnosed central DI, especially if there is a history of recent head trauma, neurosurgery, brain cancer/infiltrative disease. The next diagnostic test should be a pituitary MRI.

#### KEY FACT

Keeping up with fluid losses from massive polyuria is a key component of DI treatment.

TABLE 6.6. TFTs in Thyroid Disease

	TSH	FREET <sub>4</sub>	T <sub>3</sub> /FREET <sub>3</sub>
1° hypothyroidism	↑	↓	↓
2° (pituitary) hypothyroidism	↓/inappropriately normal	↓	↓
3° (hypothalamic) hypothyroidism	↓	↓	↓
1° hyperthyroidism	↓	↑	↑
2° hyperthyroidism (rare; TSH-secreting adenoma)	↑	↑	↑
Exogenous hyperthyroidism	↓	↑	Mildly ↑
Acute non-thyroidal illness (euthyroid sick)	↓/normal <sup>a</sup>	Rare ↑/normal/↓	↓
Recovery from non-thyroidal illness (euthyroid sick)	↑ <sup>b</sup>	Normal	Normal

<sup>a</sup>↓ (but not undetectable), especially if the patient has received dopamine, glucocorticoids, narcotics, or NSAIDs.

<sup>b</sup>Usually not >20 mIU/L.

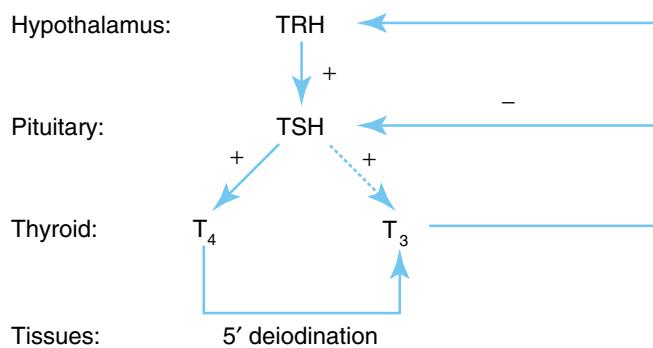
### KEY FACT

The single best screening test for evaluating thyroid function is TSH.

in early hyperthyroidism). It is not necessary to check total T<sub>3</sub> or free T<sub>3</sub> in the evaluation of routine hypothyroidism.

### Radionuclide Uptake and Scan of the Thyroid Gland

Most often used to determine the etiology of hyperthyroidism; not useful in the evaluation of hypothyroidism. <sup>123</sup>I is administered orally, and the percent of radioactive iodine (RAI) uptake is determined at 4 to 6 and 24 hours (Table 6.7).



**FIGURE 6.5. The hypothalamic-pituitary-thyroid axis.** Thyrotropin (TSH) is produced by the pituitary in response to TRH. TSH stimulates the thyroid gland to secrete T<sub>4</sub> and low levels of T<sub>3</sub>; T<sub>4</sub> is converted in the periphery by 5' deiodinase to T<sub>3</sub>, the active form of the hormone. T<sub>3</sub> is also primarily responsible for feedback inhibition on the hypothalamus and pituitary. Most T<sub>4</sub> is bound to thyroid-binding globulin and is not accessible to conversion; therefore, free T<sub>4</sub> provides a more accurate assessment of thyroid hormone level.

**TABLE 6.7. Hyperthyroidism Differential Based on Radioiodine Uptake and Scan**

DECREASED UPTAKE	DIFFUSELY INCREASED UPTAKE	UNEVEN UPTAKE
Thyroiditis	Graves disease	Toxic multinodular goiter (multiple hot and cold nodules)
Exogenous thyroid hormone ingestion		Solitary toxic nodule (one hot nodule; the remainder of the thyroid appears cold)
Struma ovarii		
Iodine-induced (amiodarone, IV contrast)		
Drug-induced (amiodarone, tyrosine kinase inhibitors)		

## Thyroid Ultrasound

Used to do the following:

- Determine if a nodule is cystic or solid.
- Stratify a nodule's malignancy risk.
- Localize a nodule for fine-needle aspiration (FNA).
- Follow up a nodule's size over time when malignancy is suspected.
- Follow up a patient after thyroid cancer resection.

## HYPOTHYROIDISM

Etiologies of hypothyroidism include:

- **Hashimoto (autoimmune) thyroiditis (chronic lymphocytic thyroiditis):** The most common cause in the United States. Characterized by goiter in early disease and by a small, firm gland in late disease.
- Late phase of subacute thyroiditis: After the acute phase of hyperthyroidism, hypothyroidism may occur but is usually transient (see below).
- **Drugs:** Amiodarone, lithium, interferon, iodide (kelp, radiocontrast dyes).
- Iatrogenic: Postsurgical or post-RAI treatment.
- **Iodine deficiency:** Rare in the United States but common worldwide. Often associated with a grossly enlarged gland.
- Rare causes: 2° hypothyroidism due to hypopituitarism; 3° hypothyroidism due to hypothalamic dysfunction; peripheral resistance to thyroid hormone.

### Symptoms/Exam

Presents with fatigue, weight gain, cold intolerance, dry skin, menstrual irregularities, depression, constipation, myalgias, and arthralgias. Exam may reveal an enlarged thyroid gland, bradycardia, edema, dry/cold skin, hoarseness, coarse/brittle hair, and a delayed relaxation phase of deep tendon reflexes.

### Diagnosis

- Labs: ↑ TSH (>10 mIU/L) and ↓ FT<sub>4</sub>. Hashimoto thyroiditis is associated with  $\oplus$  anti-thyroperoxidase (anti-TPO) and/or  $\oplus$  anti-thyroglobulin antibodies. Other lab abnormalities can include hyponatremia, normocytic anemia (pernicious anemia in 10%), and ↑ LDL cholesterol.
- Radiology: RAI scan and thyroid ultrasound are generally not indicated.

### KEY FACT

In iodine-sufficient areas such as the United States, amiodarone induces hypothyroidism more often than hyperthyroidism.

### KEY FACT

Autoimmune thyroid disease may be associated with other endocrine autoimmune disorders, most prominently pernicious anemia (type of B<sub>12</sub> deficiency) and AI.

### Management

#### ■ Thyroid HRT:

- **Levothyroxine ( $LT_4$ ) is the standard treatment.** The replacement dose is usually 1.5 to 1.7  $\mu\text{g}/\text{kg}/\text{day}$ . This drug has a long half-life and can be titrated every 6 to 8 weeks.
- **In elderly patients or those with heart disease, start low and go slow (12.5 to 25.0  $\mu\text{g}/\text{day}$ ); then slowly  $\uparrow$  the dose by 25- $\mu\text{g}$  increments every month until euthyroid.** Over replacement may predispose patients to atrial fibrillation and osteoporosis.
- Treatment of **subclinical hypothyroidism** ( $\uparrow$  TSH with normal  $FT_4$ ; mild or no symptoms) is generally **not indicated unless TSH is  $>10 \text{ mIU/L}$  or in the presence of thyroid antibodies, goiter, a  $\oplus$  family history, hyperlipidemia, or pregnancy.** If treatment is indicated, relatively small doses of  $FT_4$  are needed.

### Complications

- **Myxedema coma:** Severe, life-threatening hypothyroidism characterized by weakness, hypothermia, hypoventilation with hypercapnia, psychosis (“myxedema madness”), hypoglycemia, hyponatremia, water intoxication, shock, and death. Treatment is supportive therapy with rewarming, and intubation, while IV  $LT_4$  is given. Often precipitated by infection or other forms of stress. Test for AI but give **empiric IV glucocorticoids for AI**, which can coexist with thyroid disease, while awaiting confirmation of AI. **In a critically ill, comatose patient, give empiric antibiotics** until cultures are negative.
- Other: Anemia (normocytic), CHF, depression, hyperlipidemia, and fertility problems until hypothyroidism is corrected.

## HYPERTHYROIDISM

The etiologies of hyperthyroidism include the following (see also Table 6.8):

- **Graves disease** (the most common cause): Affects females more than males (by a ratio of 5:1). Peak incidence is at 20 to 40 years of age.
- Solitary toxic nodule.
- Toxic multinodular goiter.
- Thyroiditis.
- Rare causes: Exogenous thyroid hormone ingestion (thyrotoxicosis factitia), struma ovarii (ovarian tumor produces thyroid hormone), hydatidiform mole (hCG mimics TSH action), productive follicular thyroid carcinoma.

### Symptoms/Exam

- Presents with weight loss, anxiety, palpitations, fatigue, hyperdefecation, heat intolerance, sweating, and amenorrhea.
- General findings: **Stare and lid lag** (can be seen in any situation with thyroid hormone excess, not only in Graves ophthalmopathy, and can resolve with treatment of hyperthyroidism), tachycardia,  $\uparrow$  pulse pressure, hyperreflexia, restlessness, goiter (smooth and homogeneous in Graves disease; irregular in multinodular goiter).
- **Graves disease only:** **Graves ophthalmopathy** (see below), **infiltrative dermopathy** (pretibial myxedema, nonpitting; Figure 6.6), **thyroid bruit** (due to  $\uparrow$  vascularity), onycholysis (separation of the fingernails from the nail bed).
  - **Ophthalmopathy:** This Graves-specific disease is an autoimmune process that leads to lymphocytic infiltration and edema of orbital fibroblasts and the extraocular muscles, which can cause nerve or muscular entrapment. Patients can present with blurring of vision, diplopia, tearing of eyes, and rarely blindness (due to compression of orbital nerve or artery). Eye findings include lid retraction and **proptosis** (also called exophthalmos, bulging of the eye anteriorly out of the orbit), which can cause corneal dryness, leading to chemosis (con-

### KEY FACT

Graves disease is associated with other immune-mediated processes, such as idiopathic thrombocytopenic purpura and pernicious anemia.

### KEY FACT

All patients with hyperthyroidism may have stare and lid lag. However, two physical findings are pathognomonic of Graves disease: pretibial myxedema and exophthalmos.

**TABLE 6.8. Causes and Treatment of Hyperthyroidism**

CAUSE	THYROID EXAM	UNIQUE FINDINGS	RAI UPTAKE AND SCAN	TREATMENT
Graves disease	Diffusely enlarged thyroid; bruit may be present	<b>Exophthalmos</b> , periorbital edema, pretibial myxedema. TSI ± TPO antibodies	<b>Diffusely ↑ uptake</b>	<b>Medications (MMI, PTU), RAI; surgery for very large, obstructing goiters</b>
Solitary toxic nodule	Single palpable nodule	Autoantibodies are usually absent; may have predominantly $T_3$ toxicosis	Single focus of ↑ uptake	Definitive therapy is <b>RAI or surgery</b>
Multinodular goiter	<b>"Lumpy-bumpy," enlarged thyroid</b>	Autoantibodies are usually absent; may have predominantly $T_3$ toxicosis	Multiple hot and/or cold nodules	Definitive therapy is <b>RAI or surgery</b>
Thyroiditis (transient destruction of thyroid tissue)	<b>Tender, enlarged thyroid</b>	Subacute thyroiditis occurs following a viral infection; can also be postpartum or silent ("painless"); thought to have an autoimmune etiology  ↓ TSH, classically followed by a hypothyroid phase and then by euthyroidism  Can be caused by medications (eg, amiodarone)	<b>Diffusely ↓ uptake</b>	<b>β-blockers, NSAIDs, corticosteroids if indicated</b>
Exogenous hyperthyroidism	Normal or nonpalpable	The patient may be taking weight loss medications or have psychiatric illness  <b>Differentiate from thyroiditis by ↓ TSH levels</b>	Diffusely ↓ uptake	Discontinuation of thyroid hormone

junctival injection and edema) and superior limbic keratoconjunctivitis. Can be precipitated or worsened by RAI therapy, especially in smokers. Treatment includes high-dose glucocorticoids and eye surgery.

## Diagnosis

Diagnostic methods include the following (see also Figure 6.7):

- Labs: ↓ TSH, ↑  $FT_4$ , occasionally ↑  $FT_3$ , thyroid antibodies (see above). Don't be tricked, surreptitious use of thyroid hormone suppresses thyroglobulin levels.
- Radiology: RAI uptake and scan can help determine the etiology of hyperthyroidism. Hyperthyroidism with **diffusely ↑ uptake** is associated with **de novo** hormone synthesis (Graves disease); hyperthyroidism with **↓ uptake** suggests **thyroid tissue destruction (thyroiditis)** or an extrathyroidal source. Hold anti-thyroid medications at least 7 days prior to testing.

## Management

### Medications:

- **MMI and PTU** can be used to ↓ thyroid hormone production. PTU is the first choice in **thyroid storm** and the first trimester of pregnancy. Liver toxicity can occur (more so with PTU than with MMI). In Graves disease, treatment for 18 months can lead to complete remission in 50% of cases.
- **β-blockers** can be used in the acute phase to control tachycardia and other symptoms.

### RAI therapy:

- Radioactive iodine is the treatment of choice for **solitary toxic nodules** and **toxic multinodular goiter**, as these conditions generally do not spontaneously remit with medical therapy. **Contraindicated in pregnancy.**
- A high cure rate is achieved after one dose, but treatment usually results in hypothyroidism, requiring subsequent thyroid HRT.



### KEY FACT

Elderly patients may present with apathetic hyperthyroidism, which is characterized by depression, slow atrial fibrillation, weight loss, and a small goiter.

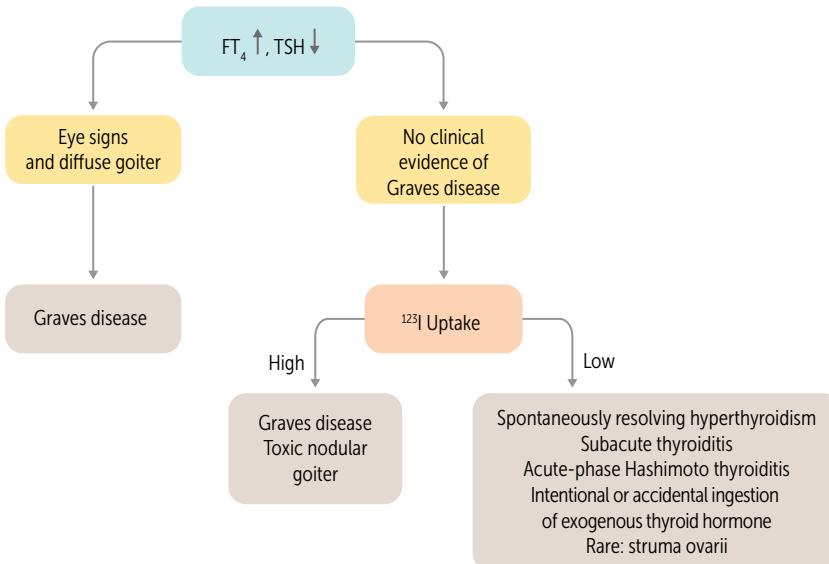


### QUESTION

A 28-year-old pregnant woman presents with 3 months of palpitations, double vision, exophthalmos, and sinus tachycardia. TSH is <0.05 mIU/L with an ↑  $T_4$  and  $T_3$  and thyroid-stimulating immunoglobulin (TSI). What is the best initial treatment?



**FIGURE 6.6. Pretibial myxedema of Graves disease.** Leg edema and mild erythema in a 50-year-old man with anterior cervical swelling, heat intolerance, and anxiety. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 6.7. Algorithm for the diagnosis of hyperthyroidism.** (Reproduced with permission from USMLE-Rx.com.)

#### ■ Surgery:

- Indicated for uncontrolled disease during pregnancy; for extremely large goiters causing obstruction; for amiodarone-induced thyroiditis that is refractory to medical management; or for patients who object to RAI therapy and cannot tolerate anti-thyroid drugs.
- Risks include hypoparathyroidism and recurrent laryngeal nerve injury.

#### Complications

- Treatment of thyroid storm involves:
- **Glucocorticoid therapy** is most important, as it inhibits conversion of  $T_4$  to  $T_3$ , and treats relative AI.
- High-dose propranolol reduces cardiovascular symptoms (such as tachycardia, tremors, nervousness) and may inhibit the peripheral conversion of  $T_4$  to the more biologically potent  $T_3$ .
- PTU, as it is superior to MMI.
- Iodine to inhibit preformed thyroid hormone release.
- Empiric antibiotics, if infection is suspected.

#### KEY FACT

#### THYROIDITIS

Thyroiditis can present with hyper-, hypo-, and/or euthyroid states (Table 6.9).

#### ■ Symptoms vary by stage:

- Early stage: Characterized by thyroid inflammation (high ESR) and release of preformed thyroid hormone, leading to clinical hyperthyroidism, suppressed TSH, and low RAI uptake.
- Late stage: Characterized by thyroid “burnout” and hypothyroidism.
- **Management:** Most patients with acute thyroiditis eventually recover thyroid function. See Table 6.9.

A

#### ANSWER

Propylthiouracil (PTU). In the first trimester of pregnancy, PTU is the first choice because methimazole (MMI) may be teratogenic. At the start of second trimester, switch to MMI.

**TABLE 6.9.** Clinical Features and Differential Diagnosis of Thyroiditis

TYPE	ETOLOGY	CLINICAL FINDINGS	TESTS	TREATMENT
Subacute thyroiditis (de Quervain's)	Viral	Hyperthyroid early; then hypothyroid <b>Tender</b> , large thyroid; <b>fever</b>	↑ ESR; no antithyroid antibodies; low RAI uptake	β-blockers, NSAIDs, acetaminophen ± corticosteroids Typically self-limited
Hashimoto thyroiditis	Autoimmune associated with other autoimmune conditions (eg, type 1 DM, vitiligo, AI, pernicious anemia)	Usually hypothyroid; painless ± goiter	Ninety-five percent have $\oplus$ antibodies; <b>anti-TPO</b> is most sensitive	Levothyroxine
Suppurative thyroiditis	Bacteria > other infectious agents	Fever, neck pain, tender thyroid	TFTs are normal. No uptake on RAI scan; $\oplus$ <b>cultures</b>	Antibiotics and drainage if abscess develops
Amiodarone	AmIODarone contains IODine	Destructive thyroiditis is seen in the United States; iodine-induced hyperthyroidism is seen in iodine-deficient areas	Three possible changes: ■ ↑ FT <sub>4</sub> and total T <sub>4</sub> ; then low T <sub>3</sub> and high TSH ■ High TSH; low FT <sub>4</sub> and T <sub>3</sub> ■ Low TSH; high FT <sub>4</sub> and T <sub>3</sub>	No treatment is needed; will normalize eventually Gradual titration of levothyroxine As for other thyroiditis; stop amiodarone if possible
Other medications	Lithium, α-interferon, interleukin-2 tyrosine kinase inhibitors		Lithium typically causes hypothyroid profile	Stop medication if possible
Postpartum thyroiditis	Lymphocytic infiltration; seen after up to 10% of pregnancies	Small, nontender thyroid	May see hyper- or hypothyroidism Antibodies are often $\oplus$ ; RAI uptake is low	No treatment unless propranolol is needed for tachycardia Annual follow-up to monitor for possible hypothyroidism development Monitor TFTs in future pregnancies

### THYROID DISEASE IN PREGNANCY

See the discussion in the Women's Health chapter.

### NONTHYROIDAL ILLNESS (EUTHYROID SICK SYNDROME)

Seen in hospitalized or terminally ill patients, typically without symptoms. Nonthyroidal illness results from impaired ability to convert T<sub>4</sub> to T<sub>3</sub> in peripheral tissues during acute illness. In mild illness, the **most common abnormality is a low T<sub>3</sub> level, with normal FT<sub>4</sub> and TSH levels**. During the course of the illness, FT<sub>4</sub> and T<sub>3</sub> may decline while TSH levels vary, often rising during the recovery phase; this should not be confused with hypothyroidism.

### KEY FACT

In nonthyroidal illness (euthyroid sick syndrome), the TSH is usually low initially and then elevated in the recovery phase. Normalization occurs in 4 to 8 weeks. Treatment is focused on the underlying illness; thyroid medications are not indicated.

## THYROID NODULES AND CANCER

Thyroid nodules are more common in women but are more likely to be malignant in men. **Radiation** exposure is a major risk factor. The “90%” mnemonic applies:

- 90% of nodules are **benign**.
- 90% of nodules are **cold** on RAI uptake scan; 5% to 10% of these are malignant (1% of hot nodules are malignant).
- 90% of **thyroid malignancies** present as a **thyroid nodule**.
- >90% of cancers are either **papillary** or **follicular**, which carry the best prognoses.

Other factors that ↑ the risk of a thyroid nodule representing cancer include:

- Age <20 or >70 years.
- Family history of thyroid cancer.
- **Growing nodule.**
- Nodule characteristics: Firm or hard consistency. Fixed.
- Lymphadenopathy.
- Symptoms of compression (eg, dysphonia, dysphagia).
- Ultrasound characteristics: hypoechoogenicity, irregular margins, local invasion into adjacent structures, hypoechoic halo around the nodule.

### Symptoms/Exam

- Nodules are firm, palpable.
- Cervical lymphadenopathy and hoarseness are concerning signs.
- Often found incidentally on radiologic studies that are ordered for other purposes.

### Differential

Thyroid nodules may be benign or represent one of four main types of 1° thyroid cancer:

- **Papillary:** Most common; spreads lymphatically. Has an excellent prognosis overall, with more than a 95% five-year survival rate for all but metastatic disease.
- **Follicular:** More aggressive; spreads locally and hematogenously. Can metastasize to the bone, lungs, and brain. Rarely produces thyroid hormone. Staging includes total thyroidectomy.
- **Medullary:** A tumor of parafollicular C cells. May secrete calcitonin. Fifteen percent are familial or associated with **multiple endocrine neoplasia (MEN) 2A or 2B** (associated with **RET** proto-oncogene).
- **Anaplastic:** Undifferentiated. Has a poor prognosis; usually occurs in older patients.
- **Other:** Metastases to the thyroid (breast, kidney, melanoma, lung); lymphoma (primary or metastatic).

### Diagnosis

The evaluation of a thyroid mass includes the following (see also Figure 6.8):

- Thyroid/neck ultrasound to determine nodule size, detect lymphadenopathy, and evaluate for other nodules. **Size >3 cm, high intravascular flow, irregular shapes/borders, and microcalcifications** should raise concern for malignancy (Figure 6.9).
- Check TSH. If TSH level is **normal**, proceed to FNA of the nodule.
- FNA (if the nodule is not palpable, this can be done under ultrasound guidance): Four pathologic results are possible—malignant, benign, insufficient for diagnosis, and follicular neoplasm or “suspicious for malignancy.”
- If TSH level is low (ie, **hyperactive thyroid**), proceed to **RAI uptake and scan**, as this indicates that there is an ↑ likelihood of a hot nodule. **Do not biopsy a hot nodule.**

#### KEY FACT

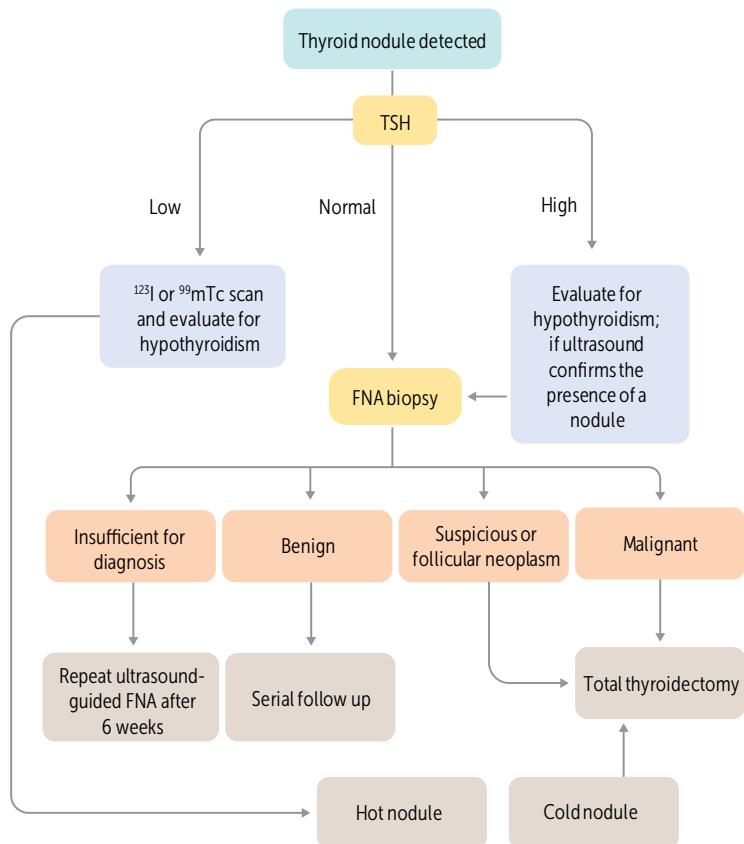
Papillary and follicular thyroid cancers are the most common 1° thyroid cancers and have the best prognosis.

#### KEY FACT

Medullary thyroid cancer can produce ↑ levels of calcitonin and is often associated with MEN 2A or 2B.

#### KEY FACT

If a palpable nodule is associated with a normal TSH, proceed directly to FNA.

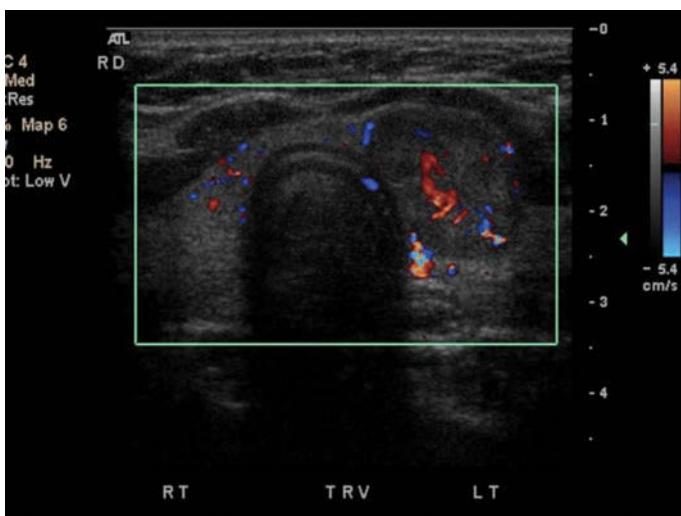


**FIGURE 6.8. Evaluation and management of a thyroid mass.** (Reproduced with permission from USMLE-Rx.com.)

- Only check calcitonin level in patients with hypercalcemia or a family history of thyroid cancer.
- If a **multinodular goiter** is present, FNA of the most suspicious nodule (by radiologic features) or the dominant nodule (largest nodule >1 cm) is acceptable, although it will not diagnose all cases of malignancy. Such patients should be followed, and nodules that ↑ in size should be considered for FNA.

**KEY FACT**

Thyroglobulin is a good marker for the presence of thyroid tissue, but it cannot be used to distinguish between benign and malignant nodules. If thyroglobulin is present after total thyroidectomy and RAI remnant ablation, it can indicate thyroid cancer recurrence.



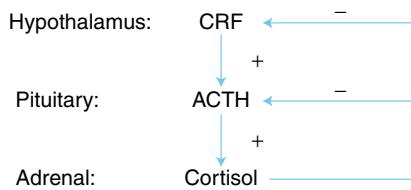
**FIGURE 6.9. Thyroid follicular carcinoma.** Doppler flow shows hypervascular nodule on transverse ultrasound in a patient with a neck mass. (Reproduced with permission from USMLE-Rx.com.)

**KEY FACT**

RAI is not used to treat medullary or anaplastic thyroid cancers because they do not uptake iodine. Treat instead with surgery ± chemotherapy.

**Management**

- **Nodules:** See Figure 6.8. The **use of levothyroxine to suppress the growth of benign nodules is no longer recommended**, as it is often ineffective and may be associated with toxicity (especially in the elderly).
- **Papillary/follicular thyroid cancer:** **Total thyroidectomy followed by RAI remnant ablation and levothyroxine** (to suppress TSH). However, if the lesion happens to only have a very small chance of recurrence/metastasis, surgery alone is okay (but this is the exception).
- **Medullary or anaplastic thyroid cancer:** Total thyroidectomy with neck dissection. Chemotherapy if metastatic disease is present.



**FIGURE 6.10. The hypothalamic-pituitary-adrenal axis.**

**Adrenal Gland Disorders**

The adrenal gland is under control of the hypothalamus and pituitary (Figure 6.10):

- **Medulla:** Produces catecholamines (epinephrine, norepinephrine, dopamine).
- **Cortex:** Composed of three zones—remember as **GFR**:
  - Glomerulosa: Produces mineralocorticoids (aldosterone).
  - Fasciculata: Produces cortisol and androgens.
  - Reticularis: Produces androgens and cortisol.
- ACTH and cortisol follow a circadian rhythm; levels are highest at around 6:00 AM, so it is best to test cortisol in the early morning.

**ADRENAL INSUFFICIENCY**

2° AI (due to ACTH deficiency from pituitary disease or iatrogenic ACTH deficiency) is much more common than 1° AI (adrenal failure); see Table 6.10 for distinguishing features.

- **1° AI (Addison disease):** Because of high adrenal reserve, >90% of both adrenal cortices must fail to cause clinical AI. You lose cortisol, aldosterone, and adrenal androgens. Causes include:
  - **Autoimmune adrenalitis:** The most common etiology of 1° AI. Approximately 50% are accompanied by other autoimmune disorders (eg, Hashimoto thyroiditis, type 1 DM), so testing for these disorders is indicated.
  - **Adrenal hemorrhage:** Seen in critically ill patients, pregnancy, anticoagulated patients, and antiphospholipid antibody syndrome.
  - **Infection:** TB, fungi (*Histoplasma*), CMV, HIV.
  - **Infiltrative disorders:** Amyloid, hemochromatosis.
  - **Metastatic malignancy:** (eg, lung, breast, stomach, colon melanoma) and lym-

**TABLE 6.10. Primary Versus Secondary Adrenal Insufficiency**

	PRIMARY	SECONDARY/TERTIALY
ACTH	High	Low
Cortisol	Low	Low
Hyperkalemia	Common	No
Hyponatremia	May be present	May be present
Hyperpigmentation	May be present	No
Mineralocorticoid replacement needed	Yes	No

phoma. However, clinically significant AI is not common in cancer because it requires loss of the majority of both adrenal cortices.

- Congenital adrenal hyperplasia.
- Adrenal leukodystrophy.
- Drugs that inhibit synthesis of cortisol: **Ketoconazole, etomidate, metyrapone.**
- **2° AI:** Any process that involves the **pituitary** and interferes with ACTH secretion. You lose cortisol and adrenal androgens but not aldosterone because it is not ACTH-dependent. Causes include:
  - Pituitary tumors.
  - Pituitary surgery or radiation.
  - Pituitary apoplexy and Sheehan syndrome.
  - Infectious or infiltrative processes (lymphocytic hypophysitis, TB, sarcoidosis).
- **3° AI:** Any process that involves the **hypothalamus** and affects CRH secretion. Again, you lose cortisol and adrenal androgens but not aldosterone because it is not ACTH-dependent.
  - Iatrogenic.
  - Hypothalamic tumors.
  - Infectious or infiltrative processes (lymphocytic hypophysitis, TB, sarcoidosis).
  - Isolated ACTH deficiency (rare).
  - Traumatic brain injury.
  - Medications: High-dose progestins (ie, megestrol, which is used to stimulate appetite in wasting syndrome or cancer), chronic opiate use.
  - Trauma or injury.

### Symptoms/Exam

- Presents with weakness, fatigue, anorexia, weight loss, nausea, vomiting, diarrhea, unexplained abdominal pain ± postural lightheadedness.
- **1° AI presents with hyperpigmentation** of the oral mucosa and palmar creases, dehydration, and **hypotension**. **Salt craving and postural dizziness** may be seen in **1° AI** but are often not seen in **2° AI**, because aldosterone is not ACTH-dependent.
- ↓ pubic/axillary hair is seen in women.

### Diagnosis

- Labs: Hyponatremia, hyperkalemia (only in **1° AI**), eosinophilia, azotemia due to volume depletion, mild metabolic acidosis, hypoglycemia, hypercalcemia.
- A morning cortisol level of **<3 µg/dL** suggests **AI**, but confirm with a **cosyntropin stimulation test** (see below).
- A random cortisol level of **≥18 µg/dL** rules out **AI**. Since cortisol is mostly bound to albumin, total cortisol level (vs free cortisol) is unreliable in hypoalbuminemia.
- **Cosyntropin stimulation test:** Obtain baseline ACTH and cortisol levels and then administer cosyntropin (synthetic ACTH) 250 µg IM or IV. After 30 to 60 minutes, post-stimulation cortisol should be **≥18 µg/dL**.
  - ↑ baseline ACTH + abnormal cosyntropin stimulation test: **1° AI**.
  - ↓ baseline ACTH + abnormal cosyntropin stimulation test: **2° or 3° AI**.
- Further considerations are as follows:
  - Critical illness: Patients diagnosed with AI while in the ICU should be retested after the acute illness resolves.
  - Imaging: If the cause of **1° AI** is not known, **adrenal imaging** can be useful in establishing the etiology. If the cause of **2° AI** is not known (eg, there is no exogenous corticosteroid exposure), order a **pituitary MRI**.

### Management

Glucocorticoid replacement: Use **hydrocortisone 10 to 30 mg/day, two-thirds in the morning and one-third in the afternoon/evening**. Dexamethasone or prednisone can also be used. When patients are under stress due to illness or surgery, they require temporarily higher doses of glucocorticoids ("stress doses"):

### KEY FACT

The most common cause of AI is exogenous corticosteroid use, presenting after withdrawal of the corticosteroid.

### KEY FACT

Hyperpigmentation indicates **1° AI** (most notable in the oral mucosa, palmar creases, and recent scars) due to compensatory high levels of ACTH that stimulate melanocytes to produce excess melanin.

### KEY FACT

A post-stimulation cortisol level of **<18 µg/dL** suggests **AI**.

### KEY FACT

If a patient presents with shock and you suspect acute **AI**, stabilize the patient with IV fluids and stress-dose steroids (dexamethasone + fludrocortisone if the cosyntropin stimulation test has not been done yet, as hydrocortisone will interfere with test results).



### QUESTION

A 56-year-old woman with RA (on prednisone 10 mg/day) and DM presents with persistent fatigue. She discontinued prednisone 2 months ago because she was concerned that it was the cause of her osteopenia. She is euvolemic with mild hypotension and has mild hyponatremia, hypoglycemia, and eosinophilia. What is the likely reason for her fatigue?

**KEY FACT**

Autoimmune diseases travel together. Think of polyglandular autoimmune syndrome type 2 if you see the following three diseases together: type 1 DM, thyroiditis, and 1° AI.

**KEY FACT**

If a type 1 DM patient who had previously been well controlled on an insulin regimen presents with new-onset hypoglycemia, consider 1° AI (Addison disease).

**KEY FACT**

If a patient with newly diagnosed 1° AI is also found to have hypothyroidism, treat the AI first with steroids + fludrocortisone or you may precipitate an adrenal crisis.

- 1° AI: Requires both mineralocorticoid and glucocorticoid replacement. Use fludrocortisone to replace the mineralocorticoid component.
- 2° AI: Requires glucocorticoid replacement only.

**Complications**

**Adrenal crisis**—acute deficiency of cortisol, usually due to major stress in a patient with preexisting AI. Characterized by shock, headache, nausea, vomiting, confusion, and fever. Fatal if not treated with immediate steroid therapy.

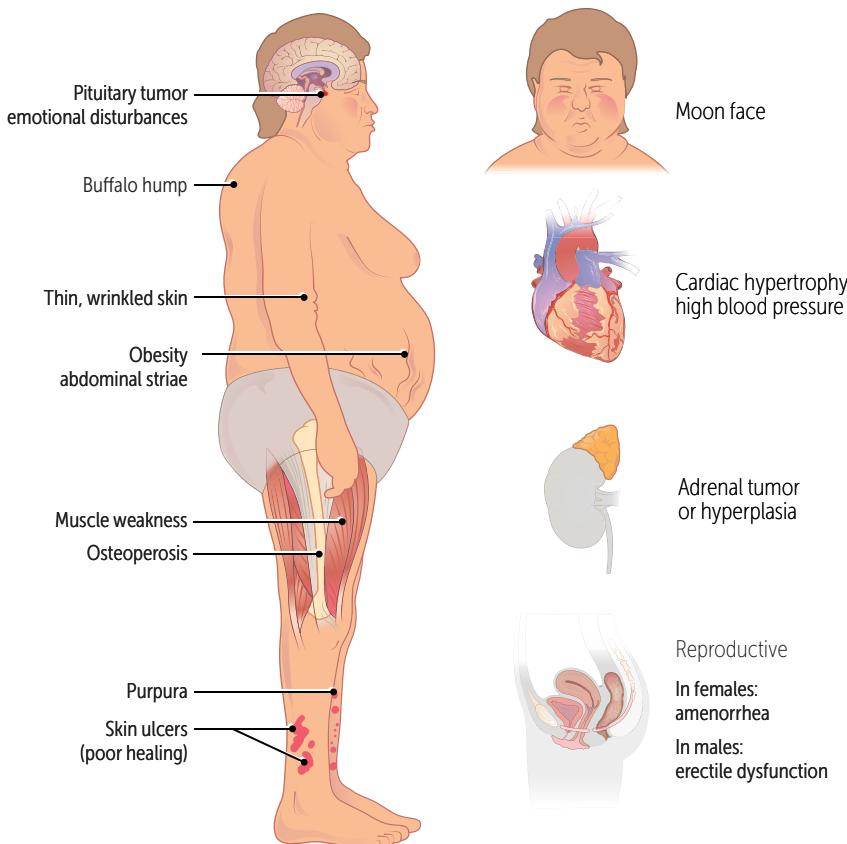
**CUSHING SYNDROME**

Cushing syndrome is due to excess cortisol resulting from exogenous or endogenous etiologies.

- **Exogenous corticosteroids:** The most common cause overall, but a dose of  $\leq 5$  mg of prednisone (this is a physiologic dose) is unlikely to suppress the HPA axis.
- Endogenous causes:
  - Cushing disease (70% of endogenous cases): Due to ACTH hypersecretion from a pituitary adenoma (most are microadenomas). More common in women.
  - Ectopic ACTH (15%): From nonpituitary neoplasms producing ACTH (eg, small cell lung, pancreatic, thymic cancers, and bronchial carcinoids). **Rapid increases in ACTH levels lead to marked hyperpigmentation, metabolic alkalosis, and hypokalemia, sometimes without other cushingoid features.** More common in men.
  - Adrenal (15%): Adenoma, carcinoma, or nodular adrenal hyperplasia.

**Symptoms/Exam**

Figure 6.11 lists the clinical characteristics of Cushing syndrome.

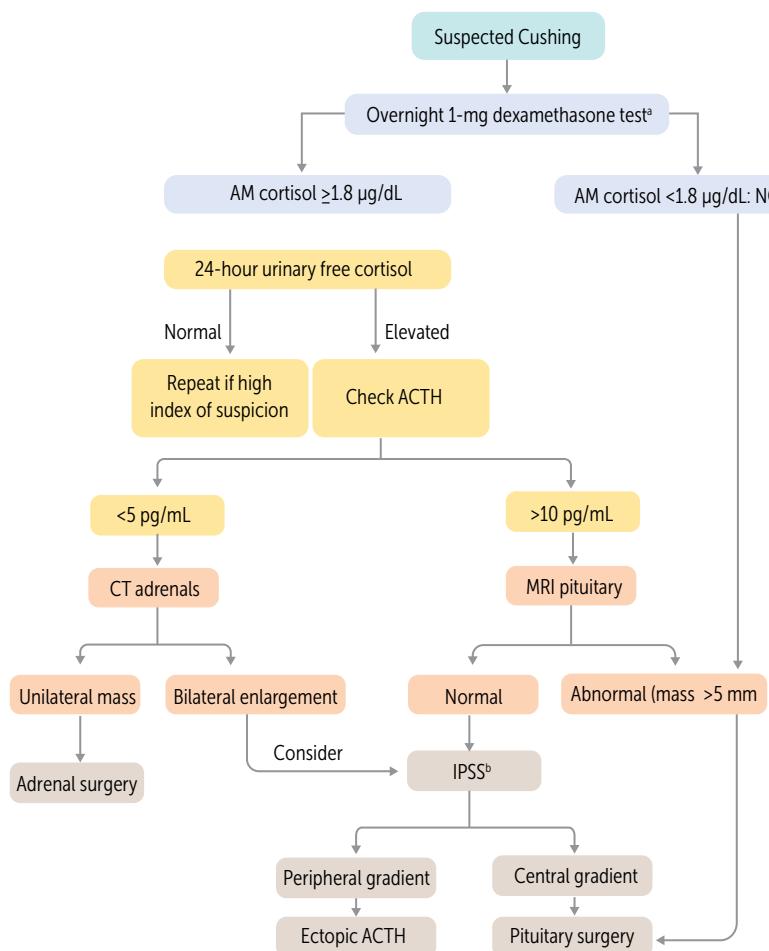
**A****ANSWER**

Central AI from chronic prednisone use that was unmasked by abrupt prednisone withdrawal.

**FIGURE 6.11. Clinical features of Cushing syndrome.** (Reproduced with permission from USMLE-Rx.com.)

## Diagnosis

- Lab abnormalities: Metabolic alkalosis, hypokalemia, hypercalcioria, leukocytosis with relative lymphopenia, glucose intolerance.
- Principles of evaluation are as follows (see also Figure 6.12):
  - Step 1: Confirm excess cortisol production.** Do either (1) 1-mg dexamethasone suppression test or (2) a 24-hour urine free cortisol level. If either test is abnormal, confirm with the other test.
  - Step 2: Check ACTH level.** High cortisol normally inhibits ACTH production completely. Thus, high or “normal” ACTH indicates ACTH-dependent Cushing syndrome (pituitary or ectopic production of ACTH, which leads to high cortisol), whereas low ACTH indicates ACTH-independent Cushing syndrome (adrenal disease that directly produces cortisol).
- ACTH-dependent:** Obtain a pituitary MRI. If the pituitary MRI is  $\ominus$  or equivocal, consider inferior petrosal sinus sampling (IPSS). Then, also look for ectopic ACTH-producing tumor with CT of the chest, abdomen, and pelvis.
- ACTH-independent:** Obtain a CT/MRI of the abdomen/pelvis to evaluate for adrenal adenoma versus carcinoma.



<sup>a</sup>Overnight 1-mg dexamethasone test: Give the patient 1 mg of dexamethasone PO to be taken at 11:00 PM.

The following morning, check cortisol between 7:00 and 9:00 AM: Normal cortisol is  $< 1.8 \mu\text{g}/\text{dL}$ .

<sup>b</sup>IPSS = inferior petrosal sinus sampling. Catheters are used to measure levels of ACTH draining from the pituitary and periphery before and after CRH simulation. If the gradient is greater from the pituitary, it suggests a central source. If greater from the periphery, the source is peripheral.

**FIGURE 6.12. Evaluation and diagnosis of Cushing syndrome.** (Reproduced with permission from USMLE-Rx.com.)

### Management

- Cushing disease: Transsphenoidal pituitary adenoma resection.
- Ectopic ACTH: Treat the underlying neoplasm. If the neoplasm is not identifiable or treatable, options are as follows:
  - Pharmacologic blockade of steroid synthesis (ketoconazole, metyrapone, aminglutethimide) or inhibition of ACTH secretion (pasireotide).
  - Potassium replacement (consider spironolactone to aid potassium maintenance as these patients require industrial doses of potassium replacement).
  - Bilateral adrenalectomy if all else fails.
- Adrenal tumors: Unilateral adrenalectomy.

### Complications

Complications are associated with long-term glucocorticoid exposure and include DM, hypertension, CAD, obesity, osteoporosis, and susceptibility to infections—such as those caused by *Nocardia*, *Pneumocystis jiroveci*, and other opportunistic pathogens.

## HYPERALDOSTERONISM

Hyperaldosteronism may account for 0.5% to 10% of patients with hypertension. Etiologies include:

- **Aldosterone-producing adenoma (Conn disease):** Accounts for 60% of cases of 1° aldosteronism.
- **Idiopathic hyperaldosteronism:** One-third of 1° aldosteronism cases; CT shows normal-appearing adrenals or bilateral hyperplasia.
- **2° hyperaldosteronism:** Refers to extra-adrenal disorders such as renin-secreting tumors, renovascular disease (renal artery stenosis, malignant hypertension), and edematous states with ↓ effective arterial volume (CHF, cirrhosis, renal disease).

### Symptoms/Exam

- Hypertension and hypokalemia are classic features, although low potassium is not necessary for diagnosis (in fact, many patients do NOT have hypokalemia). Metabolic alkalosis, mild hypernatremia, and hypomagnesemia may also be seen.
- Most patients are asymptomatic, and there are no characteristic physical findings.

### Diagnosis

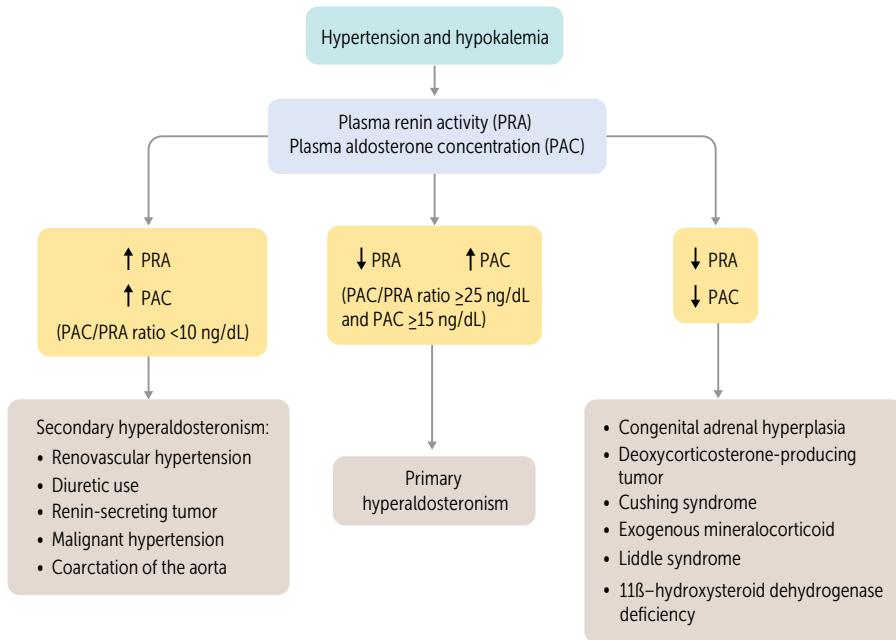
- Measure plasma aldosterone concentration (PAC) and plasma renin activity (PRA):
  - Potassium should be normalized before evaluating for hyperaldosteronism since hypokalemia suppresses aldosterone secretion.
  - The ratio of plasma aldosterone concentration to plasma renin activity (PAC/PRA) helps to distinguish primary from 2° causes of hyperaldosteronism. Because it is difficult to discontinue antihypertensives in many patients, withdraw only the agents that markedly affect this aldosterone-to-renin ratio, such as potassium-sparing diuretics (spironolactone, eplerenone, amiloride, triamterene) and potassium-wasting diuretics. If the result is not diagnostic, then proceed to discontinue other agents that may affect the ratio, including ACE inhibitors and ARB.
- **1° hyperaldosteronism:** PAC is ↑ (>15 ng/dL), PRA is suppressed, and the PAC/PRA ratio is ↑ (the cutoff is laboratory dependent and is usually ≥25).
- **2° hyperaldosteronism:** Both PAC and PRA are ↑, and the PAC/PRA ratio is <10 (Figure 6.13).

### KEY FACT

A high PAC/PRA ratio and an absolute PAC ≥15 ng/dL are characteristic of 1° hyperaldosteronism.

### KEY FACT

You can measure the PAC and PAC/PRA ratio with the patient on any antihypertensive agent EXCEPT for potassium-wasting diuretics (thiazide), and potassium-sparing diuretics (spironolactone, eplerenone, amiloride, triamterene).



**FIGURE 6.13. Evaluation of hypertension with hypokalemia.** (Reproduced with permission from USMLE-Rx.com.)

■ Confirmatory testing:

- IV saline loading (2 L of saline infused over 2-4 hours) will fail to suppress PAC into the normal range in patients with 1° aldosteronism (as opposed to low-renin essential hypertension).
- After 3 days of salt loading ( $U_{Na} > 200 \text{ mEq}$ ), 24-hour urine collection for aldosterone will not suppress PAC to  $<14 \text{ ng/dL}$  in patients with 1° aldosteronism.
- If 1° aldosteronism is diagnosed, obtain an adrenal CT to distinguish between Conn syndrome and idiopathic hyperaldosteronism (Figure 6.14).
- If CT findings are equivocal and in older patients (in whom adrenal incidentaloma is more common), consider adrenal vein sampling to localize the plasma aldosterone source.

**KEY FACT**  
If 1° aldosteronism is suspected based on the PAC and PAC/PRA ratio, confirm with a salt loading test that does not suppress aldosterone and then get an adrenal CT.



**FIGURE 6.14. Adrenal adenoma.** Cropped transaxial image from a non-contrast CT scan shows a small, low-density mass in the left adrenal gland (red arrow). Blue arrow = normal right adrenal gland, L = liver, Ao = aorta, St = stomach, S = spleen. (Reproduced with permission from USMLE-Rx.com.)



**QUESTION**

A 28-year-old woman presents with severe fatigue and weight gain for several months. She has ↑ facial hair, purple abdominal striae, central obesity, and thin skin that bruises easily. 24-hour urinary cortisol is ↑, cortisol is suppressed with high-dose but not low-dose dexamethasone, and serum ACTH level is ↑. What is the most likely diagnosis and next step in the workup?

**KEY FACT**

Treat adrenal hyperplasia with spironolactone or eplerenone; treat single adenomas with surgery.

**MNEMONIC****Pheochromocytoma rule of 10s:**

- 10% normotensive
- 10% occur in children
- 10% familial
- 10% bilateral
- 10% malignant
- 10% extra-adrenal (called paragangliomas)

**KEY FACT**

Suspect pheochromocytoma in patients with a family history of MEN 2, neurofibromatosis, or von Hippel-Lindau disease.

**KEY FACT**

Steps in diagnosis of pheochromocytoma: (1) measure metanephrenes (2) get CT or MRI of the abdomen to localize tumor. If initial imaging fails to localize the tumor, get <sup>123</sup>I-MIBG scintiscan.

**KEY FACT**

Always achieve  $\alpha$ -blockade (with phenoxybenzamine or doxazosin) before using  $\beta$ -blockers in patients with pheochromocytoma, because unopposed  $\beta$ -blockade can lead to paradoxical worsening of the hypertension.

**ANSWER**

An ACTH-secreting pituitary adenoma. A high ACTH level indicates an ACTH-dependent etiology for this patient's Cushing syndrome. The next step in the workup is a pituitary MRI.

**Management**

- Spironolactone (in high doses up to 400 mg/day) or eplerenone blocks the mineralocorticoid receptor and usually normalizes potassium. In men, the most common side effect of spironolactone is gynecomastia, but other side effects may occur (eg, rash, impotence, epigastric discomfort).
- Unilateral adrenalectomy is recommended for patients with a single adenoma.

**PHEOCHROMOCYTOMA**

Pheochromocytomas are rare tumors that produce epinephrine and/or norepinephrine. Subtypes are as follows:

- Adrenal tumor (90% of pheochromocytomas).
- Extra-adrenal locations (paragangliomas). More commonly malignant.

**Symptoms/Exam**

- Presents with episodic attacks of throbbing in the chest, trunk, and head, often precipitated by movements that compress the tumor.
- Headaches, diaphoresis, palpitations, tremor and anxiety, nausea, vomiting, fatigue, abdominal or chest pain, weight loss, cold hands and feet, and constipation may also be seen.
- Most patients are hypertensive, but hypertension is episodic in 25% of cases. Orthostasis is usually present.

**Diagnosis**

- Step 1: Make a biochemical diagnosis. Plasma fractionated free metanephrenes is the single most sensitive test. Twenty-four-hour urinary catecholamines and fractionated metanephrenes effectively confirm most pheochromocytomas detected by elevated plasma fractionated metanephrenes.
- Step 2: Localize the tumor. Obtain a CT or MRI of the abdomen/pelvis to localize the pheochromocytoma (Figure 6.15). If initial imaging is normal, further localization can be done with a <sup>123</sup>I-MIBG scintiscan (an imaging study that injects radioactive tracer).

**Management**

- Pharmacologic preparation for surgery:
  - $\alpha$ -blockers: Because surgery can precipitate hormone release, patients need to be treated with an  $\alpha$ -adrenergic blocker for a couple of weeks prior to surgery. Phenoxybenzamine (a long-acting nonselective  $\alpha$ -blocker) is commonly used, but doxazosin (a selective  $\alpha$ -1-blocker) may also be used.
  - $\beta$ -blockers: Used to control heart rate, but only after blood pressure is controlled and good  $\alpha$ -blockade has been achieved.
- Surgical resection:
  - Hydration: It is essential that patients be well hydrated before surgery.
  - Surgical resection by an experienced surgeon is the definitive treatment for these tumors. Associated with a 90% cure rate.
  - Because postoperative complications include hypotension and hypoglycemia, always hang dextrose-containing IV fluids in the recovery room!
- Follow-up: Should include 24-hour urine for metanephrenes and normetanephrenes 2 weeks postoperatively. If levels are normal, surgical resection can be considered complete. Patients should then undergo yearly biochemical evaluation for at least 10 years.



**FIGURE 6.15. Pheochromocytoma.** Abdominal CT shows a left adrenal mass of 50 mm in diameter with rounded, well-defined edges, and hyperdense areas of cystic necrosis inside (arrow). (Source: Martinez-Quintana E, et al. Acute myocardial infarction secondary to catecholamine release owing to cocaine abuse and pheochromocytoma crisis. *Int J Endocrinol Metab*. 2013;11(1):48-51.)

### Complications

Hypertensive crises, MI, cerebrovascular accidents, arrhythmias, renal failure, dissecting aortic aneurysm, cardiomyopathy.

### ADRENAL INCIDENTALOMAS

Adrenal lesions are found incidentally in approximately 2% of patients undergoing abdominal CT for unrelated reasons.

- **Symptoms/Exam:** Depends on whether the lesion is hormonally functioning or nonfunctioning (see below).
- **Differential includes:**
  - Functional adenoma: Cushing syndrome, pheochromocytoma, aldosteronoma.
  - Nonfunctional adenoma.
  - **Adrenal carcinoma:** Often large ( $>4$  cm) and high density on CT scan. Sixty percent are functional, usually secreting androgens or cortisol (or both hormones). **Virilization in the presence of an adrenal mass suggests malignancy.**
  - Metastases: Most commonly arise from the lung, GI tract, kidney, or breast.
  - Other: Myelolipoma (look for the presence of fat on CT scan), cysts, hemorrhage (usually bilateral).
- **Diagnosis:** Evaluate function:
  - Obtain plasma fractionated metanephrenes to rule out pheochromocytoma.
  - Order a 1-mg dexamethasone suppression test to rule out Cushing syndrome.
  - Determine PRA and aldosterone level to screen for aldosteronoma in patients with hypertension or hypokalemia.
- **Management:** Based on the size and functional status of the mass:
  - Resect the mass regardless of whether it is functional or nonfunctional if  $>4$  cm in diameter.
  - **Masses 3-4 cm in diameter with concerning features** on imaging (heterogeneity, irregularity, density  $>10$  Hounsfield units on noncontrast CT or  $<50\%$

#### KEY FACT

Always rule out pheochromocytoma (which can be life-threatening) and Cushing syndrome (because subclinical disease is relatively common) in a patient found to have an adrenal incidentaloma.

#### KEY FACT

If a patient has a history of malignancy, an adrenal incidentaloma will be a metastasis 25% to 30% of the time.

#### KEY FACT

Three separate indications for resection of adrenal mass: size  $>4$  cm, hormonally functioning, or imaging characteristics concerning for malignancy (eg, heterogeneity, irregularity, density  $>10$  Hounsfield units on noncontrast CT).

washout) **may be resected**. If the mass is not resected, a follow-up CT of the adrenals in 3 to 6 months is recommended to look for growth.

- If on follow-up there is no change in size, then imaging is repeated annually for 3 years. However, if the mass increases in size during follow-up, surgery should be performed.

### KEY FACT

$\text{HbA}_{1c} \geq 6.5\%$  is sufficient for the initial diagnosis of diabetes.

### KEY FACT

Autoantibodies commonly found in patients with type 1 DM:

- Anti-glutamic acid decarboxylase (GAD) antibody.
- Anti-islet cell antibody 512.
- Anti-insulin antibody (useful only in the first 1-2 weeks after insulin therapy is initiated).
- Anti-zinc transporter 8.

### KEY FACT

Age does not necessarily determine the type of DM, as more children are being diagnosed with type 2 DM, and more adults are being diagnosed with type 1 DM.

### KEY FACT

Initiate medical therapy and lifestyle changes at the time of diagnosis. Check  $\text{HbA}_{1c}$  every 3 months until the goal of <7% has been attained.

## Disorders of Lipid and Carbohydrate Metabolism

### DIABETES MELLITUS

Per the ADA, the presence of any one of the following is diagnostic for DM (see Table 6.11 for screening criteria):

- Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) plus a random glucose concentration  $\geq 200 \text{ mg/dL}$  ( $11.1 \text{ mmol/L}$ ).
- Fasting ( $\geq 8$  hours) plasma glucose level  $\geq 126 \text{ mg/dL}$  ( $7 \text{ mmol/L}$ ).
- Two-hour plasma glucose level  $\geq 200 \text{ mg/dL}$  ( $11.1 \text{ mmol/L}$ ) during an oral glucose tolerance test with a 75-g glucose load.
- $\text{HbA}_{1c} \geq 6.5\%$ .

### Symptoms/Exam

- Presents with the **three “polys”**: polyuria, polydipsia, and polyphagia.
- Rapid weight loss, dehydration, blurry vision, neuropathy, altered consciousness, acanthosis nigricans (indicates insulin resistance), and candidal vulvovaginitis may also be seen.
- Signs of DKA include **Kussmaul respirations** (rapid, deep breaths) and a fruity breath odor from acetone.

### Differential

- Type 1 DM: Autoimmune destruction of the pancreatic islet cells leading to absolute insulin deficiency; associated with a genetic predisposition. **The classic patient is young and thin and requires insulin at all times**. One or more autoantibodies are commonly found in patients with type 1 DM.
- Type 2 DM: Associated with obesity, insulin resistance, and relative insulin deficiency; accounts for roughly 90% of DM cases in the United States. Has a strong polygenic predisposition.
- 2° causes of DM: Insulin deficiency or resistance from many causes, such as CF, pancreatitis, Cushing syndrome, and medications (glucocorticoids, thiazides, pentamidine).

TABLE 6.11. Diabetes Screening Criteria

CONSIDER SCREENING EVERY THREE YEARS	CONSIDER SCREENING SOONER AND MORE FREQUENTLY
All individuals $\geq 45$ years of age	<p>If the patient is overweight (<math>\text{BMI} \geq 25 \text{ kg/m}^2</math> except in Asians <math>\text{BMI} \geq 23 \text{ kg/m}^2</math>) and:</p> <ul style="list-style-type: none"> <li>■ Is physically inactive</li> <li>■ Has a first-degree relative with diabetes</li> <li>■ Is a member of a high-risk ethnic group (African American, Hispanic, Native American, Asian American, Pacific Islander)</li> <li>■ Has delivered a baby weighing <math>\geq 9</math> lb or has been diagnosed with gestational DM</li> <li>■ Is hypertensive</li> <li>■ Has low HDL cholesterol (<math>&lt;35 \text{ mg/dL}</math>) or high TG levels (<math>&gt;250 \text{ mg/dL}</math>)</li> <li>■ Has a clinical condition associated with insulin resistance (eg, PCOS, acanthosis nigricans)</li> <li>■ Has vascular disease</li> </ul>

- Genetic defects in  $\beta$ -cell function (eg, mature-onset diabetes of the young).
- Latent autoimmune diabetes in adults: Generally considered a form of type 1 DM seen in adults. Patients have autoantibodies, but the course is less severe than that in children.

### Management

- Routine diabetic care: See Table 6.12.
- Glycemic control:** Lowering HbA<sub>1c</sub> is associated with fewer microvascular complications. The United Kingdom Prospective Diabetes Study (UKPDS) trial defined the goal HbA<sub>1c</sub> to be <7%. For therapeutic goals, see Table 6.13.
- Oral medications for type 2 DM: See Table 6.14.
- Metformin is first-line therapy** in type 2 DM (in the absence of contraindications such as estimated GFR <30 mL/min). Often a second or third oral agent or basal insulin is needed to keep HbA<sub>1c</sub> at the goal as the disease progresses. Possible second-line agents include sulfonylureas, thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors, and basal insulin.

### KEY FACT

The DPP-4 inhibitors (sitagliptin and saxagliptin) can be used in renal failure.

### KEY FACT

HbA<sub>1c</sub> may be falsely low in patients with hemolytic anemia, patients taking erythropoietin, renal failure.

### KEY FACT

Do not select sliding scale alone for inpatient DM management.

TABLE 6.12. Routine Diabetic Care

TEST	FREQUENCY	COMMENTS
<b>GLYCEMIC CONTROL</b>		
HbA <sub>1c</sub>	Every 3 months when titrating medications	Goal <7% Check every 6 months when stable
<b>MICRO- AND MACROVASCULAR COMPLICATIONS</b>		
BP	Each visit	Goal <140/90 mm Hg First-line therapy is usually ACEIs or ARBs, but calcium channel blockers, $\beta$ -blockers, and diuretics may also be used
Lipid control	At diagnosis and then every 5 years	Use a moderate-intensity statin for those >40 years of age, unless they have additional CVD risk factors, in which case, use high-intensity statin
ASA	Daily	Use if 10-year risk of CVD event is >10% or for 2° prevention in those with previous history of CVD
Dilated eye exam	Annually	<b>Type 1 DM: Within 3 to 5 years of diagnosis</b> <b>Type 2 DM: At the time of diagnosis</b> Refer more often in the setting of significant retinopathy Laser therapy can $\downarrow$ the risk of vision loss
Foot exam	Annually	<b>Comprehensive exam:</b> Note pulses, loss of peripheral sensation with monofilament, ulcers, fungal infections, calluses, or any foot deformities <b>Refer to podiatry for any abnormality</b> <b>Perform visual inspection at each visit</b>
Urine albumin	Annually	Used to screen for diabetic nephropathy after 5 years of disease duration in patients with type 1 DM and at diagnosis in patients with type 2 DM ACEIs/ARBs can slow progression to overt nephropathy
<b>OTHER HEALTH CARE MAINTENANCE</b>		
Influenza vaccine	Annually	
Pneumococcal vaccine	Once	Repeat $\times$ 1 if the first vaccine was given before age 65 and >5 years ago

TABLE 6.13. Treatment Goals for Nonpregnant Patients With DM (types 1 and 2)

	NORMAL	GOAL	ADDITIONAL ACTION SUGGESTED
Preprandial capillary plasma glucose	<100 mg/dL	80-130 mg/dL	<90 mg/dL or >150 mg/dL
Peak postprandial capillary plasma glucose	<140 mg/dL	<180 mg/dL	Target only if preprandial glucose is at target and HbA <sub>1c</sub> is still elevated
HbA <sub>1c</sub>	<5.7%	<7%	>8%

TABLE 6.14. Non-Insulin Medication Options in Type 2 DM

MEDICATION	ACTION/USE	CLINICAL APPLICATION	COMMENTS
Biguanides (metformin)	↓ glucose production and insulin resistance	First-line drug <b>Hold 2 days before elective surgery and before contrast studies</b>	<b>GI side effects, lactic acidosis (rare), no weight gain</b> <b>Contraindications: Renal insufficiency (estimated GFR &lt;30 mL/min); LFTs more than three times normal</b>
Sulfonylureas (glyburide, glipizide, glimepiride)	<b>Stimulate insulin release</b>	Second-line drug Exercise caution in the elderly because of hypoglycemia	Act like insulin ( <b>hypoglycemia, weight gain</b> ) <b>Contraindication: Severe sulfa allergy</b> Only glipizide is safe in renal failure
TZDs (pioglitazone, rosiglitazone)	↓ peripheral insulin resistance	Do not use in CHF or liver disease	<b>"Fat and fluid" retention; fracture risk</b> <b>Contraindications: CHF, active liver disease, acidosis</b> <b>Caution: Rosiglitazone carries a potential risk of MI and pioglitazone may be associated with bladder cancer and hepatotoxicity</b>
Meglitinides (repaglinide, nateglinide)	Stimulate insulin release from the pancreas	Effects are similar to those of an oral form of ultra-short-acting insulins Good for postprandial glucose Acceptable in renal failure	Hypoglycemia, weight gain
α-glucosidase inhibitors (acarbose, miglitol)	Prevent glucose adsorption from the gut	Not commonly used because of GI side effects Good for postprandial glucose	GI effects, especially flatulence and bloating
GLP-1 receptor agonists (exenatide, liraglutide)	Incretin mimetics; potentiate insulin actions Early satiety; slow gastric absorption Incretin hormones are secreted by the gut	Approved for combination use with metformin, sulfonylureas, and TZDs	Nausea, weight loss Given as an SQ injection

(continues)

TABLE 6.14. Non-Insulin Medication Options in Type 2 DM (continued)

MEDICATION	ACTION/USE	CLINICAL APPLICATION	COMMENTS
DPP-4 inhibitors (sitagliptin, saxagliptin)	Prevent breakdown of GLP-1, thus ↑ GLP-1	Approved for monotherapy or in combination with metformin or a TZD	Hypersensitivity, weight neutral
Amylin analog (pramlitide)	Hormone secreted by pancreatic β-cells to slow gastric emptying and ↓ postprandial hyperglycemia	Treat ↑ fasting glucose using combination therapy with insulin	Nausea, weight loss Cuts insulin dose by 50% Administered as an SQ injection before meals
SGLT2 inhibitors (canagliflozinn, dapagliflozin, empagliflozin)	Block reabsorption of glucose by the kidneys thereby ↑ glucose excretion	Efficacy depends on renal function, cannot use in ESRD	Vaginal yeast infections Urinary tract infections

- The goal is to minimize micro- and macrovascular risk factors, with special priority given to CVD risk reduction.
- Insulin:** For all type 1 DM and many type 2 DM patients (Table 6.15). Potential insulin regimens include “basal-bolus” (basal coverage with intermediate- to long-acting insulin plus a short-acting bolus before meals) and continuous insulin infusion delivered via an SQ catheter (“insulin pump”). See Figures 6.16 and 6.17 for recommendations on the initiation and titration of insulin.
- Pancreatic/islet cell transplant: Experimental.

#### Complications—Acute

- DKA:** Can be the initial manifestation of type 1 DM, but may also occur in patients with type 1 or type 2 DM when a stressor is present (eg, infection, infarction, surgery, medical noncompliance). Often presents with abdominal pain, vomiting, Kussmaul respirations, a fruity breath odor, and anion-gap metabolic acidosis. Mortality is <5%. Look for and treat the precipitating event when possible:
  - Close the anion gap with an IV insulin drip;** the glucose will ↓ as the gap closes. Once the glucose level is <250 mg/dL, add dextrose to IV fluids. When the anion gap has closed, insulin may be switched to SQ. **Start SQ insulin before discontinuing the insulin drip with an overlap of about 2 hours to prevent lapse in basal insulin.**
  - Fluids:** Start with NS. If the patient is not in shock, sodium is normal or ↑, and/or potassium must be repleted concurrently, switch to ½ NS or D5 ½ NS.

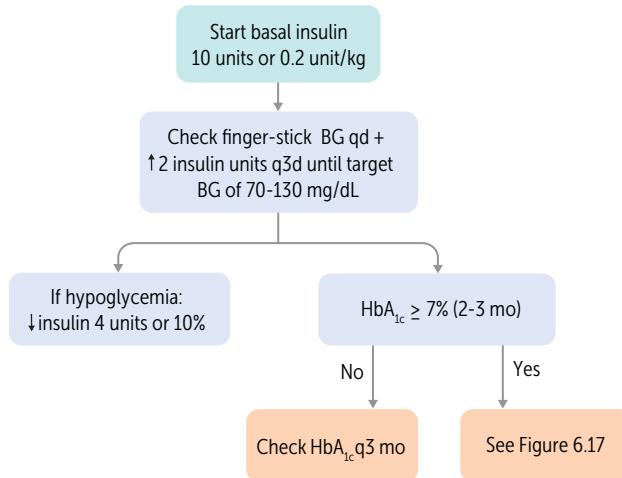
TABLE 6.15. Summary of Insulin Characteristics

INSULIN TYPE	ONSET	PEAK ACTION	DURATION
Ultrashort-acting (SQ)	Lispro, aspart, glulisine	5-15 minutes	60-90 minutes
Short-acting (SQ)	Regular	15-30 minutes	1-3 hours
Intermediate-acting (SQ)	NPH	2-4 hours	8-10 hours
Long-acting (SQ)	Glargine, detemir	3-4 hours	Glargine has virtually no peak; detemir peaks at 6-8 hours
Ultralong-acting (SQ)	Degludec	30-90 minutes	Has virtually no peak
			>24 hours

 **KEY FACT**  
First-line treatment of type 2 DM in an obese patient with normal renal function (estimated GFR >30 mL/min) is metformin.

 **KEY FACT**  
Hold metformin immediately before and after radiologic studies with IV contrast because of the risk of lactic acidosis. Do not use in CHF or liver failure.

 **QUESTION**  
A 58-year-old man with type 2 DM presents for follow-up for a high HbA<sub>1c</sub>. One year ago, his HbA<sub>1c</sub> was 8.7%, and now it is 8.2% after lifestyle modification and maximum dose of metformin. What is the best management strategy?



**FIGURE 6.16. Initiation of insulin therapy.** (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

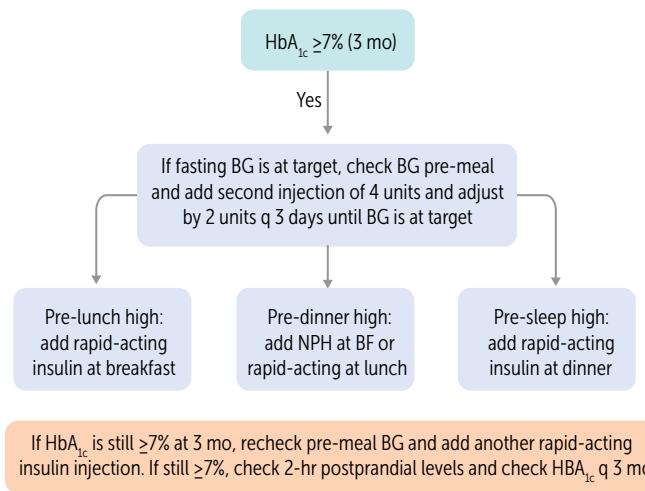
For DKA, continue an insulin drip until the anion gap closes even after glucose has normalized. For both DKA and hyperosmotic coma, continue the insulin drip until 2 hours after the first SQ injection when switching to SQ insulin; otherwise, you may risk hyperglycemia or recurrence of DKA.



### ANSWER

If HbA<sub>1c</sub> remains ≥7% for 3 months, continue metformin and add one or more of the following medications, depending on level of HbA<sub>1c</sub>: sulfonylurea, basal insulin, TZD, GLP-1 agonist, DPP-4 inhibitor, or SGLT2 inhibitor.

- **Potassium:** Usually falsely elevated due to acidosis. **Start potassium replacement at 4.0-4.5 mEq/L**, as levels will fall with treatment.
- Bicarbonate, magnesium, and phosphate are usually not needed.
- **Hyperosmolar nonketotic coma or hyperglycemic hyperosmolar state:** Seen in type 2 DM. Significant hyperglycemia (often >600 mg/dL), hyperosmolality, and dehydration without ketosis are characteristic. Mortality can reach 20% and frequently occurs in elderly patients with multiple comorbidities. There is often a precipitating event (eg, infection, infarction, intoxication, medical noncompliance). Presents with the “polys,” weakness, lethargy, and confusion (when osmolarity is >310 mOsm/L) or with coma (>330 mOsm/L). Treatment is similar to that of DKA; treat the underlying stressor and give fluids, an insulin drip, and electrolyte replacement.



**FIGURE 6.17. Titration of insulin for intensive treatment of diabetes.** (Reproduced with permission from USMLE-Rx.com.)

- **Fluids:** Often need 6 to 10 L. Start with NS and then follow with  $\frac{1}{2}$  NS; add D5 when glucose levels are <250 mg/dL. Watch for pulmonary edema and volume overload in elderly patients.
- **Insulin drip:** See the DKA section above.
- **Potassium:** See the DKA section above.
- **Sodium:** In both DKA and hyperosmotic coma, sodium is often falsely low due to hyperglycemia. For every 100 mg/dL that the patient's glucose exceeds 100 mg/dL, the Na is falsely  $\downarrow$  by 2.4 mEq/L.
- See Table 16.6 for differences between DKA and hyperosmolar coma.

### KEY FACT

Tight glycemic control prevents **microvascular** complications but has no significant effect on macrovascular outcomes.

## Complications—Chronic

- Microvascular complications:
  - Retinopathy: Occurs after DM has been present for 3 to 5 years. Prevent with a yearly eye exam and laser therapy for retinal neovascularization. Generally precedes neuropathy.
  - Nephropathy: The first sign is usually microalbuminuria. Prevent with BP control, glucose control, and ACEIs or ARBs.
  - Neuropathy: Often progressive, involving the distal feet and hands. Prevent ulcers with foot care, careful inspection, and podiatry as needed.
- Macrovascular complications:
  - Associated with an  $\uparrow$  risk of MI and stroke. Prevent with ASA therapy in high-risk patients; maintain a low threshold for cardiac stress testing; use a moderate-intensity statin for those >40 years of age, unless they have additional CVD risk factors, in which case, use a high-intensity statin.
  - Infections: DM patients are at  $\uparrow$  risk for unusual infections such as **necrotizing fasciitis or myositis, mucormycosis, emphysematous cholecystitis, and malignant otitis externa**.

### KEY FACT

Autonomic symptoms from hypoglycemia can be blunted in patients on  $\beta$ -blockers or in those whose repeated hypoglycemic episodes have rendered them unaware of hypoglycemia.

## GESTATIONAL DIABETES

See the Women's Health chapter.

## HYPOGLYCEMIA

Although most hypoglycemic reactions occur in patients being treated with insulin, they may also be seen in those on sulfonylureas, meglitinides, and, rarely, other medications—usually when used in combination with sulfonylureas or insulin (Table 6.17).

**TABLE 6.16. DKA Versus Hyperosmolar Coma**

	DKA	HYPEROSMOLAR COMA
Serum HCO <sub>3</sub>	Low (<15 mEq/L)	Normal or slightly low
pH	<7.3	>7.3
Blood glucose	<800 mg/dL; can be normal	Often >800 mg/dL
Serum ketones	>5 mmol/L	<5 mmol/L
Urine ketones	Large	Small

### QUESTION

A woman with type 2 DM and depression presents with recurrent episodes of lightheadedness, diaphoresis, and tremulousness. She has been on stable doses of glargine, mealtime insulin lispro (Humalog), benazepril, and citalopram. She undergoes a supervised fast in the hospital with the following lab results when she develops similar symptoms:  $\uparrow$  insulin levels,  $\downarrow$  C-peptide, and  $\downarrow$  glucose. What is the diagnosis?

TABLE 6.17. Diagnosis of Hypoglycemic Disorders<sup>a</sup>

	INSULIN	C-PEPTIDE	SULFONYLUREA SCREEN
Insulinoma	High	High	-
Factitious insulin ingestion	High	Low	-
Sulfonylureas	High	High	+

<sup>a</sup>A 72-hour fast is necessary to rule out insulinoma. Insulin and C-peptide levels should be measured when glucose level is <45 mg/dL and is accompanied by characteristic symptoms of hypoglycemia.



### MNEMONIC

#### Causes of hypoglycemia—

**REEXPLAIN**

**R**enal failure

**E**xogenous (eg, sulfonylurea)

**P**ituitary failure

**L**iver failure

**A**lcohol

**I**nsulinoma, **I**nfection

**N**eoplasm

### Symptoms/Exam

- Neuroglycopenic symptoms (low glucose delivery to the brain): Mental confusion, stupor, coma, focal neurologic findings mimicking stroke, death.
- Autonomic symptoms: Tachycardia, palpitations, sweating, tremulousness, nausea, hunger.

### Differential

- Insulin reaction: Too much insulin, too little food, or too much exercise can cause hypoglycemia in patients on insulin.
- Sulfonylurea overdose: Especially problematic in elderly patients or in those with renal failure causing ↓ medication clearance.
- Factitious hypoglycemia: A surreptitious or inadvertent hypoglycemic agent used in a nondiabetic patient (eg, incorrect medication dispensed).
- Insulinomas: Rare tumors of the pancreatic islets cells that secrete insulin. Usually single, benign tumors that can be surgically resected.
- Reactive hypoglycemia: Hypoglycemia after a meal may be seen in patients with “dumping syndrome” following bariatric surgery; otherwise rare.
- Autoimmune hypoglycemia: A rare condition with anti-insulin antibodies that cause hypoglycemia.

### Diagnosis

- Check glucose level when symptoms arise to confirm hypoglycemia.
- Conduct a supervised fast for up to 72 hours. When glucose levels are <45 mg/dL and the patient experiences the characteristic symptoms of hypoglycemia, measure simultaneous glucose, insulin, C-peptide, proinsulin, and sulfonylurea levels (Table 6.17).

### Management

- Conscious patients: Glucose tablets; orange juice or other sugar-containing beverages.
- Unconscious patients: Give 1 mg glucagon IM or 50% glucose solution IV. If these are not available, honey, syrup, or glucose gel may be rubbed into the buccal mucosa.



### KEY FACT

For patients with postprandial hypoglycemia or “dumping syndrome” after gastrectomy or gastric bypass surgery, treat with small mixed meals containing protein, fat, and high-fiber complex carbohydrates.



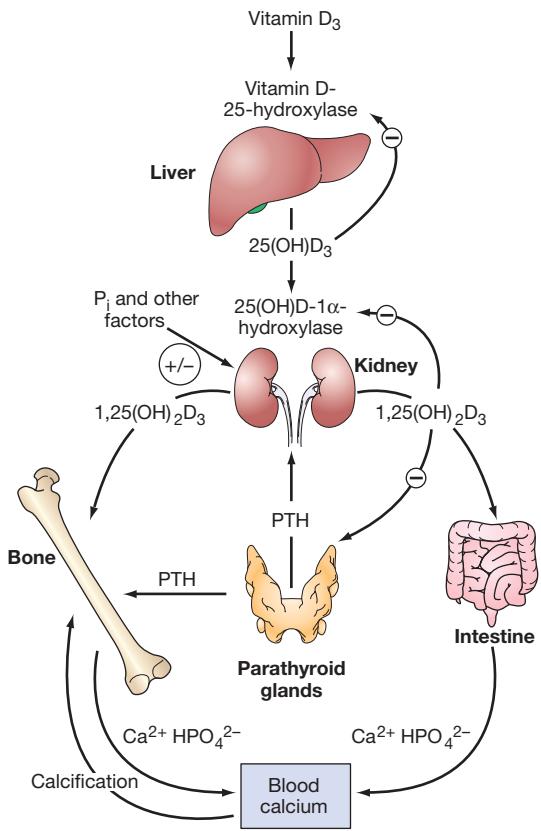
### ANSWER

Possible insulin or sulfonylurea abuse. Patients with surreptitious use of insulin will have ↑ insulin levels and ↓ C-peptide levels.

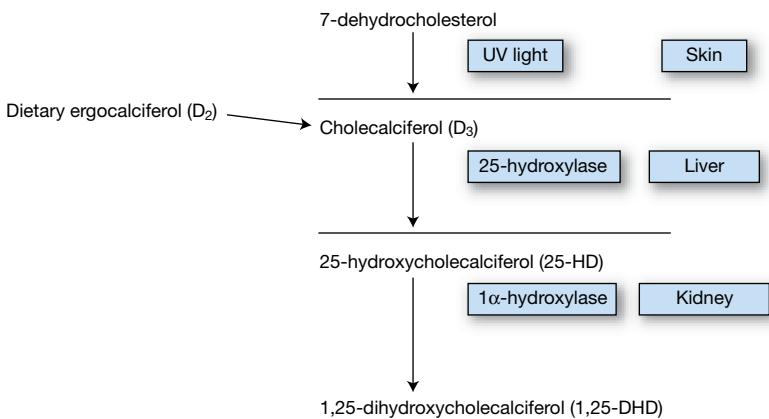
## Mineral Metabolism and Metabolic Bone Disease

### CALCIUM METABOLISM

Figure 6.18 delineates the hormonal control of calcium metabolism. Figure 6.19 graphically depicts the mechanisms of vitamin D metabolism. The 25-hydroxyvitamin D (25-HD) level indicates body vitamin D stores, and 1,25-dihydroxyvitamin D (1,25-DHD) is the biologically active hormone.



**FIGURE 6.18. Hormonal control loop for calcium metabolism and function.** Low serum calcium levels prompt a proportional ↑ in PTH concentration, which mobilizes calcium from the bone. PTH also increases the synthesis of 1,25(OH)<sub>2</sub> vitamin D in the kidney, which in turn stimulates the mobilization of calcium from bone, increases absorption of calcium in the intestine, and downregulates PTH synthesis. (Reproduced with permission from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 2246.)



**FIGURE 6.19. Vitamin D metabolism.** Vitamin D is derived when UV light from the sun hits the skin, converting 7-dehydrocholesterol into cholecalciferol (D<sub>3</sub>), or when ergocalciferol (D<sub>2</sub>) is ingested and then converted to D<sub>3</sub>. D<sub>3</sub> is 25-hydroxylated to 25-hydroxycholecalciferol (25-HD) in the liver. 25-HD is the 1° storage form. 25-HD is converted to 1,25-dihydroxycholecalciferol (1,25-DHD) in the kidney under PTH regulation. 1,25-DHD is the active form of the hormone.

## HYPERCALCEMIA

Hypercalcemia most commonly presents as an incidentally discovered laboratory abnormality in an asymptomatic patient. Can be classified as PTH-mediated or PTH-independent.

### Symptoms/Exam

Best remembered by the mnemonic “stones, bones, groans, and psychiatric overtones” (Table 6.18).

### Differential

#### KEY FACT

Eighty percent of hospitalized hypercalcemia cases are due to malignancy. Eighty percent of outpatient hypercalcemia cases are due to 1° hyperparathyroidism.

#### KEY FACT

Lithium can lead to hypercalcemia by ↑ PTH.

#### MNEMONIC

##### **Causes of hypercalcemia—**

##### **CHIMPANZEES**

Calcium supplementation

Hyperparathyroidism

Iatrogenic/Immobility

Milk-alkali syndrome

Paget disease

Adrenal insufficiency

Neoplasm

Zollinger-Ellison syndrome

Excess vitamin A

Excess vitamin D

Sarcoidosis

- 1° hyperparathyroidism: See the section below.
- Malignancy-associated hypercalcemia: Occurs in 10% to 15% of malignancies and portends a poor prognosis. Has three mechanisms:
  - Tumor release of PTHrP (most common): **Homologous to PTH** and causes bone resorption and hypercalcemia similar to those caused by PTH, but it does not ↑ 1,25-DHD production. Serum phosphate is often low. **Seen with solid tumors** (eg, breast, lung, renal cell, ovarian, and bladder carcinoma).
  - 1,25-DHD production by tumor: Due to 1 $\alpha$ -hydroxylase activity; associated with lymphomas.
  - **Local osteolysis from metastases or adjacent tumor mass:** Typically multiple myeloma, breast cancer, or lymphoma.
- **Granulomatous disorders:** Sarcoidosis and TB result in ↑ 1,25-DHD production. Can be treated with glucocorticoids to suppress 1 $\alpha$ -hydroxylase enzyme.
- Endocrinopathies:
  - Thyrotoxicity: 10% of thyrotoxic patients can have ↑ turnover of bone and occasional hypercalcemia.
  - Untreated AI.
  - Pheochromocytoma, VIPoma (rare).
- Hypervitaminosis A and D:
  - Vitamin A excess leads to bone resorption and associated hypercalcemia.
  - Vitamin D intoxication leads to ↑ 25-HD levels, which stimulate ↑ intestinal absorption of calcium and ↓ renal excretion.
- **Drug induced:** Thiazides, lithium, calcium-based antacids, estrogens, androgens, teriparatide (PTH 1-84).
- Immobilization: Serum calcium elevations are typically mild but may reach 15 mg/dL. Serum PTH levels are usually slightly elevated, consistent with mild hyperparathyroidism. It is also associated with hypercalciuria.
- **Milk-alkali syndrome:** Occurs when **large quantities of calcium are ingested with absorbable antacids** and cause hypercalcemia, alkalosis, nephrocalcinosis, and kidney dysfunction.

TABLE 6.18. Signs and Symptoms of Hypercalcemia

PSYCHIC OVERTONES	ABDOMINAL GROANS	STONES	BONES	OTHER
Lethargy	Nausea	Nephrolithiasis	Osteitis fibrosa	Weakness
Depression	Vomiting	Nephrocalcinosis	Arthritis	Pruritis
Psychosis	Constipation	Nephrogenic DI (polyuria, polydipsia)	Fractures (depending on the cause)	Pancreatitis
Ataxia	Anorexia	Uremia		Hypertonia
Stupor				Bradycardia
Coma				Shortened QT Band keratopathy <sup>a</sup>

<sup>a</sup>A mottled-looking band stretching horizontally across the cornea.

- Benign familial hypocalciuric hypercalcemia: An autosomal dominant disorder caused by a loss-of-function mutation in the gene encoding the calcium sensing receptor. Characterized by hypercalcemia and hypocalciuria with normal to ↑ PTH levels.

### Diagnosis

- Check ionized calcium or correct for albumin level:

$$\text{Corrected Ca}^{++} = \text{serum Ca (mg/dL)} + [0.8 \times (4.0 - \text{albumin (g/dL)})]$$

(ie, for each 1.0 g/dL ↓ in albumin, add 0.8 mg/dL to measured total serum calcium)

- Determine PTH: If ↑, the differential should include PTH-mediated causes of hypercalcemia; if suppressed, check PTHrP, 25-HD, and 1,25-DHD (Table 6.19).

### Management

- Hydration with NS** is the essential element in treating acute hypercalcemia. Often requires 2.5-4.0 L of NS per day; use caution in the setting of CHF. **Loop diuretics** are indicated **only after complete rehydration**.
- IV bisphosphonates** (pamidronate or zoledronic acid):
  - The treatment of choice in suspected hypercalcemia of malignancy to ↓ bone resorption.
  - Their effect on serum calcium will be **delayed at least 24 hours**, and the calcium nadir will occur approximately 3 to 5 days after injection. Hypocalcemic effects will last 2 to 3 weeks for pamidronate and 4 to 6 weeks for zoledronic acid.
  - Side effects include a mild ↑ in serum creatinine, transient fever and myalgias, and hypophosphatemia. Also rarely associated with **osteonecrosis of the jaw**.
- Calcitonin (SQ)**:
  - Use only in the presence of **severe symptomatic hypercalcemia**.
  - Works faster than bisphosphonates, but efficacy is lost after 3 days owing to **tachyphylaxis**.
- Glucocorticoids**: First-line treatment in patients with **vitamin D-** or **vitamin A-** mediated hypercalcemia, including ↑ 1,25-DHD production from **lymphoma** or **granulomatous disease**.



### QUESTION

An asymptomatic 35-year-old woman presents for an annual exam and is found to have a serum calcium level of 10.8 mg/dL. Her father also has mild hypercalcemia. Follow-up testing reveals a mildly ↑ PTH level of 65 pg/mL. What is the most likely diagnosis?



### KEY FACT

Think of 1° hyperparathyroidism in a patient with ↑ PTH and ↑ calcium. Phosphorus is usually low-normal.



### KEY FACT

First-line treatment for hypercalcemia is normal saline infusion to counteract volume depletion. If hypercalcemia is persistent and the patient has severe symptoms, add calcitonin. For patients with known cancer, add an IV bisphosphonate instead of calcitonin (eg, pamidronate, zoledronate).

TABLE 6.19. Laboratory Findings Associated With Hypercalcemia

	CALCIUM	PHOSPHORUS	PTH	PTHrP	OTHER
1° hyperparathyroidism	↑	↓	↑	↓	
2° hyperparathyroidism	↓/normal	↑/normal	↑	↓	
3° hyperparathyroidism	↑	↑	↑	↓	
PTHrP mediated	↑	↓	↓	↑	
1,25-DHD mediated	↑	↑	↓	↓	↑ 1,25-DHD
Vitamin D intoxication	↑	↑	↓	↓	↑ 25-HD

**A****ANSWER**

Benign familial hypocalciuric hypercalcemia. Urinary calcium excretion is low in this disorder but high in 1° hyperparathyroidism. No treatment is necessary, but always evaluate first-degree relatives.



**FIGURE 6.20. Hyperparathyroidism, bone resorption.** Widening of the sacroiliac joints with thinning of the iliac bones and generalized osteopenia. Other metabolic disorders resulting in Ca/PO imbalance. (Reproduced with permission from USMLE-Rx.com.)

**KEY FACT**

Hyperparathyroidism causes the greatest bone loss at the forearm, followed by the hip (sites of cortical bone). The spine (trabecular bone) is least affected.

**PRIMARY HYPERPARATHYROIDISM**

Eighty percent of cases of 1° hyperparathyroidism are due to a single parathyroid adenoma; the rest are due to multigland hyperplasia and cancer. Can be part of MEN 1 or MEN 2A syndrome.

**Symptoms/Exam**

- Eighty-five percent of patients are asymptomatic and are diagnosed on screening labs.
- Like hypercalcemia, it can present with “stones, bones, groans, and psychiatric overtones.”
  - Musculoskeletal: Osteoporosis, **weakness, and fatigue** (Figure 6.20).
  - Renal: **Nephrolithiasis**; gradual onset of **renal insufficiency** from nephrocalcinosis and nephrogenic DI.
  - Osteitis fibrosa cystica: ↑ bone turnover causing bone pain and pathologic fractures. Also characterized by ↑ alkaline phosphatase. Radiographs of the phalanges and skull reveal subperiosteal resorption of cortical bone. Osteolytic lesions due to brown tumors (cystic bone lesions containing fibrous tissue) may also be apparent.

**Differential**

- **Familial benign hypocalciuric hypercalcemia:** Distinguished from 1° hyperparathyroidism by **normal or mildly ↑ PTH and marked hypocalciuria**. Requires no therapy.
- **MEN syndromes:** See the Multiple Endocrine Neoplasia section below.
- Parathyroid carcinoma is a rare cause of hyperparathyroidism, accounting for <1% of hyperparathyroidism. Usually presents with a palpable neck mass (75%) and with serum calcium levels ≥14.0 mg/dL or serum PTH levels >5 times normal.
- **Lithium therapy:** Lithium shifts the set point for PTH secretion, resulting in hypercalcemia.

**Diagnosis**

Made by laboratory tests showing ↑ PTH (can also be **inappropriately normal in the setting of hypercalcemia**), ↑ Ca<sup>++</sup>, and ↓ or normal phosphorus. Further evaluation should include the following:

- Measurement of 24-hour urinary calcium and creatinine.
- Evaluation of renal function with creatinine.
- Bone mineral density (BMD) evaluation by dual-energy x-ray absorptiometry (DEXA).
- Measurement of 25-HD level. Low levels can cause 2° hyperparathyroidism and can predispose to hungry bone syndrome (see below).
- **Imaging studies of the parathyroid glands** (neck ultrasound and parathyroid sestamibi scan) are not useful for diagnosis but may be helpful in preoperative planning.

**Management**

- **Parathyroidectomy is the treatment of choice.** The cure rate is 95%, and the complication rate (hypoparathyroidism, recurrent laryngeal nerve injury) is <1%. Surgery is recommended under the following conditions:
  - Age <50 years.
  - Serum calcium 1.0 mg/dL above the upper limit of normal.
  - Creatinine clearance <60 mL/min.
  - BMD with a T-score < -2.5 at any site.
  - Urine calcium excretion >400 mg/day (10 mmol/day).
  - Patient preference or inability to follow up.

- **Medical therapy:** Usually reserved for **symptomatic patients who are unsuitable candidates for surgery:**
  - **Cinacalcet** is a calcimimetic agent that binds to sites of the parathyroid glands' extracellular calcium sensing receptors to ↑ the glands' affinity for extracellular calcium, thereby ↓ PTH secretion. Patients can be treated with cinacalcet for failed surgical parathyroidectomy, 2° hyperparathyroidism from CKD, hypercalcemia from parathyroid carcinoma or for the initial treatment of 1° hyperparathyroidism when surgery is not appropriate or is refused by the patient.
  - Bisphosphonates can prevent bone loss.

### Complications

- Hypercalcemia, nephrolithiasis, nephrocalcinosis with renal insufficiency, osteoporosis.
- **Hungry bone syndrome:** Severe hypocalcemia occurring after parathyroidectomy, usually as a result of chronic bone disease.

## HYPOCALCEMIA

Chronic hypocalcemia results from deficiency or failure to respond to either PTH or vitamin D. Acute hypocalcemia can occur even when PTH is high if adaptive mechanisms are overwhelmed. Etiologies are outlined in Table 6.20.

### Symptoms/Exam

- **Neuromuscular excitability:** Paresthesias, seizures, organic brain syndrome, or **tetany** (a state of spontaneous tonic muscular contraction). Often heralded by numb-

**TABLE 6.20. Etiologies of Hypocalcemia**

PATHOLOGY	MECHANISM/NOTES
Hypoparathyroidism	Most often postsurgical Also autoimmune, congenital, or infiltrative (hemochromatosis, Wilson disease, sarcoidosis)
Pseudohypoparathyroidism (PTH resistance)	A rare, heritable disorder of target organ resistance to PTH; usually presents in childhood
Vitamin D deficiency	Deficiency can result from lack of sunlight, malabsorption, or liver/renal disease; diagnosed by low 25-HD level; treat with high-dose PO ergocalciferol <b>Long-standing deficiency leads to osteomalacia in adults (myopathy, poor bone mineralization with pseudofractures) or to rickets in children</b>
Extravascular deposition	<b>Pancreatitis</b> , rhabdomyolysis, tumor lysis, osteoblastic metastases, hungry bone syndrome
Sepsis or severe illness	
Hypomagnesemia	Malabsorption, chronic alcoholism, cisplatin therapy Diuretics, aminoglycosides
Drugs	Calcium chelators ( <b>citrated blood products</b> ) Bisphosphonates, cinacalcet, <b>cisplatin</b>



### QUESTION

A 65-year-old man undergoes a thyroidectomy for papillary thyroid carcinoma. On postoperative day 2, he complains of perioral numbness and bilateral hand cramping and muscle spasms. What is the most likely explanation for his symptoms, and how should he be treated?

**KEY FACT**

Common causes of hypocalcemia are vitamin D deficiency, hypomagnesemia, neck surgery (thyroidectomy, surgery for throat cancer), or neck irradiation.

**KEY FACT**

Not all fractures in older adults are due to osteoporosis. Look for osteomalacia, particularly in nursing home residents.

**KEY FACT**

Caucasians and Asians are at higher risk for osteoporosis than African Americans.

**KEY FACT**

Screen for osteoporosis with DEXA in all women  $\geq 65$  years of age and all men  $\geq 70$  years of age. Consider screening postmenopausal women and men  $\geq 50$  years of age if risk factors are present.

ness and tingling of the fingertips and perioral zone, its classic component is carpopedal spasm.

- **Chvostek sign:** Contraction of facial muscles in response to tapping of the facial nerve.
- **Trousseau sign:** Elicited by inflating a BP cuff to 20 mm Hg above systolic BP for 3 minutes. A  $\oplus$  response is carpal spasm.
- Soft tissue calcium deposition: Cataracts; calcification of basal ganglia.
- Cardiac: Prolonged QT interval.
- Dermatologic: Dry, flaky skin with brittle nails.
- Pulmonary: Bronchospasm.
- Musculoskeletal: Chronic hypoparathyroidism can cause  $\uparrow$  bone mineral density, particularly in the lumbar spine.

**Diagnosis**

First check calcium and correct for albumin or check ionized calcium; then check phosphorus, magnesium, and PTH (Table 6.21). If PTH is  $\uparrow$  or normal, check 25-HD and renal function.

**Management**

- **Acute:** In the setting of tetany, initiate a continuous IV calcium drip while starting oral calcium; give calcitriol if needed.
- **Chronic:** Oral calcium and calcitriol if needed.

**PRIMARY OSTEOPOROSIS**

1° osteoporosis is characterized by low bone mass and  $\uparrow$  skeletal fragility leading to  $\uparrow$  risk of fractures, particularly of the vertebrae, hip, and long bones (proximal femur and distal radius). Genetic and environmental risk factors include the following:

- Female sex, although men are also at risk (due to androgen deficiency).
- Advanced age.
- Caucasian or Asian ethnicity.
- Previous fracture.
- Long-term glucocorticoid use (prednisone  $\geq 5$  mg/day for at least 3 months).
- Low body weight.
- A family history of osteoporosis or hip fracture.
- Tobacco or alcohol use.
- Premature menopause ( $<45$  years) or history of hypogonadism.
- Vitamin D and calcium deficiencies.

**Symptoms/Exam**

May be asymptomatic or present with back pain, loss of height, or nonspinal fractures. Exam may be normal. Patients may be thin and have a “dowager’s hump” (kyphosis).

**TABLE 6.21. Laboratory Findings Associated With Hypocalcemia**

	CALCIUM	PHOSPHORUS	PTH	OTHER
Hypoparathyroidism	↓	↑	↓	
PTH resistance	↓	↑	↑	
Vitamin D deficiency	↓	↓	↑	↓ 25-HD
1,25-DHD resistance	↓	↓	↑	↑ 1,25-DHD

**ANSWER**

Acquired hypocalcemia from hypoparathyroidism as a complication of thyroidectomy. Treat acutely with an IV calcium drip and correct any hypomagnesemia. Also initiate therapy with oral calcium, and add calcitriol if his symptoms persist.

## Diagnosis

- DEXA imaging is the gold standard for diagnosis of osteoporosis. DEXA measures BMD at appendicular (hip and radius) and axial (hip) sites:
  - Osteoporosis is diagnosed if the BMD T-score is  $\geq 2.5$  standard deviations below that of young healthy adults at the age of peak bone mass.
  - Osteopenia is diagnosed if the T-score is between  $-1.0$  and  $-2.5$ .
- Z-scores compare a patient's BMD with age- and gender-matched norms. A low Z-score ( $< -2$ ) should raise suspicion for 2° causes of osteoporosis. Think Z-score for "Zebra" (unusual causes of osteoporosis). Use Z-scores in men aged  $<50$  years and in premenopausal women.
- Osteoporosis can be diagnosed clinically in the presence of vertebral or other fragility fractures—eg, hip fractures, compression fractures (Figure 6.21), and Colles fracture of the wrist.

## Management

Many treatment options are available (Table 6.22). Regimen must be tailored to the individual needs of each patient. Generally, treatment is indicated for all patients with:

- Osteoporosis (T-scores below  $-2.5$ ).
- Women with previous fragility fractures of the hip or vertebra.
- T-score between  $-2.5$  and  $-1.5$ , with Fracture Risk Assessment Tool (FRAX)-determined 10-year hip fracture risk  $>3\%$  or major osteoporotic fracture risk  $>20\%$ . FRAX is an online risk calculator to better predict an individual's 10-year risk of hip or other major osteoporotic fracture.
- Management also includes:
  - Calcium 1000-1200 mg daily (combined from diet and/or supplements): Note that most healthy individuals do not require calcium supplementation:
    - Calcium supplements are generally reserved for patients with intestinal malabsorption or calcium-deficient diets that do not include dairy products, calcium-fortified foods.
    - Some reports have indicated that calcium supplements  $\uparrow$  the risk of MI. However, the Women's Health Initiative found that 7 years of vitamin D and calcium supplementation did not  $\uparrow$  CVD but did  $\uparrow$  the risk of nephrolithiasis by 13%.
    - Taking calcium supplements with meals can reduce the risk of nephrolithiasis.
  - Vitamin D: 600 IU daily for adults up to age 70 and 800 IU daily for older adults. It is well established that individuals with vitamin D deficiency need much higher doses to raise blood levels of 25-hydroxyvitamin D above 30 ng/mL. In these patients, vitamin D replacement in doses of 800-2000 IU daily or more are needed to achieve recommended levels. The upper limit of safety for vitamin D is 4000 IU/day.
  - Weight-bearing exercises, unless contraindications exist.
  - Smoking cessation and limitation of alcohol.
  - Fall prevention measures for frail patients (handrails, assistive devices for ambulation, balance exercises).

## Complications

**Fractures.** Hip fractures are associated with 30% mortality in men (higher mortality rate than for women). Vertebral fractures are associated with chronic pain and disability.

## KEY FACT

World Health Organization diagnostic criteria for individuals **older than age 50 years** based on T-scores: Osteopenia is defined as a T-score of  $-1.0$  to  $-2.5$ . Osteoporosis is diagnosed when the T-score is  $< -2.5$ , or a history of fragility fractures.



**FIGURE 6.21. Osteoporosis.** Plain radiograph shows diffuse radiolucency of the bones with biconcavity of the vertebral bodies from insufficiency fractures that occurred in a 75-year-old woman with chronic back pain.  
(Reproduced with permission from William Scott, MD.)

## KEY FACT

Bisphosphonates are the first-line agent to treat osteoporosis. Bisphosphonates, denosumab, and teriparatide are the three classes of drug that  $\downarrow$  the rate of nonvertebral fracture in osteoporotic patients.

TABLE 6.22. First- and Second-Line Therapy for Osteoporosis

TREATMENT	NOTES	TREATMENT CONSIDERATIONS
<b>FIRST-LINE THERAPY</b>		
<b>Oral bisphosphonates</b>	Pill taken daily or, more commonly, given weekly at a higher dose ↓ all types of fractures; improve BMD Side effects include esophagitis Pill taken monthly; ↓ vertebral fractures only	Most patients should start with these oral bisphosphonates Also first-line therapy to prevent and treat osteoporosis from glucocorticoids Must be taken on an empty stomach to ↓ the risk of esophagitis <b>Osteonecrosis of the jaw (ONJ) is a rare complication of bisphosphonate therapy</b> seen primarily in cancer patients treated with <b>high-dose IV formulation (zolendronate)</b> <b>Atypical low-impact fractures of the femoral shaft</b> (subtrochanteric or diaphyseal) are a rare complication of bisphosphonate therapy; risk is particularly ↑ among patients taking high-dose corticosteroids and those receiving bisphosphonates for >5 years General approach is to provide a 5-year course of bisphosphonate therapy, then evaluate whether "medication holiday" is appropriate
<b>IV bisphosphonates</b> (zolendronate)	IV annually; ↓ all types of fractures	Give to patients who cannot tolerate oral bisphosphonates Risks and complications, same as oral therapy
<b>SECOND-LINE THERAPY</b>		
Selective estrogen receptor modulators (SERMs) (raloxifene)	SERMs can prevent osteoporosis but are <b>not effective therapy for established osteoporosis</b> ↓ the risk of vertebral fractures by about 40%, but does not appear to reduce the risk of nonvertebral (eg, hip) fractures	Hot flashes are common ↑ the risk of VTE but ↓ that of breast cancer Use in patients who are at high risk for breast cancer or are unable to tolerate a bisphosphonate
Intranasal calcitonin	Not as effective as other medications for long-term therapy	<b>Use only for pain after an acute osteoporotic fracture</b> Rhinitis and epistaxis occur commonly
Teriparatide (recombinant PTH) injections	↑ bone formation (all other drugs are antiresorptive) ↓ risk of fracture, but may ↑ the risk of stroke in older women Daily subcutaneous injection	Use in postmenopausal patients with <b>severe</b> osteoporosis who are at high risk for fracture, whose <b>other treatments have failed</b> , or who have <b>contraindications</b> to other treatments Currently treatment with PTH is only recommended for 2 years May also be used to promote healing of atypical femoral fractures associated with bisphosphonate therapy
Denosumab	Human monoclonal antibody to RANKL, an osteoclast differentiating factor (inhibits osteoclast formation and bone resorption) Improves BMD, ↓ fracture SQ injection every 6 months	May be used in renal insufficiency and in those for whom <b>bisphosphonates failed</b> Similar risks to bisphosphonates: Hypocalcemia, ONJ, atypical femur fractures; ↑ risk of infection
Estrogen or HT	Can prevent osteoporosis in hypogonadal women and men but is not an effective therapy for established osteoporosis ↓ the risk of all fractures, but ↑ the risk of breast cancer, stroke, VTE, and CAD	No longer recommended for osteoporosis but for women who are taking it for other reasons, it provides some protection

## SECONDARY OSTEOPOROSIS

2° osteoporosis is defined as osteoporosis due to an identifiable underlying disease (Table 6.23).

- **Symptoms/Exam:** Typical osteoporotic fractures are hip, vertebral compression, and Colles fractures.
- **Diagnosis:** Further evaluation should include a search for 2° causes of osteoporosis (Table 6.24) based on clinical suspicion or low Z-score (< -2):
  - 25-HD level.
  - Serum calcium, phosphorus, and PTH.
  - 24-hour urinary calcium and creatinine.
  - SPEP/UPEP.
  - Testosterone level (men).
  - TSH, especially in those with a history of hyperthyroidism or on levothyroxine replacement.
  - CBC.

### KEY FACT

2° osteoporosis should also be considered in women, especially those with Z-scores < -2. Z-score indicates a 2° cause of osteoporosis (think “Z” for “Zebra” causes).

## Management

Treat underlying condition if warranted. See the Primary Osteoporosis section for additional treatment options.

## PAGET DISEASE

Accelerated bone turnover and remodeling, resulting in impaired bone integrity and overgrowth.

### Symptoms/Exam

Presents with **pain, fractures, and skeletal deformity**, most commonly in the sacrum, spine, femur, humerus, skull, and pelvis. The bony overgrowth can also lead to **cranial nerve compression and spinal stenosis**. Two-thirds of patients are asymptomatic.

Findings depend on which bones are involved. The bones can become soft, leading to bowed tibias, kyphosis, and frequent “chalkstick” fractures with minimal trauma. Exam may reveal skull enlargement, frontal bossing, bowed legs, and cutaneous erythema, warmth (due to ↑ vascularity), and tenderness over the affected site. Deafness can occur.

### Differential

Includes any localized bony tumor or cancer.

### QUESTION

A 68-year-old woman, current tobacco user, undergoes a DEXA scan (T-score, -2.0) and has a 25-HD level (9 ng/mL; normal range >20 ng/mL). What is the best treatment plan, at this time, for her osteopenia and vitamin D deficiency?

**TABLE 6.23. Secondary Causes of Osteoporosis**

ENDOCRINE CAUSES	GI DISORDERS	MARROW/HEMATOLOGIC DISORDERS	OTHER
Cushing syndrome	Liver disease (1° biliary cirrhosis)	<b>Multiple myeloma</b>	Immobilization
<b>Hypogonadism</b> (male or female)	<b>Malabsorptive conditions</b>	Leukemias/lymphomas	<b>Alcohol abuse</b>
Hyperprolactinemia (by inducing hypogonadism)	(mediated primarily via vitamin D deficiency):	Systemic mastocytosis	Tobacco use
Hyperthyroidism	<b>Celiac disease</b>	Hemophilia	Osteogenesis imperfecta
Hyperparathyroidism	Gastrectomy	Thalassemia	RA
Vitamin D deficiency	Inflammatory bowel disorders	Polycythemia vera	Ankylosing spondylitis
Acromegaly	<b>Gastric bypass</b>		Eating disorders
Osteomalacia	Pancreatic insufficiency		Corticosteroid use

TABLE 6.24. Complications of Paget Disease

RHEUMATOLOGIC	NEUROLOGIC	CARDIAC	NEOPLASTIC <sup>a</sup>	METABOLIC
Osteoarthritis	Deafness (from involvement of cranial nerves, with bony entrapment)	High-output CHF	Osteosarcoma or chondrosarcoma Giant cell tumor	Immobilization-induced hypercalcemia/ hypercalciuria Nephrolithiasis
Gout	Spinal cord compression leading to paraplegia Peripheral nerve entrapment (carpal and tarsal tunnel syndromes)			

<sup>a</sup>Occur in 1% of Paget cases.



**FIGURE 6.22. Paget disease, right femur.** Note the thickened cortex (arrow), thickened trabeculae (arrowhead), and expansion of the right femoral head and neck in comparison to the left femur. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 349-3.)

## A

### ANSWER

Treat with vitamin D supplementation (if serum 25-HD levels are below 20 ng/mL, may need to replete with high-dose ergocalciferol) and calcium (combined from diet and/or supplements) 1000-1200 mg daily. Encourage weight-bearing exercises and smoking cessation.

### KEY FACT

The most common fractures in Paget disease are vertebral crush fractures.

### KEY FACT

Paget disease is one of the rare causes of high-output CHF due to hypervascularity of bony lesions.

### Diagnosis

- Labs: ↑ alkaline phosphatase and bone turnover markers (eg, osteocalcin, urinary hydroxyproline, N-telopeptide). Ca<sup>++</sup> and phosphorus are normal.
- Imaging:
  - Plain radiography: Involved bones are expanded and denser than normal (Figure 6.22). Erosions are seen in the skull (osteoporosis circumscripta). Affected weight-bearing bones may be bowed.
  - Bone scan: ↑ uptake is seen in affected areas but can be nonspecific.

### Management

- **Asymptomatic patients:** May require only clinical surveillance and no treatment. Consider treatment for those with significant involvement of the skull, long bones, or vertebrae to prevent deformities and future complications (eg, hearing loss, vertebral fractures). Treatment is also recommended in patients undergoing orthopedic surgeries since the treatment will reduce the hypervascularity in the bone lesion.
- **Symptomatic patients:** Bisphosphonates are the treatment of choice when indicated, and lead to remission in most patients. Choices include IV pamidronate or zoledronic acid, oral alendronate, risedronate, and IV/PO ibandronate.

### Complications

See Table 6.24.

### VITAMIN D DEFICIENCY

Risk factors for vitamin D deficiency include dark skin, older age, fat malabsorption, and limited sun exposure. See the Geriatrics chapter for additional considerations.

- **Diagnosis:** Deficiency is defined as a serum 25-HD level <20 ng/mL.
- **Management:** There are no universally agreed on guidelines for repletion.
  - The Endocrine Society recommends once weekly ergocalciferol 50,000 units for 8 weeks followed by repeat serum 25-HD level.
  - Eight hundred to 2000 units of vitamin D per day is safe and generally sufficient to achieve a serum 25-HD level of 30 ng/dL; a general guideline is that 100 units of vitamin D daily will ↑ the serum 25-HD level by 1 ng/mL over the course of 3 months.

## Testicular and Ovarian Disorders

### MALE HYPOGONADISM

The testes are composed of seminiferous tubules where sperm are produced (80%-90% of testicular mass), and Leydig cells that produce androgens.

#### Symptoms/Exam

**Post-pubertal androgen deficiency:** ↓ libido, erectile dysfunction, low energy. If prolonged, a ↓ in facial and body hair may be seen.

#### Differential

- Pituitary (2° hypogonadism) and hypothalamic (3° hypogonadism) disorders: Low testosterone with normal or ↓ LH and FSH.
  - Panhypopituitarism.
  - LH and FSH deficiency associated with anosmia: **Kallmann syndrome**.
  - **Opioid and steroid use.**
- Testicular disorders (1° hypogonadism): Usually characterized by ↓ testosterone and ↑ LH and FSH.
  - **Klinefelter syndrome:** The most common genetic cause of male hypogonadism. Caused by the expression of an abnormal karyotype, classically 47,XXY. Affected men have an ↑ risk of cryptorchidism, ↓ penile size, delayed speech, learning disabilities, psychiatric disturbances, and mediastinal malignancies.
  - Adult seminiferous tubule failure: Characterized by infertility, normal virilization, and normal testosterone levels (because the Leydig cells are unaffected). May be due to orchitis, leprosy, irradiation, alcoholism, uremia, cryptorchidism, lead poisoning, and chemotherapeutic agents (eg, cyclophosphamide, methotrexate).
  - Adult Leydig cell failure (andropause): A gradual ↓ in testicular function after age 50, with declining testosterone levels.
  - Previous chemotherapy or pelvic irradiation.
  - Autoimmune destruction.
  - Atrophy secondary to mumps.
  - Obesity.
- **Defects in androgen action:**
  - Complete androgen insensitivity: Also known as testicular feminization—XY, with female phenotype, absence of uterus, absence of sexual hair, and infertility. Patients are usually raised as girls.
  - Incomplete androgen insensitivity: Phenotype varies with degree of insensitivity.

#### Diagnosis

Check total testosterone or free testosterone (or both) first. If low, repeat testosterone with LH and FSH. Diagnosis requires low testosterone measured with a reliable assay in the morning (due to normal diurnal variation) on several occasions (Table 6.25).

#### Management

- **Androgen replacement:** IM testosterone injections, patches, or gel.
- If an underlying disorder is diagnosed (eg, pituitary tumor), treat appropriately.
- Treatment with testosterone requires monitoring for adverse effects such as prostatic enlargement or unmasking of clinically silent prostate cancer (PSA), erythrocytosis (CBC), low HDL (lipid panel), and worsening of obstructive sleep apnea.

#### KEY FACT

Hypogonadism is suggested with a low serum testosterone. If LH and FSH are ↑, the cause is testicular damage (1° hypogonadism). If LH and FSH are ↓ or normal, the cause is the pituitary or hypothalamus (2° and 3° hypogonadism, respectively).

#### KEY FACT

If LH and FSH are ↓ and a patient has delayed puberty and anosmia along with male relatives with similar symptoms, consider Kallmann syndrome.

#### KEY FACT

If LH and FSH are ↑, consider Klinefelter syndrome (47,XXY), the most common cause of male hypogonadism. The patient may be lanky and youthful-looking and may have gynecomastia, small testicles, executive functioning impairment, and fertility problems.

#### KEY FACT

If LH is low in the setting of a low testosterone level, check a prolactin level to rule out hyperprolactinemia.

#### KEY FACT

Androgen therapy in hypogonadal men can lead to gynecomastia, because excess androgen is converted to estrogen.

#### KEY FACT

In the aging male with androgen deficiency (testosterone level, 150-300 ng/dL) and normal FSH/LH and prolactin, treat with testosterone if the patient is <60 years of age. Treatment in patients >60 years of age is controversial and it should only be started after an explicit discussion of the risks and benefits of testosterone therapy.

**TABLE 6.25.** Diagnosis of Male Hypogonadism Based on Lab Tests

ETIOLOGY	TESTOSTERONE	LH/FSH	PROLACTIN	NEXT STEPS
Testicular failure	↓	↑	Normal	Testosterone supplementation
Age-related decline	↓	Normal	Normal	Testosterone supplementation controversial
Pituitary disease	↓	↓	↑	Pituitary MRI, lab tests

**KEY FACT**

Inappropriate testosterone replacement (anabolic stress use) results in acne, oily skin, gynecomastia (which is more common, but still rare), reduced sperm production, and infertility.

**KEY FACT**

MEN 1 can be remembered as the “**3 P’s**”—Parathyroid, Pancreas, and Pituitary.

**KEY FACT**

MEN 2 can be remembered as the “**2 C’s**”—Carcinoma of the **thyroid** and Catecholamines (pheochromocytoma) plus parathyroid (MEN 2A) or mucocutaneous neuromas (MEN 2B).

**KEY FACT**

Any sporadic medullary thyroid cancer patient needs to be considered for genetic screening with the RET proto-oncogene.

**KEY FACT**

Carcinoids cause the classic syndrome only when they are gut carcinoids, metastatic to the liver, or 1° lesions draining into the systemic circulation.

**Complications**

- Infertility: Testosterone therapy may suppress spermatogenesis. Therapy is not appropriate in men who desire fertility.
- Osteoporosis can develop in the absence of androgens but can usually be prevented with appropriate testosterone replacement.

**AMENORRHEA**

See the discussion in the Women’s Health chapter.

**Endocrine Tumors and Polyglandular Disorders****MULTIPLE ENDOCRINE NEOPLASIA**

Multiple endocrine neoplasia is a group of **autosomal dominant** syndromes characterized by multiple endocrine tumors due to defective tumor suppressor genes.

- MEN 1: Parathyroid, pancreatic, and pituitary tumors.** If there is a  $\oplus$  family history, screen with serum calcium/PTH, serum gastrin, and serum prolactin.
- MEN 2: Medullary thyroid cancer and pheochromocytoma  $\pm 1^\circ$  hyperparathyroidism.** Screen for the RET proto-oncogene mutation if there is a  $\oplus$  family history of MEN 2 or in any patient with medullary thyroid cancer or bilateral pheochromocytomas. Prophylactic thyroidectomy is recommended in the setting of a  $\oplus$  RET mutation, as 95% of patients will develop thyroid cancer.

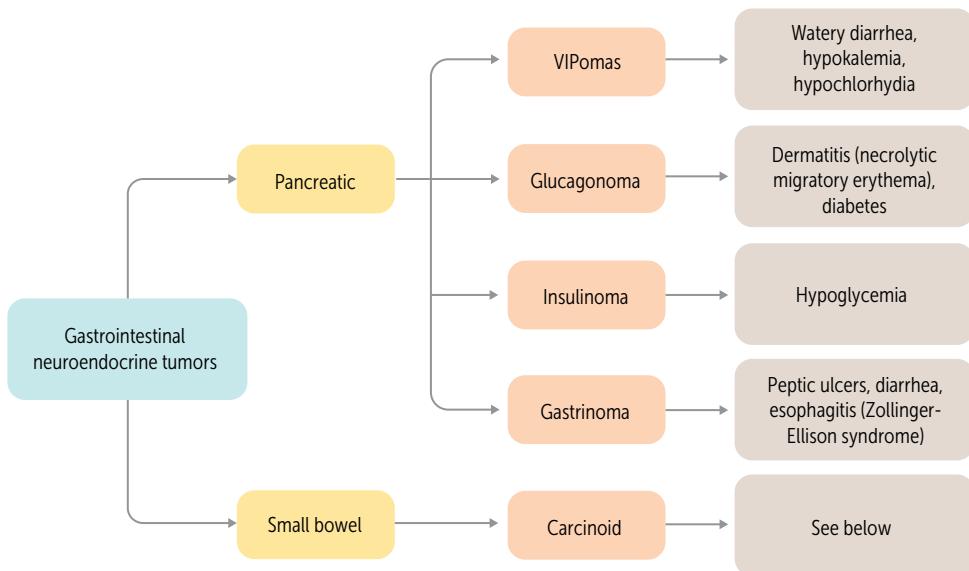
**GASTROINTESTINAL NEUROENDOCRINE TUMORS**

Gastrointestinal neuroendocrine tumors can arise from either the pancreas or small bowel (Figure 6.23).

- Diagnosis:** Made by measuring the associated hormone levels. Localized using either endoscopic ultrasound (EUS) or pentetetotide scintigraphy (octreotide scan).
- Management:** Surgical resection if localized. Metastatic disease is treated with chemotherapy or radiolabeled somatostatin analogues (eg, octreotide, lanreotide).

**Carcinoid Tumors**

GI neuroendocrine tumors that are most commonly located in the small bowel, but can also arise from the colon, esophagus, or lung (bronchial carcinoid). About 20% of cases present with metastases without a known 1° location. **Most are hormonally inert, but some can secrete excessive serotonin, prostaglandins, and kinins.**



**FIGURE 6.23. Symptoms and signs associated with various gastrointestinal neuroendocrine tumors.** (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

■ **Symptoms/Exam:**

- Classic carcinoid syndrome consists of episodic **flushing** (39% of patients), **watery diarrhea**, **abdominal pain**, **weight loss**, and **hypotension** with or without asthma.
- Valvular heart disease** is a common complication.
- Emotional stress, certain foods (eg, tryptophan-containing foods), and straining with defecation can provoke symptoms.



**FIGURE 6.24. Carcinoid in the terminal ileum.** Axial contrast-enhanced CT of the abdomen shows an enhancing mass at the ileocecal valve. (Reproduced with permission from USMLE-Rx.com.)



**QUESTION**

A 54-year-old man receives a diagnosis of bilateral pheochromocytomas. His father had a history of a pheochromocytoma and medullary thyroid carcinoma. What genetic test should he undergo and why?

**KEY FACT**

Carcinoid tumors can lead to carcinoid crisis, in which multiple proteins (serotonin, histamine, tryptophans) are released acutely, causing extreme BP changes, bronchoconstriction, and arrhythmias.

**KEY FACT**

Carcinoid crises can be fatal and should be treated with an octreotide drip and supportive care.

- Carcinoid crisis can occur spontaneously or after tumor palpation, chemotherapy, or hepatic arterial embolization. Symptoms include labile blood pressure, bronchoconstriction, and arrhythmias.

**■ Diagnosis:**

- Labs: Order a **24-hour urine for 5-HIAA** (5-hydroxyindoleacetic acid, a serotonin metabolite).
- Imaging: Stage with CXR and a chest/abdominal CT (Figure 6.24). An indium-labeled octreotide scan can detect occult lesions. <sup>18</sup>F-DOPA PET/CT may be helpful in detecting occult carcinoid tumors.
- **Management:** Surgical resection—1° initial treatment and a reasonable option even for patients with metastatic disease. Symptomatic relief may be obtained with octreotide.

**ANSWER**

Testing for the RET proto-oncogene mutation, which is responsible for most cases of MEN 2. When inherited, MEN 2 is transmitted in an autosomal dominant pattern.

## CHAPTER 7

# Gastroenterology and Hepatology

Leslie Sheu, MD

Veeral Ajmera, MD

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## Upper GI Tract

### DYSPHAGIA

Typically defined as difficulty swallowing (as opposed to **odynophagia**, which is pain with swallowing). Patients often will be able to point to where food feels stuck. One approach to dysphagia is to first distinguish oropharyngeal dysphagia from esophageal dysphagia:

- Oropharyngeal: Neuromuscular disorders. Diagnose with videofluoroscopy.
- Esophageal: Further separate into mechanical obstruction or dysmotility (Figure 7.1).

### INFECTIOUS ESOPHAGITIS

#### KEY FACT

Oral thrush with odynophagia likely reflects underlying *Candida* esophagitis. But lack of oral thrush in a patient with risk factors does not rule out *Candida* esophagitis.

Most common in immunosuppressed patients (eg, those with AIDS, malignancies, posttransplant patients, and patients undergoing chemotherapy) and in the setting of chronic steroid or recent antibiotic use. *C albicans* is the etiologic agent in 75% of cases and cytomegalovirus (CMV) or herpes simplex virus (HSV) in <50%.

#### Symptoms/Exam

Presents with odynophagia (pain as food passes through the esophagus), dysphagia (inability to swallow), and chest pain.

#### Diagnosis

- In **immunocompromised** patients, attempt a trial of **empiric** antifungal therapy (eg, fluconazole). In **immunocompetent** hosts, odynophagia and dysphagia are alarm symptoms; proceed with **endoscopy**.
- Upper endoscopy with biopsy is the diagnostic test of choice if the empiric trial yields no response. Findings are as follows:
  - ***C albicans***: Linear, adherent plaques that may be yellow or white (Figure 7.2).
  - **CMV**: Few large, superficial ulcerations.
  - **HSV**: Numerous small, deep ulcerations.
  - **Idiopathic AIDS ulcers**: Low CD4 count; large ulcerations.

#### Management

- Treat or adjust underlying immunosuppression.
- ***C albicans***: For oropharyngeal candidiasis, treat with topical therapy (eg, nystatin)

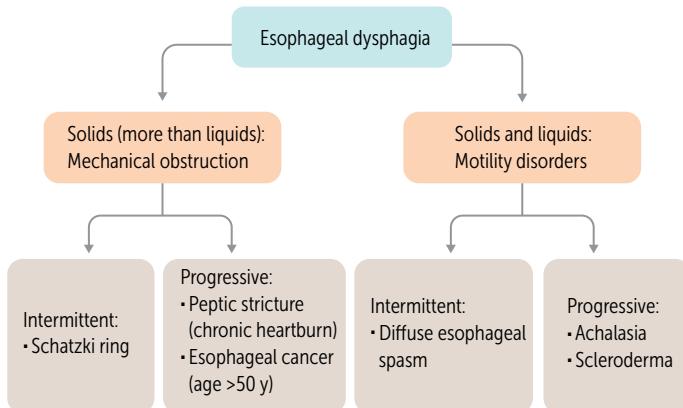
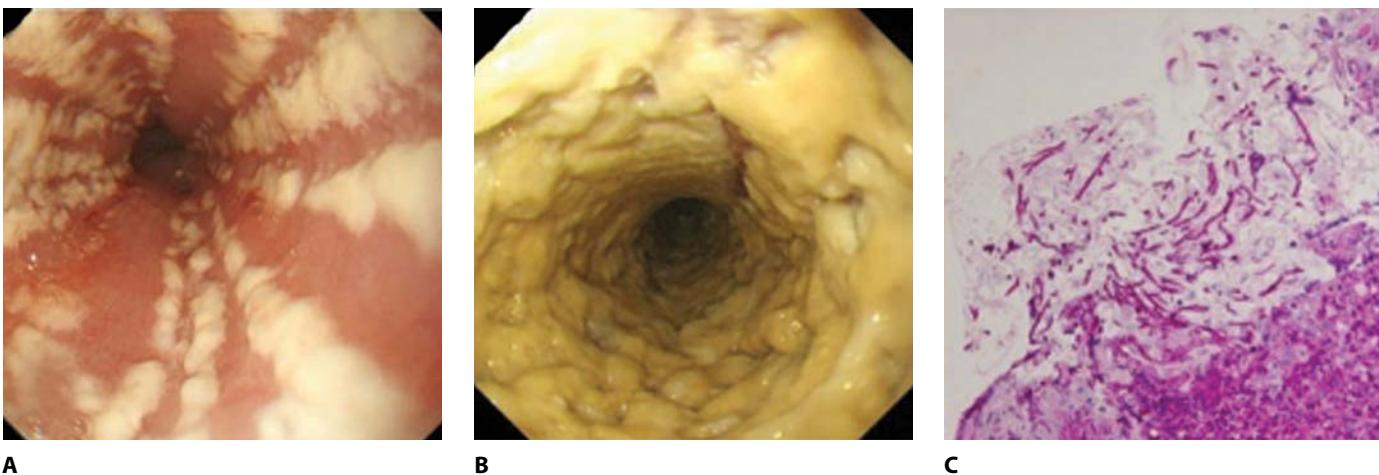


FIGURE 7.1. Causes of esophageal dysphagia. (Reproduced with permission from USMLE-Rx.com.)

**A****B****C**

**FIGURE 7.2. *Candida esophagitis.*** Endoscopic views show confluent, linear, and nodular elevated plaques (A), thick white plaque cover on esophageal mucosa circumferential narrowing the lumen (B). Pathology (C) reveals numerous *Candida* pseudohyphae and spores in the exfoliated esophageal epithelium and detached superficial squamous epithelium ( $\times 400$ ). (Source: Takahashi Y, et al. Long-term trends in esophageal candidiasis prevalence and associated risk factors with or without HIV infection: Lessons from an endoscopic study of 80,219 patients. *PLoS One.* 2015;10(7):e0133589.)

as first line. For esophageal candidiasis, treat with oral therapy (eg, fluconazole 200–400 mg/day). Test for HIV.

- CMV: Ganciclovir IV  $\times 3$  to 6 weeks.
- HSV: Acyclovir 200 mg PO five times a day or valacyclovir 1000 g PO BID.
- Idiopathic ulcers: Trial of prednisone.

#### MEDICATION-INDUCED ESOPHAGITIS

Variables include contact time, drug type, and pill characteristics. Most cases arise without preexisting swallowing problems. The risk is higher if pills are large, round, lightweight, or extended-release formulations.

- **Symptoms/Exam:** Presents with odynophagia, dysphagia, and chest pain.
- **Diagnosis:**
  - **Review medications.** Common causative agents include bisphosphonates, tetracyclines (especially doxycycline) and clindamycin (look for a young patient with acne or malaria prophylaxis presenting with odynophagia).
  - **Upper endoscopy:** Proceed with upper endoscopy to evaluate for stricture or mass lesion if no response is elicited after the suspected offending agent.
- **Management:**
  - Discontinue the suspected drug. Expect symptom relief within 1 to 6 weeks.
  - Proton pump inhibitors (PPIs) may facilitate healing in the setting of concurrent GERD.
  - To minimize pill esophagitis, patients should drink 8 ounces of water with each pill and remain upright at least 30 minutes afterward.
- **Complications:** Stricture formation.

#### EOSINOPHILIC ESOPHAGITIS

A chronic, immune-mediated esophageal disorder.

- **Symptoms/Exam:** Presents with dysphagia or food impaction without odynophagia. Fails to respond to PPI alone. Classically seen in young men, often associated with asthma and allergies.

#### KEY FACT

You can diagnose pill esophagitis by history alone. There is no need for endoscopy.



#### QUESTION

A 37-year-old man presents with pain and difficulty swallowing. His mouth has some small superficial and painful ulcerations, along with white exudate that can be scraped off with a tongue depressor. While an HIV test is pending, what treatment should you start?

- **Diagnosis:** Eosinophilic esophagitis can be suspected clinically, but to diagnose, need symptoms and histologic findings. Perform **esophagogastroduodenoscopy (EGD)** with **biopsies** after 2 months of PPI treatment to rule out GERD as a cause of esophageal eosinophilia.
- **Management:**
  - Dietary therapy: Avoid allergens, as directed by skin prick or atopy patch testing, or empiric elimination diet of common allergic foods.
  - Pharmacologic therapy: **Swallowed fluticasone** via metered dose inhaler without a spacer for 6 to 8 weeks. **Acid suppression** is used prior to endoscopy as part of diagnosis, but its role in treatment of eosinophilic esophagitis is unclear.
  - Evaluation by an allergist to guide avoidance of dietary or environmental allergens.
  - Watch for complications of esophageal rings or strictures that may require **dilation**.

### ACHALASIA

An idiopathic esophageal motility disorder with loss of peristalsis, ↑ lower esophageal sphincter (LES) resting pressure, and failure of LES relaxation when swallowing. Age at onset is 25 to 60 years; incidence ↑ with age. Indistinguishable from esophageal dysmotility caused by **Chagas disease**.

#### Symptoms/Exam

- Presents with progressive dysphagia to solids and then to liquids as well as with slow eating (“**last person at the table to finish meal**”).
- Regurgitation of undigested food, weight loss, and chest pain are also characteristic. Heartburn may result from the fermentation of retained food.

#### Differential

Chagas disease (*Trypanosoma cruzi*), esophageal tumors, pseudoachalasia (a process mimicking achalasia that is typically secondary to tumor invasion into the esophageal neural plexus), webs, strictures, Zenker diverticulum, oropharyngeal dysphagia (muscular dystrophies, myasthenia gravis, Parkinson disease), spastic dysmotility (diffuse esophageal spasm, nutcracker esophagus), esophageal hypomotility (scleroderma). See Table 7.1.

**TABLE 7.1. Characteristics of Common Esophageal Motility Disorders**

	ACHALASIA	DIFFUSE ESOPHAGEAL SPASM	SCLERODERMA
Peristalsis	Absent	Simultaneous contractions	Absent
LES tone	↑ with incomplete relaxation	Normal to ↑	↓
Esophageal body tone (amplitude)	↓	Normal to ↑	↓
Predominant symptom	Progressive dysphagia	Chest pain	Heartburn and dysphagia



#### ANSWER

Fluconazole. This patient has oral thrush and likely *Candida* esophagitis. Although his oral ulcerations could be due to HSV, CMV, or *Histoplasma* infection, empiric treatment for *Candida* is reasonable, as this is the most likely diagnosis.

## Diagnosis

- **CXR:** Demonstrates an air-fluid level in a dilated esophagus.
- **Barium esophagram:** May reveal a dilated esophagus with loss of peristalsis and poor emptying or a smooth, symmetrically tapered distal esophagus with a “bird’s beak” appearance (Figure 7.3A).
- **Esophageal manometry:** Should be done to confirm diagnosis before treatment is offered.
- **Endoscopy:** Required to exclude esophageal strictures and tumor.

## Management

First, determine if the patient is high or low surgical risk. If low risk, **pneumatic dilation** or **surgical myotomy** is indicated. If high risk, **botulinum toxin**, followed by **nitrates** or **calcium channel blockers (CCBs)**, is indicated.

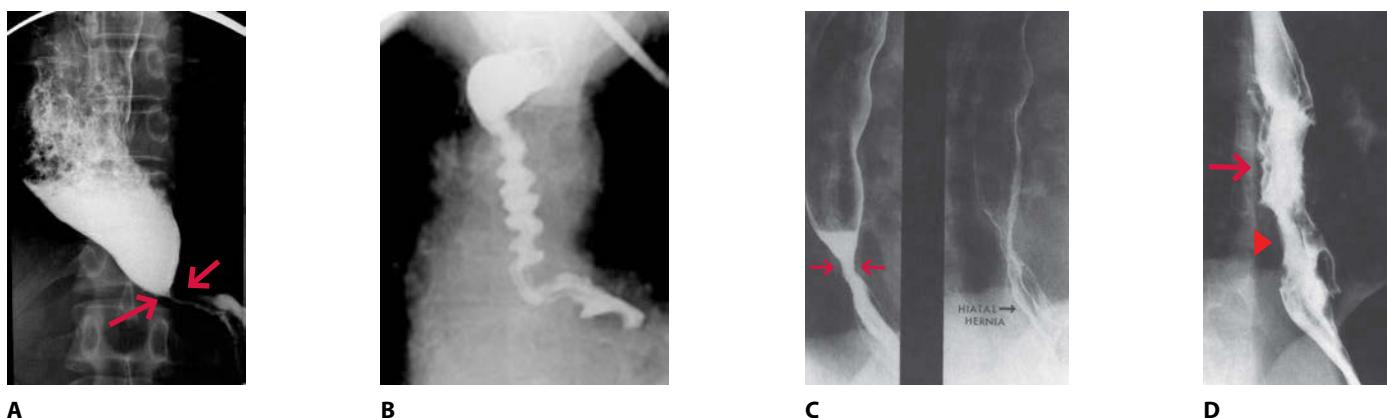
- **Pneumatic dilation:** Of those treated, >75% have a durable response. The perforation rate is 3% to 5%. Does not compromise surgical therapy.
- **Surgery:** Laparoscopic Heller myotomy with partial fundoplication (preventing severe reflux that can occur with myotomy). Of all cases, >85% have a durable response.
- **Botulinum toxin injection:** Injected into the LES. Performed endoscopically and associated with an 85% initial response, but >50% of patients require repeated injection within 6 months. Ideal if the patient is a poor candidate for more invasive treatment.
- **Nitrates and calcium channel antagonists:** Relax LES tone, but have only modest efficacy.

## Complications

- Aspiration, weight loss.
- ↑ risk of esophageal cancer (squamous > adenocarcinoma).

## DIFFUSE ESOPHAGEAL SPASM

Diffuse esophageal spasm is marked by uncoordinated contractions. There is a female predominance; onset is usually after age 40 years.



**FIGURE 7.3. Esophageal disease on barium esophagram.** (A) Achalasia. Note the dilated esophagus tapering to a “bird’s-beak” narrowing (arrows) at the lower esophageal sphincter. (B) Esophageal spasm. (C) Peptic stricture (arrows) secondary to GERD above a hiatal hernia (right). (D) Barrett esophagus with adenocarcinoma. Note the nodular mucosa of Barrett esophagus (arrow) and the raised filling defect (arrowhead) representing adenocarcinoma in this patient. (Image A reproduced from Doherty GM. *Current Diagnosis & Treatment: Surgery*, 13th ed. New York: McGraw-Hill, 2010, Fig. 20-5. Image B reproduced with permission from USMLE-Rx.com. Images C and D reproduced with permission from Chen MY, et al. *Basic Radiology*. New York: McGraw-Hill, 2004, Figs. 10-14 and 10-19.)

**KEY FACT**

Unlike achalasia, diffuse esophageal spasm often presents with chest pain rather than with dysphagia.

**Symptoms/Exam**

- Substernal **chest pain** is seen in 80% of patients; pain is nonexertional and worsens with meals.
- A **globus** (“lump in the throat”) sensation is also characteristic.
- Associated with **dysphagia** to both solids and liquids.
- Regurgitation is less common than in achalasia. Weight loss is rare.
- Can be triggered by cold or carbonated drinks.

**Diagnosis**

Diagnose as follows (see also Table 7.1):

- **Barium esophagram:** Peristalsis is present but with delayed transit; esophageal spasms occur at multiple sites and have a “**corkscrew**” or “**rosary bead**” appearance (see Figure 7.3B). Can be normal between episodes.
- **Endoscopy:** Not useful in diagnosis, but excludes other differential diagnoses, such as stricture, tumor, and esophagitis.
- **Esophageal manometry:** Shows simultaneous contractions.
- **Ambulatory esophageal pH:** Used to evaluate for gastroesophageal reflux.

**Management**

- **Reassurance is key.**
- First line: CCB (diltiazem), followed by TCA (eg, imipramine) to relax LES tone.
- Second line: Botulinum toxin or nitric oxide–contributing drug (isosorbide, sildenafil).
- **No clear benefit** is derived from esophageal dilation or surgical myotomy.

**ESOPHAGEAL DIVERTICULUM (ZENKER DIVERTICULUM)**

Zenker diverticulum is a sac-like outpouching of mucosa and submucosa through an area of muscular weakness at the level of the cricopharyngeal muscles. Symptoms are caused by motor abnormalities and are seen typically in older men.

- **Symptoms/Exam:** Dysphagia, aspiration, malodorous breath, neck mass, regurgitation of food.
- **Diagnosis:** Barium esophagram, preferably combined with dynamic continuous fluoroscopy during swallow.
- **Management:**
  - **Surgery:** Cricopharyngeal myotomy with or without diverticulectomy (look out for **mediastinitis** as a complication).
  - **Endoscopic:** Endoscopic diverticulectomy is becoming a treatment of choice, especially for patients who cannot tolerate surgery, but a limited number of endoscopists are trained to do this.

**ESOPHAGEAL RINGS, WEBS, AND STRICTURES**

Esophageal rings, webs, and strictures are distinguished as follows (see also Figure 7.1 and Table 7.2):

**TABLE 7.2. Esophageal Rings, Webs, and Strictures**

	RING	WEB	STRUCTURE
Etiology	Congenital or peptic injury	Congenital	Peptic injury, caustic injury
Esophageal location	Distal	Proximal	Mid-distal
Treatment	Dilation	Dilation	Dilation

- **Lower esophageal (Schatzki) rings:** Common (found in 6%-14% of upper GI exams); located in the distal esophagus. Often associated with hiatal hernia, congenital defects, or GERD.
- **Webs:** Less common; located in the proximal esophagus. Congenital.
- **Strictures:** Result from injury (eg, reflux, caustic, anastomosis).
- Rings are more common in **younger patients**, while cancer and strictures are more common in older patients.
- **Symptoms/Exam:** Dysphagia with solids is more severe than that with liquids for obstructive lesions (rings, webs, and strictures).
- **Diagnosis:**
  - **Barium esophagram:** May be diagnostic. Normal peristalsis; luminal abnormality is seen (see Figure 7.3C).
  - **Endoscopy:** Required to exclude esophageal stricture or tumor.
- **Management:** Esophageal dilation; PPIs to ↓ the recurrence of peptic stricture.

**KEY FACT**

Schatzki rings cause intermittent large-bolus solid-food dysphagia ("steakhouse syndrome").

**KEY FACT**

Plummer-Vinson syndrome includes esophageal webs, dysphagia, and iron deficiency anemia.

**GASTROESOPHAGEAL REFLUX DISEASE**

Caused by transient relaxation of the LES. In the United States, 40% of adults report having GERD symptoms at least once per month, and 7% report having daily symptoms. Although most patients have mild GERD, 40% to 50% develop esophagitis, 5% ulcerative esophagitis, 4% to 20% esophageal strictures, and 5% to 10% Barrett esophagus. Risk factors include pregnancy and hiatal hernia.

**Symptoms/Exam**

- **Typical presentation:** A retrosternal burning sensation (heartburn) accompanied by regurgitation that begins in the epigastrium and radiates upward (typically occurring within one hour of a meal, during exercise, or when lying recumbent) and is at least partially relieved by antacids. **Water brash** (excess salivation), **bitter taste**, and **globus sensation** (throat fullness) are also commonly seen.
- **"Atypical" symptoms (up to 50%):** Nocturnal cough, asthma, hoarseness, noncardiac chest pain.
- Exam is often normal, or patients may present with **poor dentition** and wheezing.

**KEY FACT**

Atypical symptoms (cough, wheezing, chest pain) often occur without typical heartburn symptoms.

**Diagnosis**

- For **typical symptoms**, treat with an empiric trial of PPIs × 4 to 6 weeks. **Response to empiric trial of PPIs is diagnostic.**
- If the patient is **unresponsive** to therapy or has **alarm symptoms** (dysphagia, odynophagia, weight loss, anemia, long-standing symptoms, blood in stool, age >50 years), proceed as follows:
  - **Barium esophagram:** Has a limited role, but can identify strictures (see Figure 7.3C).
  - **Upper endoscopy with biopsy:** The standard exam in the presence of **alarm symptoms** (dysphagia, odynophagia, weight loss, bleeding, anemia). Normal in >50% of patients with GERD (most have nonerosive reflux disease), or may reveal endoscopic esophagitis grades 1 (mild) to 4 (severe erosions, strictures, Barrett esophagus). Strictures can be dilated.
  - **Ambulatory esophageal pH monitoring:** The gold standard, but often unnecessary. Indicated for correlating symptoms with pH parameters when endoscopy is normal and (1) symptoms are unresponsive to medical therapy, (2) antireflux surgery is being considered, or (3) there are atypical symptoms (eg, chest pain, cough, wheezing).

**QUESTION**

A 60-year-old man with a history of hypertension and tobacco use presents with 4 months of ↑ difficulty swallowing solid foods, such as meats. He is still able to drink liquids. What is the most appropriate diagnostic test for this patient?

### Management

- **Behavioral modification:** Elevate the head of the bed 6 inches; stop tobacco and alcohol use. Advise patients to eat smaller meals, reduce fat intake, lose weight, avoid recumbency after eating, and avoid certain foods (eg, mint, chocolate, coffee, tea, carbonated drinks, citrus and tomato juice). Effective in 25% of cases.
- **Antacids (calcium carbonate, aluminum hydroxide):** For mild GERD. Fast, but afford only short-term relief.
- **H<sub>2</sub>-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine):** For mild GERD or as an adjunct for nocturnal GERD while the patient is on PPIs. Effective in 50% to 60% of cases.
- **PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole):** The mainstay of therapy for mild to severe GERD. Daily dosage is effective in 80% to 90% of patients. Fewer than 5% of patients are refractory to twice-daily dosage. Long-term use of PPIs has been associated with an ↑ risk of fractures, osteoporosis, hypomagnesemia, and *C difficile*. Long-term use of PPIs is discouraged if possible, unless indicated (eg, for Barrett esophagus). Watch for **rebound acid hypersecretion** when PPIs are stopped.
- **Surgical fundoplication (Nissen or Belsey wrap):**
  - Often performed laparoscopically. Indicated for patients who cannot tolerate medical therapy or who have persistent regurgitation. **Contraindicated** in patients with an esophageal motility disorder.
  - **Outcome:** More than 50% of patients require continued acid-suppressive medication, and >20% develop new symptoms (dysphagia, bloating, dyspepsia).
  - **Endoscopic antireflux procedures:** Remain investigational.

#### KEY FACT

For true GERD, PPIs are highly effective, with <5% of patients unresponsive to twice-daily doses.

#### KEY FACT

After surgical fundoplication for GERD, >50% of patients still require continued acid-suppressive medication, and >20% develop new symptoms (dysphagia, bloating, dyspepsia).

#### KEY FACT

Screen for Barrett esophagus in patients >50 years old with chronic GERD symptoms, especially in Caucasian men. If it is not present, there is no need for further screening.

A

#### ANSWER

Upper endoscopy. This patient is high risk for esophageal cancer given his age, tobacco use, and description of slowly progressive dysphagia for solids more than liquids. With a high suspicion for cancer, endoscopy will allow for definitive diagnosis with biopsy.

### Complications

- **Peptic strictures:** Affect 8% to 20% of GERD patients; present with dysphagia. Malignancies must be excluded via endoscopy and biopsy; can then be treated with endoscopic dilation followed by indefinite PPI therapy.
- **Upper GI bleeding:** Hematemesis, melena, anemia 2° to ulcerative esophagitis.
- **Posterior laryngitis:** Chronic hoarseness from vocal cord ulceration and granulomas.
- **Asthma:** Typically has an adult onset; nonatopic and unresponsive to traditional asthma interventions.
- **Cough:** Affects 10% to 40% of GERD patients, most without typical GERD symptoms.
- **Noncardiac chest pain:** After a full cardiac evaluation, consider an empiric trial of PPIs or ambulatory esophageal pH monitoring.
- **Other:** Barrett esophagus, adenocarcinoma.

### BARRETT ESOPHAGUS

**Intestinal metaplasia** of the distal esophagus secondary to chronic GERD. Normal esophageal squamous epithelium is replaced by columnar epithelium and goblet cells (“specialized epithelium”). Found in 5% to 10% of patients with chronic GERD, and incidence ↑ with GERD duration. Most common in Caucasian men >55 years of age; overall incidence is greater in men than in women. The risk of adenocarcinoma is 0.5% per year. Risk factors include male gender, Caucasian ethnicity, and smoking.

### Diagnosis

- **Upper endoscopy:** Suggestive but not diagnostic, as it is a histologic diagnosis. **Salmon-colored islands or “tongues”** are seen extending upward from the distal esophagus (Figure 7.4).

- **Biopsy:** Diagnostic. Shows metaplastic **columnar epithelium** and **goblet cells**. Specialized intestinal metaplasia on biopsy is associated with an ↑ risk of adenocarcinoma (not squamous cell carcinoma).

### Management

- **Treatment:** Indefinite PPI therapy (GERD should be treated prior to surveillance, as inflammation may confound the interpretation of dysplasia).
- **Screening:** Adenocarcinoma surveillance is necessary only if patients are candidates for esophagectomy. Upper endoscopy with four-quadrant biopsies every 2 cm of endoscopic lesions. Screening (based on criteria from the American Society of Gastrointestinal Endoscopy) is as follows:
  - After initial diagnosis, repeat EGD in 1 year for surveillance with biopsies.
  - Proceed according to EGD findings:
    - **No dysplasia:** Repeat EGD every 3 to 5 years.
    - **Low-grade dysplasia:** Endoscopic eradication (resection of mucosal irregularities, followed by ablation of remaining metaplastic epithelium). If eradication is not performed, perform surveillance EGD every 6 to 12 months.
    - **High-grade dysplasia:** Endoscopic eradication if no evidence of submucosal invasion (rather than esophagectomy). Ablative therapies may be attempted (eg, photodynamic therapy, argon plasma coagulation, endoscopic mucosal resection).
    - **Adenocarcinoma:** Invasive adenocarcinoma should be referred to an oncologist for staging and treatment, which may include chemoradiation, esophagectomy, or endoscopic resection.



**FIGURE 7.4. Barrett esophagus on endoscopy.** (Source: Biyani RSS, et al. Barrett's esophagus: review of diagnosis and treatment. *Gastroenterol Rep (Oxf)*. 2013;1(1):9-18.)

## DYSPEPSIA AND PEPTIC ULCER DISEASE

Typically defined as one or more of the following: postprandial fullness, early satiety, and epigastric burning or pain. Distinct from but can present with GERD (retrosternal burning). In the United States, the prevalence of dyspepsia is 25%, but only 25% of those affected seek care. Of these, >60% have nonulcerative dyspepsia and <1% have gastric cancer.

### Symptoms/Exam

May present with upper abdominal pain or discomfort, fullness, bloating, early satiety, belching, nausea, and retching or vomiting.

### Differential

Food intolerance (overeating, high-fat foods, alcohol, lactose intolerance), drug intolerance (NSAIDs, iron, narcotics, alendronate, theophylline, antibiotics), peptic ulcer disease (PUD) (10%-25%), GERD (15%-20%), gastric cancer (<1%), chronic pancreatitis, pancreatic cancer, biliary colic, irritable bowel syndrome (IBS).

### Diagnosis

Look for alarm features: **May include new-onset dyspepsia in patients >50 years of age, unintended weight loss, melena, iron deficiency anemia, persistent vomiting, hematemesis, dysphagia, odynophagia, abdominal mass, a history of PUD, previous gastric surgery, and a family history of gastric cancer.**

### Management

- **If alarm features are present:** Perform prompt endoscopy.
  - **Endoscopy unrevealing:** Diagnose with nonulcerative dyspepsia and provide reassurance; consider a trial of low-dose TCAs (desipramine 10-25 mg QHS) and possible CBT.
  - **Endoscopy revealing:** Manage as indicated.

### KEY FACT

In patients <50 years of age with no alarm features, gastric cancer is a rare etiology of dyspepsia, and direct endoscopy is not a cost-effective measure.

**KEY FACT**

Endoscopic biopsy, *H pylori* stool antigen, and urea breath test can assess active *H pylori* infection and gauge treatment success. *H pylori* serology can also be used for diagnosis if the patient has never been treated, but it cannot be used to test for eradication because it can remain  $\oplus$  even after adequate treatment.

- **If no alarm features are present:** Assess diet and provide education; discontinue suspect medications. Consider a trial of empiric acid suppression  $\pm$  *H pylori* testing (Table 7.3) and treatment (Table 7.4).
- **Determine the local prevalence of *H pylori*:**
  - If  $>10\%$ : Test for *H pylori* by serology, stool antigen, or breath test. If  $\oplus$ , institute *H pylori* eradication therapy. If  $\ominus$ , initiate a trial of acid suppression  $\times 4$  to 8 weeks.
  - If  $<10\%$ : Institute a trial of acid suppression  $\times 4$  to 8 weeks.
- **For persistent symptoms:** If the patient received *H pylori* therapy, test for eradication with a stool antigen, **not with serology**. Breath test can also be considered if patient has had no PPI for 8 weeks. If disease is not eradicated, attempt a different regimen. If eradicated, refer to endoscopy.
- Table 7.4 summarizes treatment options for PUD.

**GASTROPARESIS**

Delayed gastric emptying in the absence of obstruction. Most commonly related to diabetes, viral infection, neuropsychiatric disease, or postsurgical complications.

**Symptoms/Exam**

- Presents with postprandial fullness, bloating, abdominal distention, early satiety, nausea, and vomiting of digested food.
- Exam is normal. Mild to moderate upper abdominal tenderness may be seen during episodes. Occasionally, a **succussion splash** is heard on auscultation while rocking the patient.

**Differential**

- Poor glycemic control, postsurgical complications (**post-vagotomy or Roux-en-Y**), non-ulcer dyspepsia, medications (anticholinergics, opiates, TCAs, CCBs,  $\beta$ -blockers, and more).
- Hypothyroidism, scleroderma, muscular dystrophies, paraneoplastic syndrome (small cell lung cancer), amyloidosis.

**Diagnosis**

- **Solid-phase nuclear medicine gastric emptying scan:** Following the administration of a radiolabeled meal, normal gastric retention is  $<90\%$ ,  $<60\%$ , and  $<10\%$  at 60, 120, and 240 minutes, respectively.

**TABLE 7.3. Testing for *H pylori***

TEST	USE
Serum IgG	Most widely used for initial testing Most helpful in high prevalence areas Not useful to confirm eradication Does not determine whether one has active infection
Urea breath test	Identifies active infection (urease activity) Can have false negatives if using bismuth, PPI, or antibiotic Can be helpful in confirming eradication or testing for reinfection
Stool antigen	Same as urea breath test, but cheaper option
Endoscopic biopsy	Tissue culture for <i>H pylori</i> if endoscopy is indicated for other reasons

TABLE 7.4. Peptic Ulcer Disease Treatment

INDICATION	MEDICATION OPTIONS
<b>Active ulcer—associated with <i>H pylori</i></b> <i>H pylori</i> eradication regimen × 10-14 days	PPI BID + Clarithromycin 500 mg BID, amoxicillin 1 g BID (or metronidazole 500 mg BID if penicillin allergic) <b>OR</b> Bismuth subsalicylate two tablets QID, tetracycline 500 mg QID, metronidazole 250 mg QID
Treatment after <i>H pylori</i> eradication regimen × 4-8 weeks	PPI QD <b>OR</b> $H_2$ -receptor antagonists (as below)
<b>Active ulcer—not attributable to <i>H pylori</i></b> Uncomplicated duodenal ulcers	PPI × 4 weeks <b>OR</b> $H_2$ -receptor antagonist × 6 weeks
Uncomplicated gastric ulcers	PPI × 8 weeks <b>OR</b> $H_2$ -receptor antagonist × 8 weeks
Complicated ulcers	PPIs are the preferred drugs
<b>Ulcer relapse prevention</b> NSAID-induced ulcers: Prophylactic therapy for high-risk patients (prior ulcer disease or ulcer complications, corticosteroid or anticoagulant use, >70 years with serious comorbid illnesses)	PPI QD <b>OR</b> COX-2-selective NSAIDs (celecoxib) <b>OR</b> In special circumstances, misoprostol 200 µg TID-QID
Recurrent ulcers: “Maintenance” therapy is indicated in patients who are <i>H pylori</i> $\ominus$ or who have recurrence despite eradication therapy	PPI once-daily <b>OR</b> $H_2$ -receptor antagonists at bedtime (cimetidine 400-800 mg, nizatidine or ranitidine 150-300 mg, famotidine 20-40 mg)

(Data from McPhee SJ, et al. *Current Medical Diagnosis & Treatment 2010*. New York: McGraw-Hill, 2010, Table 15-10.)

- **Labs:** Electrolytes, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), ANA, TSH.
- **Endoscopy:** To rule out structural lesions and ulcers causing obstruction.
- **Esophageal manometry:** Not widely available, but can often distinguish myopathic from neuropathic patterns.

### Management

- **Dietary:** Small, frequent meals; low-fat, low-fiber diet.
- Tight glycemic control in diabetics.
- ↓ or discontinue opiates and anticholinergics.
- **Medications:**
  - **Cisapride:** Most effective, but its use is restricted owing to QT-interval prolongation.
  - **Metoclopramide:** A dopamine antagonist used as an antiemetic. ↓ effectiveness and adverse effects (extrapyramidal symptoms) are seen with long-term use.
  - **Domperidone:** A dopamine antagonist that is not approved for use in the United States.
  - **Erythromycin:** IV use has short-term efficacy; PO is less effective chronically.

- **Jejunostomy tube:** For intractable, severe gastroparesis without small bowel dysmotility.
- **Total parenteral nutrition (TPN):** For intractable, severe gastroparesis with small bowel dysmotility.
- **Gastric pacing:** Investigational.

## Lower GI Tract

### ACUTE DIARRHEA

Defined as diarrhea of <4 weeks' duration. Usually toxin-mediated or infectious, mild, and self-limited; cases are managed on an outpatient basis. Diarrhea accounts for 1.5% of all hospitalizations in the United States. ↑ morbidity is seen in children, the elderly, and the immunosuppressed. Etiologies include the following:

- Infection (Table 7.5):
  - **Bacterial:** *E coli*, *Campylobacter* (associated with Guillain-Barré syndrome), *Salmonella*, *Shigella*, *C difficile*, *Yersinia*, *Aeromonas*.
  - **Viral:** Adenovirus, rotavirus, norovirus.
  - **Parasites:** *Entamoeba histolytica* (associated with liver abscesses); *Giardia lamblia*; *Cryptosporidium*, *Microsporidium*, and *Mycobacterium avium* complex (MAC) in those with AIDS.
  - **Drugs:** Antibiotics, NSAIDs, quinidine, β-blockers, magnesium-base antacids, PPIs, colchicine, theophylline, acarbose.
  - **Other:** Food allergies; initial presentation of chronic diarrhea.

### Symptoms/Exam

- Diarrhea accompanied by urgency, tenesmus, abdominal bloating, and pain.
- Exam may reveal evidence of dehydration: tachycardia, orthostasis, ↓ skin turgor, dry mucous membranes. Also may have fevers, abdominal pain, distention.

### Diagnosis

- **Alarm features:** fever of >38.5°C (101.3°F), severe abdominal pain, **bloody diarrhea**, immune compromise, pregnancy, age >70 years, or severe dehydration. Evaluation is indicated!
- **No alarm features** (short duration, nonbloody diarrhea, nontoxic exam): Treat with oral rehydration and symptomatic therapy. If no improvement is seen, evaluation is indicated.



### KEY FACT

Acute diarrhea (diarrhea of <4 weeks' duration) is usually toxic/infectious and self-limited (or the start of a chronic cause of diarrhea).

TABLE 7.5. Infectious Causes of Acute Infectious Diarrhea

	NONINFLAMMATORY DIARRHEA	INFLAMMATORY DIARRHEA
Viral	Norovirus, rotavirus	CMV
Protozoal	<i>Giardia lamblia</i> , <i>Cryptosporidium</i>	<i>E histolytica</i>
Bacterial	<b>Preformed endotoxin production:</b> <i>S aureus</i> , <i>Bacillus cereus</i> , <i>Clostridium perfringens</i> <b>Enterotoxin production:</b> Enterotoxigenic <i>E coli</i> (ETEC), <i>Vibrio cholerae</i>	<b>Cytotoxin production:</b> Enterohemorrhagic <i>E coli</i> (EHEC), <i>Vibrio parahaemolyticus</i> , <i>C difficile</i> <b>Mucosal invasion:</b> <i>Shigella</i> , <i>Campylobacter jejuni</i> , <i>Salmonella</i> , enteroinvasive <i>E coli</i> (EIEC), <i>Aeromonas</i> , <i>Plesiomonas</i> , <i>Yersinia enterocolitica</i> , <i>Chlamydia</i> , <i>Listeria monocytogenes</i>

- Evaluation includes the following:
  - History is key:** Recent medication changes, recent travel, food exposure.
  - Blood tests:** CBC, electrolytes, BUN, creatinine, ameba serology.
  - Stool tests:** Stool culture and sensitivity, O&P, *C difficile* toxin, fecal leukocytes, *Giardia* antigen.
  - CT scan:** Consider if bloody diarrhea and significant abdominal pain (concern for colitis).
  - Endoscopy:** Consider flexible sigmoidoscopy or colonoscopy with biopsy if concern for colitis.

### Management

- Mild diarrhea:**
  - Oral rehydration (Pedialyte, Gatorade).
  - BRAT diet (bananas, rice, applesauce, toast).
  - Antidiarrheals:** Loperamide 4 mg initially and then 2 mg after each stool (maximum 8 mg/day).
- Severe diarrhea:** Oral or IV rehydration.
- Empiric antibiotics:**
  - Indicated if **immunocompromised, very young/old, traveler's diarrhea, or moderate/severe with fever and bloody stools.** Otherwise, wait for culture data.
  - Ciprofloxacin × 3 to 5 days. Second line: TMP-SMX.
  - Antibiotics are **not recommended** for nontyphoidal *Salmonella*, *Campylobacter*, *Aeromonas*, *Yersinia*, or *E coli* O157:H7. For *E coli* O157:H7, antibiotics can ↑ the risk of typical hemolytic uremic syndrome.
  - Antibiotics are recommended for shigellosis, cholera, extraintestinal salmonellosis, traveler's diarrhea, and amebiasis.
  - Giardiasis is treated with metronidazole.
  - C difficile* treatment is based on severity of infection (oral metronidazole, oral vancomycin, IV metronidazole, surgery). See the Infectious Diseases chapter for further details.



#### KEY FACT

Do not give antidiarrheals for bloody diarrhea.



#### KEY FACT

**Antibiotics are contraindicated** with *E coli* O157:H7 as this can precipitate hemolytic uremic syndrome!

### CHRONIC DIARRHEA

Diarrhea of >4 weeks' duration. Affects 3% to 5% of the population and leads to poor quality of life. Can be divided into three categories:

- Watery: Osmotic, secretory, functional.
- Fatty: Malabsorption/maldigestion.
- Inflammatory: IBD, invasive infectious disease, malignancy, radiation colitis.

Table 7.6 lists the etiologies of chronic diarrhea.

### Symptoms/Exam

- Medications are a common culprit! Ask about recent medication changes and an accurate medication list.
- Ask patient to describe stool. Watery, fatty diarrhea typically floats and is malodorous, inflammatory diarrhea has blood/pus.
- Exam can reveal evidence of dehydration, abdominal pain, but usually generally reassuring exam.
- Alarm symptoms:** Blood in stool, nocturnal diarrhea, progressive pain, weight loss.



#### QUESTION

A 21-year-old woman presents with diarrhea, cramps, and fever 10 days after she returned from a trip to India. She did not eat any raw meat but did stay with her family while there. She is febrile and mildly hypotensive. While stool samples are ordered, should she receive antibiotics?

TABLE 7.6. Causes of Chronic Diarrhea

TYPE	CLUES	CAUSES
Osmotic diarrhea	↓ stool volume with fasting; ↑ stool osmotic gap	<b>Medications:</b> Antacids, lactulose, sorbitol <b>Disaccharidase deficiency:</b> Lactose intolerance <b>Factitious diarrhea:</b> Magnesium (antacids, laxatives)
Secretory diarrhea	Large volume (>1 L/day); Little change with fasting; normal stool osmotic gap	<b>Hormonally mediated:</b> VIPoma, carcinoid, medullary carcinoma of the thyroid (calcitonin), Zollinger-Ellison syndrome (gastrin) Factitious diarrhea (laxative abuse); senna Villous adenoma Bile salt malabsorption (ileal resection, Crohn ileitis, postcholecystectomy) Medications
Motility disorders (functional)	Systemic disease or prior abdominal surgery	<b>Postsurgical:</b> Vagotomy, partial gastrectomy, blind loop with bacterial overgrowth <b>Systemic disorders:</b> DM, hyperthyroidism <b>IBS</b>
Malabsorption syndromes	Weight loss, abnormal lab values, fecal fat >10 g/24 hrs	<b>Small bowel mucosal disorders:</b> Celiac sprue, tropical sprue, Whipple disease, small bowel resection (short bowel syndrome), Crohn disease <b>Lymphatic obstruction:</b> Lymphoma, carcinoid, infectious (TB, <i>Mycobacterium avium-intracellulare</i> ), Kaposi sarcoma, sarcoidosis <b>Pancreatic disease:</b> Chronic pancreatitis, pancreatic carcinoma <b>Bacterial overgrowth:</b> Motility disorders (diabetes, vagotomy), scleroderma, fistulas, small intestinal diverticula
Inflammatory conditions	Fever, hematochezia, abdominal pain	<b>IBD:</b> Ulcerative colitis, Crohn disease <b>Malignancy:</b> Lymphoma, adenocarcinoma (with obstruction and pseudodiarrhea) <b>Other:</b> Microscopic colitis, radiation enteritis
Chronic infections		<b>Parasites:</b> <i>G lamblia</i> , <i>E histolytica</i> <b>AIDS related:</b> <ul style="list-style-type: none"><li>■ <b>Viral:</b> CMV</li><li>■ <b>Bacterial:</b> <i>C difficile</i>, MAC</li><li>■ <b>Protozoal:</b> Microsporidia (<i>Enterocytozoon bieneusi</i>, <i>Cryptosporidium</i>, <i>Isospora belli</i>)</li></ul>

(Modified with permission from McPhee SJ, et al. *Current Medical Diagnosis & Treatment 2010*. New York: McGraw-Hill, 2010, Table 15-5.)

## A

### ANSWER

Yes. Given her travel history to India visiting relatives, this patient's risk for typhoid fever is high. Although she could have traveler's diarrhea, the relative delay from her arrival makes typhoid more likely. Start empiric quinolones or a cephalosporin while stool and blood cultures are pending.

### Diagnosis

Initial workup is as follows:

- Rule out acute diarrhea, lactose intolerance, parasitic infection, ileal resection, medications, and systemic disease.
- **Characterize the diarrhea** as watery, fatty/malabsorption, inflammatory.

■ **Watery:**

- Determine if osmotic, secretory, functional. Calculate **stool osmotic gap**:

$$290 - 2 \times (\text{stool Na} + \text{stool K})$$

- Also check **stool weight**: If the 24-hour stool weight is  $>1000$  g, suspect secretory diarrhea; if  $<250$  g, suspect factitious diarrhea or IBS.

■ **Fatty (malabsorption/maldigestion):**

- Exclude anatomic defect (radiography, flexible sigmoidoscopy/colonoscopy, biopsy).
- Exclude exocrine pancreatic insufficiency (stool elastase, chymotrypsin level).
- Quantitative fat stain (24-hour collection).
- Empiric trial of pancreatic enzymes.
- Ultimately, may need small bowel biopsy (exclude infection, Whipple disease, lymphoma, amyloid, celiac).

■ **Inflammatory:**

- Need stool analysis, colonoscopy and biopsy for diagnosis. Consider CT scan.
- Microscopic colitis is a histologic diagnosis with normal appearance on colonoscopy.

Other clues to diagnosis:

■ **Blood test clues:**

- **Iron deficiency anemia**: Divalent cations such as iron are absorbed through the duodenum. The presence of iron deficiency anemia may point to celiac sprue.
- **Antigliadin or antiendomysial antibodies**: Associated with celiac sprue.
- **Neuroendocrine tumors**: VIP (VIPoma), calcitonin (medullary thyroid carcinoma), gastrin (Zollinger-Ellison syndrome), glucagon (glucagonoma).

■ **Stool test clues:**

- **pH**: A pH  $<5.6$  implies carbohydrate malabsorption.
  - **Leukocytes**: Presence suggests inflammatory diarrhea.
  - **Fat**: Spot testing is not specific; a 24-hour fat  $>7-10$  g implies malabsorption.
  - **Laxative screen**: ↑ magnesium ( $>45$  mmol/L), phosphate, sulfate levels.
- **Urine test clues**: Neuroendocrine tumors: 5-HIAA (carcinoid), VMA, metanephrenes, histamine.
- **Endoscopy**: Flexible sigmoidoscopy or colonoscopy with biopsy; consider upper endoscopy.
- **Other**: A  $\oplus$   $H_2$  breath test after a glucose/lactulose load suggests bacterial overgrowth or lactose intolerance.

### Management

- For all types of diarrhea, **find and treat the underlying cause!**
- **Mild diarrhea**: See the previous section.

### CELIAC SPRUE

**Gluten-sensitive enteropathy** interfering with the digestion and absorption of food nutrients. Often presents with diarrhea and failure to thrive, although it may be asymptomatic. Prevalence estimated at 1 in 300 to 1 in 500—highest among those of **Western European** descent. Shows a bimodal presentation in the first 8 to 12 months of life and between 20 and 40 years of age. Has strong hereditary component (10% prevalence among first-degree relatives). Mechanism is cross-reaction of T cells to gluten peptides, leading to duodenal **villous atrophy**, **intraepithelial lymphocytes**, and **crypt hyperplasia**. Disease course may be complicated by intestinal **lymphomas** and **adenocarcinomas**.

### KEY FACT

Osmotic diarrhea improves with fasting; secretory does not.

### KEY FACT

Ten percent of patients with acute severe infectious diarrhea have post-infection IBS.

### KEY FACT

**AIDS diarrhea**: Look for MAC, cryptosporidium, CMV. Always rule out CMV! About 87% of cases resolve following immune reconstitution inflammatory syndrome with highly active antiretroviral therapy (HAART) when CD4 levels are  $>50/\mu\text{L}$ .

### KEY FACT

In the United States, surreptitious laxative use accounts for 15% of referrals for chronic diarrhea and 25% of documented cases of secretory diarrhea.



### QUESTION

A 34-year-old woman presents with chronic diarrhea and steatorrhea, iron deficiency anemia, and pruritic vesicles over her elbows and knees. Tests to rule out celiac sprue (anti-TTG and antiendomysial antibodies are  $\ominus$ ). What should the next test be?

**KEY FACT**

Iron deficiency anemia may be present in celiac sprue as a result of iron malabsorption.



**FIGURE 7.5. Dermatitis herpetiformis.** Note the grouped papulovesicles. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 52-8.)

**KEY FACT**

Celiac sprue improves with the removal of gluten from the diet. Consider steroid therapy or rule out malignancy in those failing to respond to dietary changes.

**Symptoms/Exam**

- Presents with **chronic diarrhea**, steatorrhea, bloating, abdominal pain, flatulence, and weight loss.
- Fatigue, anemia, bleeding diathesis, osteopenia, and stunted growth are also seen.
- **Dermatitis herpetiformis** (pruritic papulovesicles over the extensor surfaces; Figure 7.5) is a common feature, as are cheilosis and glossitis.
- Associated conditions include diabetes, Down syndrome, abnormal AST/ALT, hypothyroidism, and hyposplenism.

**Diagnosis**

- **Serology:** Anti-TTG and **antiendomysial antibodies** have high sensitivity and specificity. Levels may fluctuate with disease activity and **may be absent in IgA deficiency** ( $>95\% / 98\%$ ). Antigliadin antibody is less sensitive and specific.
- **Labs:** May reveal anemia (iron deficiency from iron malabsorption, folate), hypocalcemia, hypokalemia, and hypomagnesemia.
- **Endoscopy:** Shows **blunted duodenal villi**. Small bowel biopsy is diagnostic, however can be  $\ominus$  in patients adhering to a gluten-free diet.

**Management**

- **Diet:** Removal of gluten is essential but may be difficult given the ubiquity of wheat flour.
- **Steroids:** Consider in the small percentage of patients who are refractory to a gluten-free diet. Consider malignancy in patients who are unresponsive to corticosteroids.
- **Calcium and vitamin D** for osteopenia; **pneumococcal vaccine** for hyposplenism.

**Complications**

- $\uparrow$  risk of **malignancy** (enteropathy-associated T-cell and non-Hodgkin lymphoma, **adenocarcinoma**).
- Compliance in pregnant women is important because of the  $\uparrow$  risk of miscarriage and congenital malformation.
- Noncompliance during childhood leads to failure to thrive or stunted growth.

**IRRITABLE BOWEL SYNDROME**

Abdominal **discomfort** or pain during the **prior 3 months** that is relieved by defecation and associated with a change in stool frequency or form. Forty percent of patients have impaired ability to work, avoid social functions, cancel appointments, or stop travel because of the severity of their symptoms. Onset is typically in the late teens to 20s and/or **after infectious gastroenteritis**. In the developed world, women are more commonly affected than men, but in India the opposite is the case. Thirty percent to 40% of patients have a **history of physical or sexual abuse**.

**A****ANSWER**

Quantitative IgA level. A high percentage of patients with celiac sprue will also have IgA deficiency, and as the antibodies tested are IgA in nature, they may be falsely  $\ominus$  in this patient population. This patient presents with features highly suggestive of celiac sprue (including dermatitis herpetiformis), so the possibility of a false-negative result should be considered. If she were to have IgA deficiency, endoscopy with biopsy might be appropriate for making the diagnosis.

**Symptoms/Exam**

- Intermittent or chronic abdominal discomfort or pain; bloating, belching, excess flatus, early satiety, nausea, vomiting, diarrhea, constipation.
- Exam is often normal, or patients present with mild to moderate abdominal tenderness.

**Differential**

IBD, colon cancer, chronic constipation (low-fiber/low-fluid intake, drugs, hypothyroidism), chronic diarrhea (**celiac sprue**, parasitic infections, bacterial overgrowth, lactase deficiency), chronic pancreatitis, endometriosis.

## Diagnosis

- Diagnosis of exclusion. Rome IV Criteria for Diagnosing IBS requires that the patient has recurrent abdominal pain, on average,  $\geq 1$  day/week in the last 3 months (with symptom onset  $\geq 6$  months before diagnosis), associated with two or more of the following criteria:
  - Related to defecation.
  - Associated with a change in frequency of stool.
  - Associated with a change in form (appearance) of stool.
- **Labs:** CBC, TFTs, serum albumin, FOBT. Consider anti-TTG to rule out celiac. Also consider breath testing for lactase deficiency or small intestinal bacterial overgrowth.
- **If diarrhea:** Stool for O&P and *C difficile* toxin. **Twenty-four-hour stool collection**—value  $>300$  g is atypical for IBS.
- **Severe upper abdominal pain/dyspepsia:** Consider upper endoscopy.
- Lower GI tract symptoms: Flexible sigmoidoscopy for those  $<40$  years of age; colonoscopy for those  $>40$  years with a change in bowel habits.

### KEY FACT

Consider celiac sprue whenever you are considering a diagnosis of IBS in a young woman. Like IBS, celiac sprue may manifest as abdominal bloating and cramping. Celiac sprue may also present with iron deficiency anemia, which may be incorrectly attributed to menses.

### KEY FACT

New-onset IBS often follows a diagnosis of infectious gastroenteritis.

## Management

- Provide reassurance.
- Tactfully explain visceral hypersensitivity and validate symptoms.
- **Dietary trials:** Lactose-free, high-fiber diet. Low fermentable sugar (low FODMAP diet).
- **Antispasmodics:** Dicyclomine, hyoscyamine, peppermint oil.
- **Antidepressants:** Desipramine, amitriptyline, fluoxetine, paroxetine.
- **Constipation-predominant type:**  $\uparrow$  fluid intake, provide bowel habit training, osmotic laxatives, lubiprostone if severe and other approaches unsuccessful.
- **Diarrhea-predominant type:** Loperamide, cholestyramine.

## CONSTIPATION

Normal bowel movement frequency is 3 to 12 per week. Constipation is defined as  $<3$  bowel movements per week or excessive difficulty and straining at defecation. Prevalence is  $\uparrow$  in the Western world and is **highest among children and elderly patients**. Etiologies can be divided into **mechanical** and **motility disorders** (Table 7.7).

### KEY FACT

Normal bowel movement frequency ranges from 3 to 12 per week.

## Symptoms/Exam

- Presents with abdominal bloating or pain as well as with nausea and anorexia.
- Exam: Often normal; findings may include abdominal distention, tenderness, and/or mass; external hemorrhoids, anal fissures, and fecal impaction; or rectal prolapse with straining.

**TABLE 7.7. Causes of Constipation**

MECHANICAL
Colonic mass
Stricture
Rectal prolapse
Hirschsprung disease
MOTILITY
Diet: Low fiber/inadequate fluid
Behavioral: Short-term stress, travel, disrupted routine
Metabolic: DM, hypothyroidism, hypokalemia, hypercalcemia, autonomic dysfunction
Medications: Narcotics, diuretics, CCBs, anticholinergics, psychotropic drugs, clonidine

### Diagnosis

- Labs: CBC, serum electrolytes (especially potassium and calcium), TSH, FOBT.
- Age <50 years and normal labs: Initiate a trial of ↑ fiber (20-30 g/day); fluid intake.
- Age ≥50 or <50 failed fiber/fluid trial, + FOBT, or anemia: Barium enema; flexible sigmoidoscopy or colonoscopy.

### Management

- Patients with no obstructive or medical disease: ↓ or discontinue suspect drugs, followed by addition of stool softeners (docusate), osmotic laxatives (magnesium hydroxide, lactulose, sorbitol, polyethylene glycol), enemas (tap water, mineral oil, soap suds, phosphate), and/or colonic stimulants (bisacodyl, senna).
- Refractory constipation:
  - Pelvic floor dysfunction: Anorectal manometry and balloon expulsion studies and defecography. Treat with biofeedback.
  - Slow-transit constipation: Radiopaque marker studies and scintigraphy with serial examination of marker transit using radiographs.

### DIVERTICULOSIS

Results from weakening of the colonic wall. In industrialized nations, has 30% to 50% prevalence in patients >50 years of age. Rates ↑ with low dietary fiber and advancing age. In the United States, the predominant location is the left colon.

- Symptoms/Exam: Approximately 70% of patients with diverticula remain asymptomatic; diverticulitis develops in 20%, and diverticular bleeding develops in 10%. In asymptomatic patients, the disorder is associated with excessive flatulence and pellet-like stools. Exam may be normal, or patients may present with mild abdominal distention.
- Diagnosis: Typically diagnosed on colonoscopy in evaluation of GI bleeding or routine cancer screening.
- Management: Dietary fiber 20 to 30 g/day; coarse bran or supplements (psyllium) to ↑ stool bulk and ↓ colonic pressure. May also prevent the formation of new diverticula.
- Complications: Diverticular bleeding:
  - Presents with painless rectal bleeding, usually from a single diverticulum.
  - Spontaneous cessation is common (80%), but approximately one-third of patients have recurrent bleeding.
  - Treat with colonoscopy and angiography with embolization; consider elective colonic resection after the second recurrence.

### DIVERTICULITIS

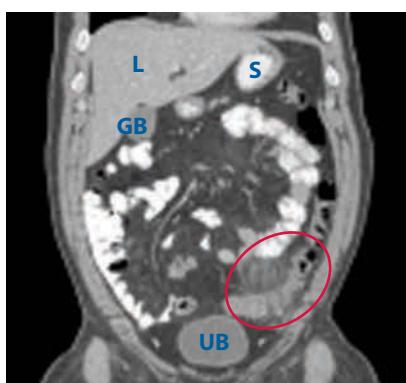
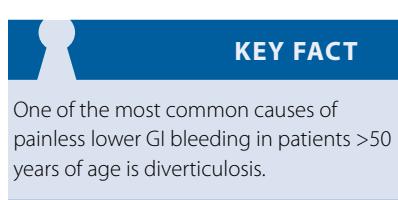
Microperforation of the diverticula with associated inflammation, commonly in the sigmoid colon. Frequency ↑ with advancing age.

#### Symptoms/Exam

- LLQ pain (93%-100%); fever, nausea, vomiting, constipation, diarrhea, urinary frequency ("sympathetic cystitis"). Bleeding is rare.
- Exam may reveal LLQ tenderness, localized involuntary guarding, percussion tenderness, and tender LLQ fullness or mass.

### Diagnosis

- CT with IV contrast: The test of choice; has high accuracy. Look for a thickened bowel wall, diverticula, and pericolonic fat stranding (Figure 7.6). Evaluate for complications (bowel perforation, abscess, fistula, obstruction).
- Colonoscopy: Exclude malignancy 8 weeks after resolution.



**FIGURE 7.6. Acute diverticulitis.**

Coronal reconstruction from a contrast-enhanced CT demonstrates sigmoid diverticula with perisigmoid inflammatory "fat stranding." The area of abnormality is circled in red. L = liver; S = stomach; GB = gallbladder; UB = urinary bladder. (Reproduced with permission from USMLE-Rx.com.)

## Management

- Outpatient treatment is sufficient if there are no significant comorbidities, minimal symptoms, and no peritoneal signs. Often requires hospitalization.
- Treat with IV fluids, bowel rest, and NG suction for ileus or obstruction.
- Broad-spectrum antibiotics:** Cover anaerobes, gram-negative bacilli, and gram-positive coliforms. Administer a 7- to 10-day course. IV ampicillin/sulbactam or piperacillin/tazobactam; PO quinolones; amoxicillin/clavulanate.
- Surgery:** Indicated for perforation, abscess, fistula, obstruction, or considered in recurrent diverticulitis ( $>2$  episodes).

## Complications

- Perforation:** Not excluded by the absence of free air. Associated with  $\uparrow$  mortality (6%-35%); **necessitates urgent surgical intervention.**
- Abscess:** Pelvic abscess is most common. Percutaneous CT-guided drainage is often possible.
- Fistula:** Colovesical fistulas (to the bladder) are found more often in men than in women. Other fistulas are to the vagina, small bowel, and uterus. Surgical intervention is often postponed until the infection is treated.
- Obstruction:** Colonic obstruction in the setting of severe inflammation is possible. Treatment is supportive.

## GI Bleeding

### ACUTE UPPER GI BLEEDING

Peptic ulcer disease is the most common cause of acute UGIB (Figures 7.7 and 7.8). Other etiologies include vascular ectasias, variceal bleeds, Mallory-Weiss tears, esophagitis, gastritis, duodenitis, malignancy. Less common causes include Dieulafoy lesions, aortoenteric fistulas, hemobilia.

#### Symptoms/Exam

- Patients present with nausea, retching, hematemesis (bright red blood or “coffee ground” emesis), dyspepsia, abdominal pain, melena or hematochezia, and orthostasis.
- Exam may reveal melena or hematochezia, pallor, hypotension, and tachycardia. Stigmata of chronic liver disease (spider angioma, ascites, jaundice) or a history of alcohol use is usually found among those with variceal hemorrhage.

#### Diagnosis

- History:** Assess NSAID use (peptic ulcer), retching prior to hematemesis (Mallory-Weiss tear), alcohol abuse (esophagitis, Mallory-Weiss tear, varices), prior abdominal aortic graft (aortoenteric fistula), chronic GERD (esophagitis), and weight loss/iron deficiency (malignancy).
- NG tube lavage:** Useful if  $\oplus$  (red blood, coffee grounds); if  $\ominus$  (clear or bilious), does not exclude UGIB.
- EGD:** Perform after stabilization and resuscitation; diagnostic, prognostic (Table 7.8), and therapeutic.
- H pylori testing:** Perform on all patients with peptic ulcers.

## Management

- Stabilization:** As with LGIB (see above).
- Medical therapy:**  $H_2$ -receptor antagonists do not alter the outcome. Give **high-dose oral PPIs twice daily** or PPI drip on presentation. Initiate an IV PPI drip if EGD suggests a high risk of rebleeding (ie, active bleeding, visible vessel, adherent clot).

### KEY FACT

Diverticulitis is the most common cause of colovesical fistula.

### KEY FACT

Mild diverticulitis may be treated on an outpatient basis if there are no significant comorbidities, minimal symptoms, and no peritoneal signs.



**FIGURE 7.7. Gastric ulcer on barium upper GI.** A benign gastric ulcer can be seen as pooling of contrast (arrowhead) extending beyond the adjacent gastric wall. (Reproduced with permission from Chen MY, et al. *Basic Radiology*. New York: McGraw-Hill, 2004, Fig. 10-21.)

### KEY FACT

As little as 50 mL of blood in the GI tract can cause melena.

### KEY FACT

Antibiotics are indicated for any GI hemorrhage in a cirrhotic patient.



**FIGURE 7.8. Gastric ulcer on endoscopy.** This 1-cm benign gastric antral ulcer was discovered serendipitously in a gastrectomy specimen removed for adenocarcinoma of the fundus (not shown in the photo). The gross appearance is classic for a benign ulcer in that it is relatively small, the mucosa surrounding the ulcer base does not appear tumefactive, and the radiating rugal folds extend nearly all the way to the margins of the base. (Reproduced from Wikimedia; courtesy of Dr. Ed Uthman.)

TABLE 7.8. Risk Assessment in Patients With UGIB

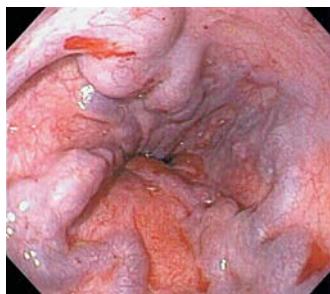
VARIABLE	RISK		
	LOW	MODERATE	HIGH
History	Age <60	Age <60	Age >60, comorbidities, onset while in hospital
Exam	SBP >100 mm Hg; HR <100 bpm	SBP >100 mm Hg; HR >100 bpm	SBP <100 mm Hg; HR >100 bpm
EGD	Small, clean-based ulcer; erosions; no lesion found	Ulcer with pigmented spot or adherent clot	Active bleeding, varices, ulcer >2 cm, visible vessel
Rebleed risk	<5%	10%-30%	40%-50%
Triage	Ward/home	Ward	ICU

Reduces the relative risk of bleeding by 50%. IV octreotide and antibiotics (ceftriaxone) for suspected variceal hemorrhage; continue for 3 to 5 days if verified by EGD.

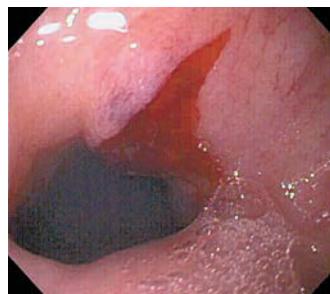
- **Endoscopy:** Of all patients with active UGIB at EGD (Figure 7.9), >90% can be effectively treated with banding, epinephrine, clipping, and/or electrocautery. Predictors of rebleeding include significant comorbidities, lesion size, and high-risk stigmata (visible vessel, adherent clot).
- **Refractory or recurrent UGIB:**
  - Esophageal balloon tamponade (Minnesota or Sengstaken-Blakemore tubes) for varices as a bridge to transjugular intrahepatic portosystemic shunt (TIPS).
  - Angiogram with intra-arterial **embolization** or surgery for refractory nonvariceal bleeding.
- **H pylori eradication:** For all peptic ulcers causing UGIB. Given the 20% treatment failure rate, eradication should be confirmed with a stool antigen or urea breath test.
- Reinitiation of antiplatelets and anticoagulation is a balance between risk of rebleeding and risk of thrombosis. In general, aspirin can be resumed within 3 to 5 days if patient has cardiovascular disease. Restarting clopidogrel for patients on dual antiplatelets depends on severity and etiology of bleed. Resumption of anticoagulation depends on reason for anticoagulation. If a patient is at high thrombotic risk, consider bridging with heparin with careful observation, or resuming oral anti-coagulation 7 days after bleeding.

#### KEY FACT

Ten percent of documented UGIB cases have a  $\ominus$  NG tube lavage.



A



B



C



D

**FIGURE 7.9. Causes of upper GI bleed at endoscopy.** (A) Esophageal varices. (B) Mallory-Weiss tear. (C) Gastric ulcer with protuberant vessel. (D) Duodenal ulcer with active bleeding (arrow). (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Figs. 285-16, 285-18, and 285-15D and E.)

## LOWER GI BLEEDING

Defined as bleeding from a source distal to the ligament of Treitz, which divides the third and fourth portions of the duodenum. Of all cases of lower GI bleeding (LGIB), >95% are from a colonic source and >85% are self-limited. Etiologies include the following:

- Diverticulosis (40%).
- Vascular ectasia.
- Neoplasm, hemorrhoids, postpolypectomy.
- IBD, ischemic colitis, infectious.
- NSAID ulcers, radiation colitis.
- Rectal varices, solitary rectal ulcer syndrome. Consider an upper GI source.

### Symptoms

Usually painless, but may present with abdominal cramps. Orthostasis is seen in severe cases.

### Exam

Hematochezia (bright red blood, maroon stools) or melena; pallor; abdominal distension with mild tenderness; hypotension; tachycardia.

### Diagnosis

- Rectal exam and anoscopy to exclude an anorectal source.
- Stool cultures if infection is suspected.
- **Moderate to severe LGIB:** Consider nasogastric lavage because 10% of upper GI bleeding (UGIB), especially if brisk, can present as hematochezia. Urgent colonic purge (over 4-6 hours); then colonoscopy.
- **Massive LGIB:**
  - EGD: UGIB must be excluded with EGD; **10% of UGIB cases present with hematochezia.**
  - Technetium-labeled RBC scan, CT angiography, and/or mesenteric angiography to localize source of bleed.
  - **Diagnostic colonoscopy:** Typically performed 12-48 hours after presentation and stabilization. Technically difficult with poor visualization during brisk bleed.

### Management

- **Stabilization and supportive care are key.** NPO, consider NG tube, place two large-bore IVs. Aggressive IV fluids, cross-matched blood and transfuse to goal Hg of 7, or higher if active bleeding. In the presence of active LGIB and a platelet count of <50,000/ $\mu$ L or if there is known impaired function (uremia, ASA), transfuse platelets or administer desmopressin. With active LGIB and an INR of >1.5, transfuse FFP.
- **Medical therapy:** Discontinue ASA and NSAIDs. Reverse anticoagulants.  $H_2$ -receptor antagonists and PPIs have no role in the treatment of LGIB.
- **Mesenteric angiography/embolization:** Intervention of choice for brisk LGIB. Associated with 80% to 90% cessation rates for those with a diverticular or vascular ectasia etiology, although 50% experience rebleeding.
- **Surgery:** Indicated with active LGIB involving >4 to 6 units of blood in 24 hours or >10 units total. If the site is well localized, consider hemicolectomy; otherwise, perform total abdominal colectomy.

## Inflammatory Bowel Disease

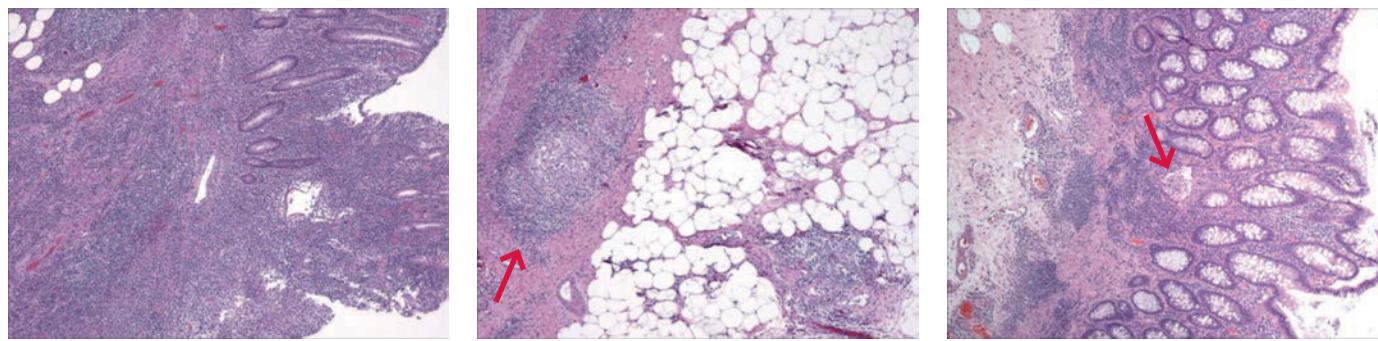
Crohn disease and ulcerative colitis are the 1° chronic autoimmune inflammatory diseases of the bowel (Figure 7.10).

### KEY FACT

Painless bleeding is usually either diverticular or from vascular ectasias. Painful bleeding is usually inflammatory, infectious, or ischemic. Occult bleeding with  $\oplus$  FOBT suggests a polyp or cancer.

### KEY FACT

Colonoscopy is technically challenging with brisk LGIB with poor visualization so is usually deferred until after stabilization. Can cauterize, inject epinephrine, or clip if a source of bleeding is found.



**A**                    **B**                    **C**

**FIGURE 7.10. Inflammatory bowel disease.** (A)–(B) Crohn disease. Transmural inflammation with noncaseating granulomas (arrow) is seen deep in the serosal fat on pathology. (C) Ulcerative colitis. Inflammation is confined to the mucosa and submucosa, with a crypt abscess (arrow). (Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

Smoking is associated with worsening Crohn disease, while ulcerative colitis may **improve** with smoking.

#### KEY FACT

Crohn is generally ASCA  $\oplus$  (**A**lways **S**een in **C**rohn), whereas ulcerative colitis is generally p-ANCA  $\oplus$  (**A**lmost **N**ever in **C**rohn).

#### KEY FACT

Crohn colitis carries a risk of colon cancer similar to that of ulcerative colitis.



**FIGURE 7.11. Crohn disease.**

Endoscopic view of the ascending colon shows cobblestone appearance with surrounding erythema and extensive ileocolonic aphthous ulceration. (Source: Bataduwaarachchi VR, et al. The concurrent association of inflammatory polyomyositis and Crohn's ileo-colitis in a Sri Lankan man: a case report of a rare association and literature review. *BMC Gastroenterol*. 2014;14:35.)

#### CROHN DISEASE

A chronic, recurrent disease with patchy or “skipped” transmural inflammation of **any segment** of the GI tract from the mouth to the anus. Demonstrates a propensity for the **ileum** and proximal colon. Can see **strictures** and **fistulas**, which are not characteristic of ulcerative colitis. More common among **Ashkenazi Jews**, those with a  $\oplus$  family history, and smokers; **smoking** may exacerbate disease. Shows a **bimodal** age of onset at 15 to 25 and 55 to 65 years of age. **NOD2** mutations confer susceptibility.

#### Symptoms/Exam

- RLQ or periumbilical pain, **nonbloody diarrhea**, low-grade fever, malaise, weight loss, anal pain, oral aphthous ulcers, postprandial bloating, kidney stones ( $\uparrow$  oxalate absorption  $\geq$  2° to fat malabsorption).
- Fever, tachycardia, abdominal tenderness and/or mass, perianal fissures/fistulas/skin tags, extraintestinal manifestations (pyoderma gangrenosum, erythema nodosum, ankylosing spondylitis, sacroilitis, uveitis).

#### Diagnosis

- **Stool studies:** Rule out infection with culture, O&P, and *C difficile* toxin.
- **Colonoscopy with biopsies is diagnostic:** Also assesses extent and severity of disease. Key words are skipped lesions, cobblestone, stricture, fistula, and ulcerations (Figure 7.11). Biopsies demonstrate acute and chronic inflammation; **noncaseating granulomas** are seen <25% of the time but are highly suggestive of Crohn disease.
- Other tests to consider: **Small bowel follow-through** to evaluate for small bowel involvement. **CT scan** when there is concern for abdominal abscess/fistula. **Immunologic markers (p-ANCA and ASCA)** can be helpful in indeterminate disease (Crohn vs ulcerative colitis, particularly if surgery is indicated) (Table 7.9).

**TABLE 7.9. Interpretation of p-ANCA and ASCA Values**

TEST	RESULT	INTERPRETATION	CHARACTERISTICS
p-ANCA	–	Suggests Crohn disease	95% PPV, 92% specificity
ASCA	+		
p-ANCA	+	Suggests ulcerative colitis	88% PPV, 98% specificity
ASCA	–		

## Management

- Induction and maintenance:** In general, think about treatment in these two categories. For **induction** (active disease), use steroids (IV vs oral depending on severity), anti-TNF or other biologics. For **maintenance**, use **immunomodulatory drugs** (azathioprine, 6-mercaptopurine [6-MP], methotrexate) or biologic drugs (infliximab, adalimumab, certolizumab, vedolizumab). The efficacy of 5-ASA drugs in Crohn disease is mixed in clinical trials. It is reasonable for the treatment of isolated colonic disease.
- Surgery:** Fifty percent of patients will require surgery for obstruction or abscess if the condition is refractory to medical therapy. Surgery is not curative.

## Complications

- Strictures/obstruction, fistulas, abscess, colorectal cancer.
- From terminal ileum involvement/resection:** Malabsorption (vitamin B<sub>12</sub>, vitamin D), nephrolithiasis (**calcium oxalate stones**), cholelithiasis, bile acid-induced diarrhea.

## ULCERATIVE COLITIS

A chronic, recurrent disease with diffuse **continuous** mucosal inflammation of the colon **extending proximally** from the rectum. Age of onset is typically 20 to 40 years, but the disease also occurs in patients <10 years of age and in the elderly. More common among Ashkenazi Jews, nonsmokers, and those with a family history; **smoking may attenuate disease**. Course is marked by repeated flares and remissions.

## Symptoms/Exam

- Bloody diarrhea**, crampy abdominal pain, fecal urgency, **tenesmus**, and weight loss are characteristic.
- Fever, tachycardia, and abdominal tenderness; red blood on DRE.
- Extraintestinal findings may include ankylosing spondylitis, sacroiliitis, erythema nodosum, pyoderma gangrenosum, and uveitis.

## Diagnosis

- Stool studies:** Rule out infection with culture, O&P, and *C difficile* toxin.
- Imaging:** For moderate and severe activity (Figure 7.12). KUB reveals loss of haustrations, leading to a “lead pipe” appearance and colonic dilation.
- Colonoscopy with biopsies is diagnostic:**
  - Avoid if there is a severe flare. Evaluate the colon and terminal ileum. Look for rectal involvement (95%-100%), **continuous circumferential ulcerations**, and **pseudopolyps** (Figure 7.13). The terminal ileum is occasionally inflamed from “backwash ileitis.”
  - Biopsies demonstrate acute and chronic inflammation, **crypt abscesses**, and absence of granulomas.

## Management

- Treatment depends on **severity** and on the **location** of active disease.
- Distal disease:** Mesalamine or hydrocortisone suppository (rectal involvement) or enema (up to the splenic flexure).
- Distal and proximal disease:** Oral or IV agents. 5-ASA, steroids or biologic therapy depending upon severity.
- Mild to moderate activity** (<4-6 bowel movements daily, occasional blood in stool, normal vital signs and Hct): 5-ASA or 6-MP for maintenance therapy; prednisone 40 to 60 mg PO QD if no response after 2 to 4 weeks.

## KEY FACT

Budesonide is an oral steroid with less systemic absorption.

## KEY FACT

TB exposure and hepatitis B must be ruled out before infliximab is administered.

## KEY FACT

For Crohn disease, lab values (hematocrit, albumin, ESR) are poorly correlated with disease severity. For ulcerative colitis, correlation is good.

## KEY FACT

Elevated alkaline phosphatase can suggest coexisting primary sclerosing cholangitis.

## KEY FACT

NSAID use can induce a flare of ulcerative colitis or Crohn disease.

## QUESTION

A 20-year-old man with a history of diarrhea presents with flank pain and is noted to have kidney stones. He reports years of having RLQ pain and occasional low-grade fevers. He is of Ashkenazi Jewish descent and has a family history of Crohn disease. As he awaits outpatient colonoscopy, serum anti-neutrophilic cytoplasmic antibody (p-ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) are sent. What pattern are these tests likely to show?



**FIGURE 7.12. Ulcerative colitis on CT scan enterography.** Pancolonic ulcerative colitis with wall thickening and enhancement (arrow). (Source: Deepak P, et al. Radiographical evaluation of ulcerative colitis. *Gastroenterol Rep (Oxf)*. 2014;2:169-177.)

- **Severe activity** (>6 bowel movements daily, bleeding, fever, tachycardia, elevated ESR, anemia):
  - Methylprednisolone IV or hydrocortisone IV often with anti-TNF or biologic therapy. Roughly 50% to 75% of patients achieve remission in 7 to 10 days.
  - If no response is seen within 7 to 10 days, **colectomy** is usually indicated. Consider a trial of cyclosporine or an anti-TNF agent prior to colectomy.
- **Maintenance therapy:** 5-ASA, immune modulator (6-MP, azathioprine) or biologic therapy (anti-TNF, integrin blocker).
- **Surgery:** Proctocolectomy with ileostomy is **curative** and can eliminate the risk of colon cancer. Proctocolectomy with ileoanal anastomosis is often curative, but 25% have “pouchitis,” or inflammation of the neorectum.

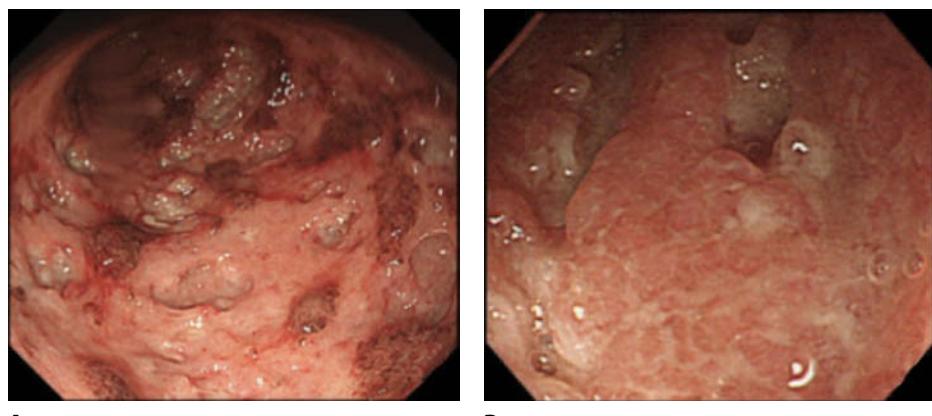
#### Complications

- **Toxic megacolon** (dilated colon, leukocytosis, fever, rebound tenderness), primary sclerosing cholangitis, colorectal cancer, extraintestinal manifestations (Table 7.10).

A

#### ANSWER

Labs will likely be p-ANCA  $\ominus$  and ASCA  $\oplus$ . This patient's symptoms, family history, and risk factors (Ashkenazi Jewish ethnicity) are highly suggestive of Crohn disease. p-ANCA and ASCA can be useful in distinguishing Crohn disease from ulcerative colitis in that Crohn is generally ASCA  $\oplus$  (**Always Seen in Crohn**), whereas ulcerative colitis is generally p-ANCA  $\oplus$  (**Almost Never in Crohn**).



**FIGURE 7.13. Ulcerative colitis colonoscopy findings.** (A) Punched-out ulcer. (B) Extensive ulcer. (Source: Ishikawa D, et al. Images of colonic real-time tissue sonoelastography correlate with those of colonoscopy and may predict response to therapy in patients with ulcerative colitis. *BMC Gastroenterol*. 2011;11:29.)

**TABLE 7.10. Extraintestinal Manifestations of Ulcerative Colitis and Their Relationship to Disease Activity**

RELATED	OFTEN RELATED	UNRELATED
Arthritis	Pyoderma gangrenosum	Ankylosing spondylitis
Erythema nodosum	Uveitis	Primary sclerosing cholangitis
Oral aphthous ulcers		
Episcleritis		

- **Colorectal cancer** risk is ↑, and depends on duration and extent of UC. Colonoscopy for colon cancer screening is recommended every 1 to 2 years beginning 8 years after diagnosis.

### KEY FACT

The risk of colon cancer in those with ulcerative colitis for >10 years is 0.5% to 1.0% per year; colonoscopy is recommended every 1 to 2 years beginning 8 years after diagnosis.

## Ischemic Bowel Disease

**Mesenteric ischemia** is ischemia of the small bowel, whereas **ischemic colitis** refers to the large bowel.

### ACUTE MESENTERIC ISCHEMIA

Caused most commonly by **emboli**, but thrombosis, vasoconstriction, and vasculitis are also possible. Most common in elderly patients and in those with valvular heart disease, atrial fibrillation (AF), or atherosclerotic disease. In young patients, it occurs with AF, vasculitis, hypercoagulable states (OCP use in young female smokers), and vasoconstrictor abuse. After infarction, mortality is 70% to 90%.

#### Symptoms/Exam

Presents with **sudden-onset**, severe abdominal pain (“**out of proportion to exam**”) as well as with sudden forceful bowel movements, often with maroon or bright red blood and nausea.

- **Early findings:** Agitation, writhing, a soft abdomen with hyper- or hypoactive bowel sounds, ⊕ fecal blood.
- **Late findings:** Distention, progressive tenderness, peritoneal signs, hypotension, fever.

### KEY FACT

Chronic mesenteric ischemia is characterized by pain with meals and weight loss.

#### Diagnosis

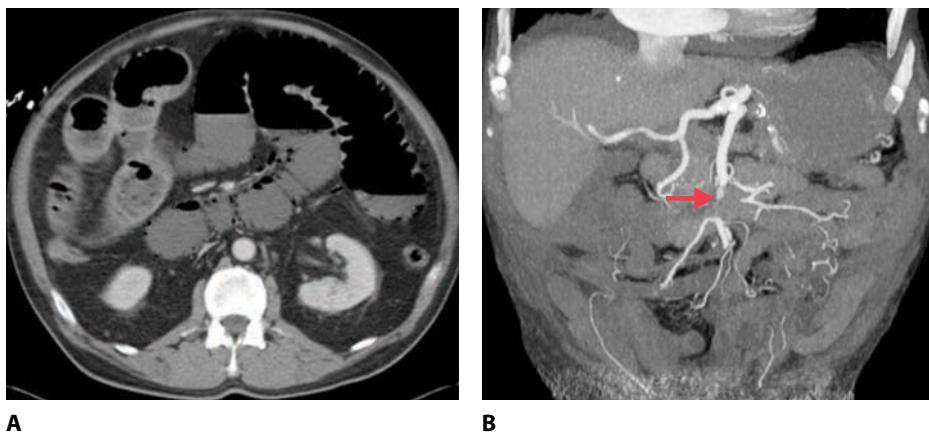
- Maintain a **high index of suspicion** for patients >50 years of age with CHF, cardiac arrhythmias, recent MI, recent catheterization, or hypotension.
- Labs, AXR, and CT may be suggestive (inflammatory markers, “thumbprint sign,” bowel wall thickening), but diagnosis of **acute mesenteric ischemia** is with **selective mesenteric angiography** (Figure 7.14) or made in the operating room in the setting of ischemic bowel. Diagnosis of **chronic mesenteric ischemia** is with MR or CT angiography.

### KEY FACT

For acute mesenteric ischemia with peritoneal signs, **urgent laparotomy** is indicated. If there are no peritoneal signs, consider **surgical embolectomy** or **intrarterial thrombolysis**.

#### Management

- IVF, bowel rest, and broad-spectrum IV antibiotics.
- Angiography followed by thrombolysis or immediate surgery.
- Anticoagulation should be postponed until >48 hours after laparotomy.



**FIGURE 7.14. Acute mesenteric ischemia.** (A) Transaxial image from a contrast-enhanced CT in a patient with a history of atrial fibrillation and acute-onset, severe abdominal pain. Note the dilated loops of bowel in the midabdomen with pneumatosis intestinalis and a nonenhancing bowel wall. (B) Coronal MIP reconstructions of CTA, revealing a segmental, occlusive acute embolism of the mid portion of SMA stem (arrow). (Image A reproduced with permission from USMLE-Rx.com. Image B source: Kuhelj D, et al. Percutaneous mechanical thrombectomy of superior mesenteric artery embolism. *Radiol Oncol*. 2013;47:239-243.)

### ISCHEMIC COLITIS

#### KEY FACT

Ischemic colitis typically affects the colonic “watershed” areas of the splenic flexure and rectosigmoid junction but spares the rectum.

#### KEY FACT

Patients with **acute mesenteric ischemia** often have small bowel ischemia or infarction and require urgent intervention while patients with **ischemic colitis** often recover with supportive care.

## Pancreatic Disorders

### ACUTE PANCREATITIS

#### KEY FACT

Gallstones and alcohol are the main causes of pancreatitis in the United States.

In the United States, >80% of acute pancreatitis cases result from binge drinking or biliary stones; pancreatitis develops in only 5% of heavy drinkers. Twenty percent of cases are complicated by necrotizing pancreatitis. Etiologies are as follows:

- **Alcohol and gallstones** and, to a lesser extent, trauma.
- **Drugs:** Azathioprine, pentamidine, sulfonamides, thiazide diuretics, 6-MP, valproic acid, didanosine.
- **Genetic:** PRSS1 (familial autosomal dominant), SPINK1, CFTR mutations.
- **Metabolic:** Hypertriglyceridemia or hypercalcemia.
- **Mechanical:** Pancreas divisum, sphincter of Oddi dysfunction, masses.

- Infectious:** Viruses (eg, mumps) and, to a lesser extent, bacteria and parasites (eg, *Ascaris lumbricoides*).
- Other:** Scorpion bites, vasculitis, idiopathic.

### Symptoms/Exam

- Presents with sudden-onset, persistent, deep epigastric pain, often with radiation to the back, that **worsens when patients are supine and improves when they sit or lean forward**.
- Severe nausea, vomiting, and fever are also seen.
- Exam reveals upper abdominal tenderness with guarding and rebound. In severe cases, can see fevers, shock. Rarely on exam, can see umbilical (**Cullen sign**) or flank (**Grey Turner sign**) ecchymosis.

### Diagnosis

Usually clinical diagnosis + elevated lipase  $>3 \times$  ULN. Some labs have prognostic value (Table 7.11). Obtain **RUQ ultrasound** to rule out gallstones. **CT scan** can show severity of inflammation or complications (Figure 7.15), and should be performed at 48 to 72 hours to exclude necrotizing pancreatitis in patients who are not showing clinical improvement.

### Management

- Bowel rest, aggressive IV hydration, and pain control with narcotics.
- Early enteral nutrition, consider nasojejunal tube feeds. TPN is associated with an ↑ risk of infection and is NOT preferred.
- Antibiotics are **not indicated** unless there is evidence of **infected** necrotizing pancreatitis. For this, begin broad-spectrum IV antibiotics (imipenem).
- For **gallstone pancreatitis** (↑ serum bilirubin, signs of biliary sepsis), perform cholecystectomy following recovery preferably during the same hospitalization and reserve ERCP for patients with evidence of biliary sepsis.

### Complications

- Necrotizing pancreatitis:** Patients are often critically ill (shock, multiorgan failure). Poor prognosis with up to 30% mortality and 70% risk of complications. If infected necrosis is suspected, initiate empiric antibiotics and consider percutaneous aspiration if there is a failure to respond. If organisms are present on smear, surgical debridement is indicated.
- Pancreatic pseudocyst:** A collection of pancreatic fluid walled off by granulation tissue. Occurs in approximately 30% of cases but resolves spontaneously in about 50%. Drainage is not required unless the pseudocyst is present for >6 to 8 weeks and is enlarging and symptomatic.
- Other:** Abscesses, pseudoaneurysm, renal failure, ARDS, splenic vein thrombosis (which can lead to isolated gastric varices).

TABLE 7.11. Assessment of Pancreatitis Severity by Ranson's Criteria<sup>a</sup>

24 HOURS: "GA LAW"	48 HOURS: "C HOBBS"
Glucose >200 mg/dL	Ca <8 mg/dL
Age >55 years	Hematocrit drop 10%
LDH >350 U/L	O <sub>2</sub> arterial Po <sub>2</sub> <60 mm Hg
AST >250 U/L	Base deficit >4 mEq/L
WBC >16,000/ $\mu$ L	BUN rise >5 mg/dL
	Sequestered fluid >6 L

<sup>a</sup>Mortality risk: 1% with 0-2 criteria; 16% with 3-4 criteria; 40% with 5-6 criteria; 100% with 7-8 criteria.

### KEY FACT

*A lumbricoides* causes up to 20% of cases of acute pancreatitis in Asia.

### KEY FACT

An ALT >3 times normal suggests biliary stones over alcohol; an AST/ALT ratio of >2 favors alcohol.

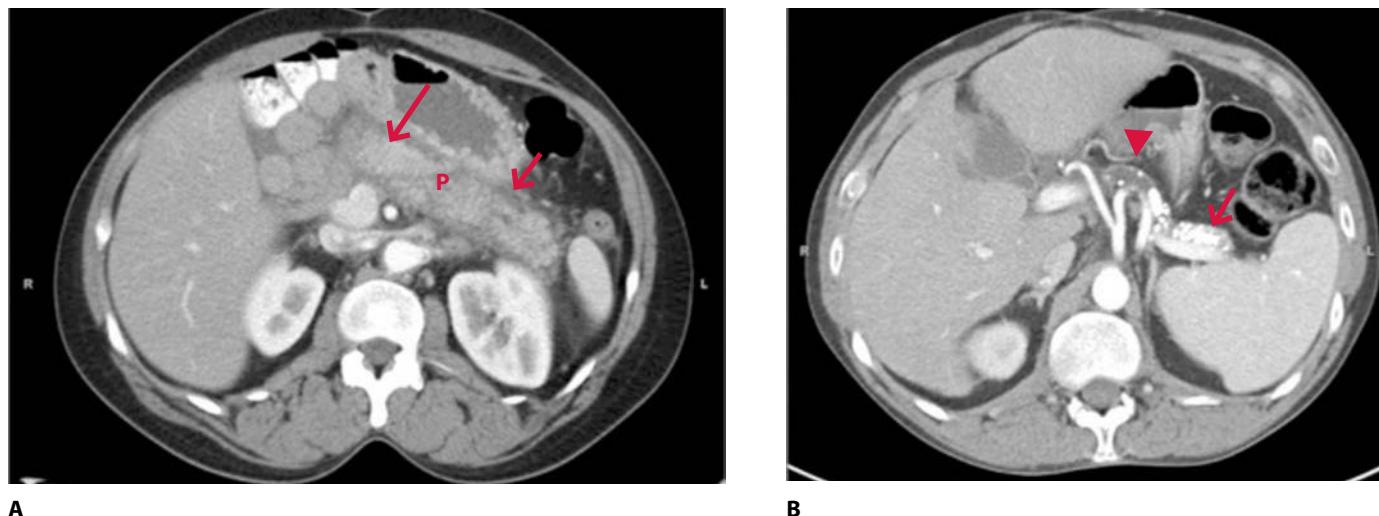
### KEY FACT

For persistent pancreatitis, consider CT with FNA to rule out infected necrosis, which requires surgical debridement.



### QUESTION

A 43-year-old woman with a history of diabetes presents with severe abdominal pain of acute onset. Exam is notable for a fever, tachycardia and hypotension, and tenderness to palpation in the epigastric region and RUQ. Lab results: ↑ WBC count, ↑ amylase and lipase, and ↑ total bilirubin. What is the next therapeutic step for this patient?



**FIGURE 7.15. Pancreatitis.** Transaxial contrast-enhanced CT images. (A) Uncomplicated acute pancreatitis. Peripancreatic fluid and fat stranding can be seen (arrows). P = pancreas. (B) Chronic pancreatitis. Note the dilated pancreatic duct (arrowhead) and pancreatic calcifications (arrow). (Reproduced with permission from USMLE-Rx.com.)

### CHRONIC PANCREATITIS

Persistent inflammation of the pancreas with irreversible histologic changes, recurrent abdominal pain, and loss of exocrine/endocrine function. Marked by atrophic gland, dilated ducts, and calcifications, although all are late findings. Characterized by the size of pancreatic ducts injured; “big duct” injury is from alcohol. Risk factors include **alcohol and smoking**. Associated with an ↑ risk of **pancreatic cancer**; 10- and 20-year survival rates are 70% and 45%, with death usually resulting from nonpancreatic causes. Etiologies are as follows:

- **Alcohol (80%).**
- **Autoimmune:** Rare and associated with diffuse enlargement of the pancreas, ↑ IgG4, and autoantibodies; associated with other autoimmune disorders (eg, Sjögren syndrome, SLE, primary sclerosing cholangitis).
- **Obstructive:** Pancreas divisum, sphincter of Oddi dysfunction, mass.
- **Metabolic:** Malnutrition, hyperlipidemia, hyperparathyroid-associated hypercalcemia.
- **Other:** Hereditary (cystic fibrosis, trypsinogen mutation).

#### Symptoms/Exam

- Presents with recurrent, deep epigastric pain, often radiating to the back, that worsens with food intake and when patients lie supine and **improves when they sit or lean forward**. Episodes may last anywhere from hours to 2 to 3 weeks.
- Also presents with anorexia, fear of eating (**sitophobia**), nausea/vomiting, and, later, weight loss, steatorrhea, insulin-dependent diabetes.
- Exam is normal. Mild to moderate upper abdominal tenderness may be found during episodes.
- Rarely, there may be a palpable epigastric mass (pseudocyst) or spleen (from splenic vein thrombosis).

### A

#### ANSWER

This patient appears to have gallstone pancreatitis with evidence of biliary sepsis. While she is resuscitated and given empiric antibiotics, it will be important to treat cholangitis by removing the obstruction, preferably within the first 48 hours of presentation.

#### Diagnosis

- No single test is adequate; routine labs, including amylase and lipase, are normal. Histology is gold standard but rarely obtained. Endoscopic ultrasound is the most sensitive test. CT scan may show inflammation, dilated ducts, or calcifications.

- Functional tests such as 72-hour fecal fat test on 100 g/day fat diet may be positive (>7 g of fat in stool). Stool chymotrypsin and elastase may also be absent/low.

### Management

- Alcohol abstinence and smoking cessation.
- Fat-soluble vitamins (vitamins A, D, E, and K); pancreatic enzymes.
- Pain control with narcotics and celiac plexus injection.
- ERCP with short-term pancreatic duct stenting and stone removal.
- **Surgical therapy** is appropriate for intractable pain and failure of medical therapy; modalities include pancreatectomy and autoislet transplantation, pancreaticojejunostomy (Puestow), and pseudocyst drainage.

### Complications

- **Malabsorption:** Deficiency of fat-soluble vitamins (A, D, E, and K); pancreatic enzymes.
- **Metabolic bone disease:** Osteopenia (33%) and osteoporosis (10%). Manage with calcium, vitamin D, and bisphosphonates.
- **Other:** Brittle DM (when >80% of pancreas is destroyed), pancreatic pseudocyst, pseudoaneurysm, hemosuccus pancreaticus (bleeding from the pancreatic duct into the GI tract), splenic vein thrombosis, pancreatic cancer. For diabetes from chronic pancreatitis, because insulin *and* glucagon production is impaired, patients are more prone to hypoglycemia.

## Biliary Disease

Tables 7.12 and 7.13 classify diseases with jaundice and biliary tract disease.

**TABLE 7.12. Classification of Jaundice**

TYPE OF HYPERBILIRUBINEMIA	LOCATION AND CAUSE
Unconjugated hyperbilirubinemia (predominant indirect-acting bilirubin)	↑ bilirubin production (eg, hemolytic anemias, hemolytic reactions, hematoma, pulmonary infarction) Impaired bilirubin uptake and storage (eg, posthepatitis hyperbilirubinemia, Gilbert syndrome, Crigler-Najjar syndrome, drug reactions)
Conjugated hyperbilirubinemia (predominant direct-acting bilirubin)	<b>Hereditary cholestatic syndromes:</b> Faulty excretion of bilirubin conjugates (eg, Dubin-Johnson syndrome) <b>Hepatocellular dysfunction:</b> <ul style="list-style-type: none"> <li>■ Biliary epithelial damage (eg, hepatitis, hepatic cirrhosis)</li> <li>■ Intrahepatic cholestasis (eg, certain drugs, biliary cirrhosis, sepsis, postoperative jaundice)</li> <li>■ Hepatocellular damage or intrahepatic cholestasis resulting from miscellaneous causes (eg, spirochetal infections, infectious mononucleosis, cholangitis, sarcoidosis, lymphomas, industrial toxins)</li> </ul> <b>Biliary obstruction:</b> Choledocholithiasis, biliary atresia, carcinoma of the biliary duct, sclerosing cholangitis, choledochal cyst, external pressure on the common duct, pancreatitis, pancreatic neoplasms

(Modified with permission from McPhee SJ, et al. *Current Medical Diagnosis & Treatment 2010*. New York: McGraw-Hill, 2010, Table 16-1.)

TABLE 7.13. Diseases of the Biliary Tract

PATHOLOGY	CLINICAL FEATURES	LABORATORY FEATURES	DIAGNOSIS	TREATMENT
Asymptomatic gallstones (cholelithiasis)	None	Normal	Ultrasound	None
Symptomatic gallstones (cholelithiasis)	Biliary colic	Normal	Ultrasound	Laparoscopic cholecystectomy
Porcelain gallbladder	Usually asymptomatic; high risk of gallbladder cancer	Normal	X-ray or CT	Laparoscopic cholecystectomy
Acute cholecystitis	Epigastric or RUQ pain, nausea, vomiting, fever, Murphy sign	Leukocytosis	Ultrasound, HIDA scan, or CT	Antibiotics, laparoscopic cholecystectomy
Chronic cholecystitis		Normal	Oral cholecystography, ultrasound (stones), cholecystectomy (nonfunctioning gallbladder)	Laparoscopic cholecystectomy
Choledocholithiasis	Asymptomatic or biliary colic, jaundice, fever; gallstone pancreatitis	Cholestatic LFTs; ↑ amylase and lipase in pancreatitis	Ultrasound or CT (dilated ducts), ERCP	Endoscopic sphincterotomy and stone extraction; antibiotics for cholangitis
Ascending cholangitis	Charcot triad: jaundice, RUQ pain, fever Reynold pentad: Charcot triad + AMS and hypotension	Cholestatic LFTs, leukocytosis, positive blood cultures	Same as choledocholithiasis	IV antibiotics, ERCP or percutaneous biliary drain for decompression if too sick for ERCP
Cholangiocarcinoma	Persistent biliary colic	Cholestatic LFTs	Ultrasound or CT, followed by cytology from ERCP	Palliative stenting of bile ducts, consider surgical resection for palliation

(Modified with permission from McPhee SJ, et al. *Current Medical Diagnosis & Treatment 2010*. New York: McGraw-Hill, 2010, Table 16-7.)

### CHOLELITHIASIS (GALLSTONES) AND ACUTE CHOLECYSTITIS

More common in women; incidence ↑ with age. In the United States, 10% of men and 20% of women >65 years of age are affected; >70% are cholesterol stones (Table 7.14). Among patients with incidental asymptomatic gallstones, only 15% have biliary colic at 10 years, and 2% to 3% have cholecystitis/cholangitis.

- **Cholecystitis:** The most common complication of cholelithiasis. More than 90% of cases are due to cholelithiasis with stone impacted in the cystic duct. Spontaneous resolution occurs in >50% of cases within 7 to 10 days.
- **Acalculous cholecystitis (without gallstones):** Usually seen in critically ill patients with no oral intake or following major surgical procedures; occurs after ischemia-related chronic gallbladder distention.

#### KEY FACT

Acalculous cholecystitis is generally seen in the critically ill with no oral intake or after major surgical procedures.

#### Diagnosis

- **RUQ ultrasound:** Less sensitive than HIDA scan but more readily available. Shows gallbladder wall thickening, pericholecystic fluid, and localization of stones (Figure

**TABLE 7.14.** Types of Gallstones

VARIABLE	CHOLESTEROL	BLACK PIGMENTED	BROWN PIGMENTED
Regional/ethnic predictors	Western countries, Pima Indians, Caucasians >> blacks	Africans, Asians	Africans, Asians
Risk factors	Age, female gender, pregnancy, estrogens, DM, obesity, rapid weight loss, ↑ triglycerides, prolonged fasting, ileal disease ( <b>Crohn</b> ), ileal resection, CF	Chronic hemolysis ( <b>sickle cell</b> ), cirrhosis, high-protein diet	Biliary infections, foreign bodies (stents, sutures), low-protein diet

7.16). A sonographic **Murphy sign** (focal gallbladder tenderness under a transducer) has a 90% positive predictive value. Low sensitivity (50%) for choledocholithiasis.

- **HIDA scan:** High sensitivity (95%) and specificity (90%). Assesses cystic duct patency;  $\oplus$  in the setting of a  $\ominus$  gallbladder uptake with preserved excretion into the small bowel. CCK stimulation assesses gallbladder contractility and aids in the diagnosis of acalculous cholecystitis.

### Management

- **Asymptomatic cholelithiasis:** No specific treatment is indicated (even in DM).
- **Symptomatic cholelithiasis:** Consider prophylactic cholecystectomy.
- **Cholecystitis:** bowel rest, antibiotics, and cholecystectomy after symptom resolution.

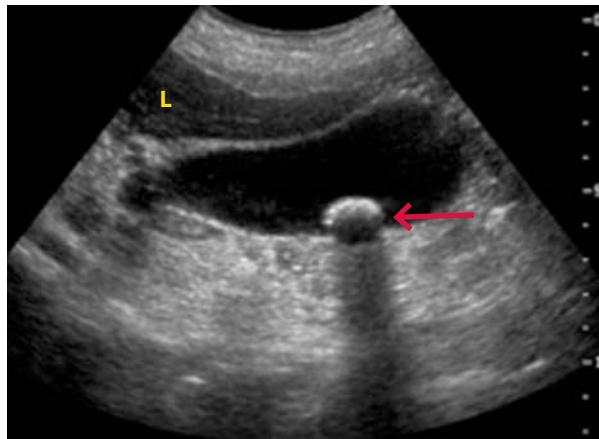
### Complications

- **Gangrenous cholecystitis:** The most common complication of cholecystitis (affects up to 20%), particularly in diabetics and the elderly. Patients appear septic.
- **Emphysematous cholecystitis:** 2° infection of the gallbladder with gas-forming organisms. More common in diabetics and the elderly; associated with high mortality. Gangrene and perforation may follow.

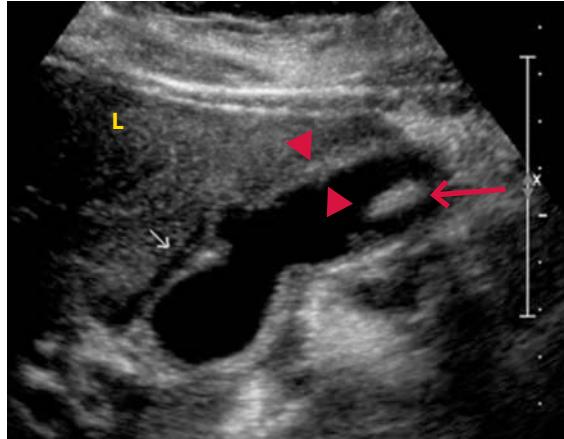


### QUESTION

A 50-year-old woman presents with abdominal pain after having suffered recurrent bouts of abdominal pain for years. KUB shows a normal bowel gas pattern but heavily calcified gallbladder. What is the next most appropriate step for this patient?



A



B

**FIGURE 7.16. Gallstone disease.** (A) Cholelithiasis. Ultrasound image of the gallbladder shows a gallstone (arrow) with posterior shadowing. (B) Acute cholecystitis. Ultrasound image shows a gallstone (red arrow), a thickened gallbladder wall (arrowheads), and pericholecystic fluid (white arrow). L = liver. (Reproduced with permission from USMLE-Rx.com.)

- **Cholecystenteric fistula:** Uncommon. Stone erodes through the gallbladder into the duodenum. Large stones (>2.5 cm) can cause small bowel obstruction (**gallstone ileus**).
- **Mirizzi syndrome:** Common bile duct compression by an inflamed impacted cystic duct, leading to obstruction. Uncommon.
- **Gallbladder hydrops:** Gallbladder mucocele with massive enlargement of the gallbladder due to cystic duct obstruction.
- **Porcelain gallbladder:** Intramural calcification. Associated with an ↑ risk of gallbladder cancer; cholecystectomy is indicated.

### CHOLEDOCHOLITHIASIS AND CHOLANGITIS

Choledocholithiasis is defined as stones in the common bile duct. Cholangitis can be defined as biliary tree obstruction and subsequent suppurative infection.

#### KEY FACT

**Charcot triad** = RUQ pain, jaundice, and fever/chills. **Reynold pentad** = Charcot triad plus hypotension and altered mental status.

#### A

#### ANSWER

Cholecystectomy. This patient is demonstrating evidence of a porcelain gallbladder, which carries a risk of gallbladder cancer. For this reason, prophylactic cholecystectomy may improve symptoms and may also prevent the development of malignancy.

#### Symptoms/Exam

- **Choledocholithiasis:** Similar to cholelithiasis, except **jaundice is more common in choledocholithiasis**. Other symptoms include biliary colic (crampy, wavelike RUQ pain), abdominal bloating, and dyspepsia. May be asymptomatic.
- **Cholangitis:** Similar to cholecystitis but frequently more severe, presenting with fever, jaundice, and RUQ pain (Charcot triad). May also include mental status changes and hypotension (Reynold pentad).

#### Differential

Rule out alternative causes of common bile duct obstruction: Mass lesions (eg, pancreatic and ampullary carcinoma, cholangiocarcinoma, bulky lymphadenopathy), parasitic infection (eg, ascariasis), AIDS cholangiopathy, primary sclerosing cholangitis, recurrent pyogenic cholangitis.

#### Diagnosis

- Clinical diagnosis based on exam and lab results. Confirm with dilated common bile duct on RUQ ultrasound or CT (RUQ ultrasound and CT have low sensitivity for visualizing choledocholithiasis). **MRCP** is noninvasive and sensitive for diagnosis.
- **ERCP:** Should not be used for diagnosis unless very high clinical suspicion (ie, bilirubin >4 mg/dL, clinical cholangitis, or visualized bile duct stone on imaging). Both diagnostic and therapeutic.

#### Management

- **Choledocholithiasis:** ERCP with sphincterotomy/stone removal followed by laparoscopic cholecystectomy.
- **Cholangitis:** Broad-spectrum IV antibiotics followed by **decompression**. Options for decompression include **ERCP** (with sphincterotomy, stone removal, biliary stenting), and percutaneous transhepatic biliary drainage (temporary). **Cholecystectomy** should follow after recovery from cholangitis due to gallstones.
- **Recurrent pyogenic cholangitis:** Affects Southeast Asians between 20 and 40 years of age; characterized by pigmented intrahepatic bile duct stones, biliary strictures, and repeated cholangitis. Treatment includes stenting and drainage. Often isolated to the left lobe of the liver; resection may be considered.

#### Complications

Gallstone pancreatitis, gram-negative sepsis, intrahepatic abscesses.

## AIDS CHOLANGIOPATHY

An opportunistic biliary infection caused by CMV, *Cryptosporidium*, or *Microsporidium*. CD4 count is usually <200/mL.

- **Symptoms/Exam:** Presents with RUQ pain/tenderness, fever, hepatomegaly, and diarrhea. Jaundice is **uncommon**.
- **Diagnosis:** Lab results show markedly ↑ alkaline phosphatase. ERCP or MRCP show intra- and/or extrahepatic biliary stricturing; papillary stenosis. **Aspiration and culture of bile are key to diagnosis.**
- **Management:** ERCP with sphincterotomy and biliary stenting. IV antibiotics based on bile cultures. Treat underlying immunosuppression/HIV.

## PRIMARY SCLEROSING CHOLANGITIS

A chronic cholestatic disease characterized by fibrosing inflammation of the intrahepatic and extrahepatic biliary system **without an identifiable cause**. Most common among middle-aged men; median survival from the time of diagnosis is 12 years. Commonly associated with **IBD** (more frequently ulcerative colitis than Crohn) and, to a lesser extent, with other autoimmune disorders (sarcoidosis, Sjögren syndrome, SLE, autoimmune hepatitis). Also associated with an ↑ risk of **cholangiocarcinoma** and **gallbladder cancer**.

### Symptoms/Exam

- Presents with gradual onset of fatigue and **severe pruritus** followed by jaundice and weight loss. Fever occurs with recurrent cholangitis.
- Exam reveals jaundice, hepatosplenomegaly, hyperpigmentation, xanthomas, excoriations, and stigmata of fat-soluble vitamin deficiency.

### Differential

**Secondary sclerosing cholangitis**—biliary stones, congenital anomalies, infections, AIDS cholangiopathy, recurrent pyogenic cholangitis.

### Diagnosis

- Maintain a high clinical suspicion in patients with IBD, as the **diagnosis of IBD typically precedes that of primary sclerosing cholangitis**. Look for an elevated alkaline phosphatase and  $\oplus$  p-ANCA (75% sensitive).
- **ERCP:** Can confirm diagnosis. Shows irregularity of the intra- and extrahepatic biliary tree, classically with a “**beads on a string**” appearance (Figure 7.17). 2° causes of sclerosing cholangitis usually have **only** extrahepatic bile duct involvement except with recurrent pyogenic cholangitis (intrahepatic biliary dilation and stones). Magnetic resonance cholangiography is less sensitive and less specific.
- **Liver biopsy:** Look for pericholangitis and the classic “**onion skin**” periductal fibrosis, focal proliferation and obliteration of bile ducts, cholestasis, and copper deposition.

### Management

- Focus on symptom control and on the prevention and management of complications. Medical therapy to prevent or delay disease progression is largely ineffective.
- **Symptom control:** Treat pruritus (cholestyramine, ursodiol, phenobarbital, rifampin).
- **Liver transplantation:** The treatment of choice for end-stage liver failure; 5-year survival is 75%.

## KEY FACT

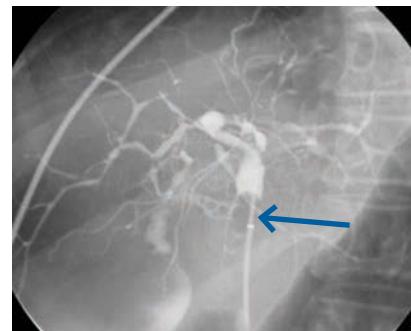
Of patients with primary sclerosing cholangitis, 75% have IBD (ulcerative colitis > Crohn), but only a small subset of IBD patients develop primary sclerosing cholangitis.

## KEY FACT

Primary sclerosing cholangitis is diagnosed by ERCP or MRCP that shows a “beads on a string” appearance involving both intra- and extrahepatic bile ducts.

## KEY FACT

Unlike primary biliary cholangitis, the natural history of primary sclerosing cholangitis is not improved by ursodeoxycholic acid.



**FIGURE 7.17. Primary sclerosing cholangitis.** Image from ERCP after contrast injection through a catheter in the common bile duct with the balloon (arrow) inflated. Multifocal stricturing and dilation of the intrahepatic bile ducts is present. (Reproduced with permission from USMLE-Rx.com.)



## QUESTION

A 46-year-old man with recent diagnosis of ulcerative colitis presents with fatigue and pruritus that have been worsening over several months. Exam is largely normal; lab results are notable for ↑ alkaline phosphatase and total bilirubin levels. RUQ ultrasound shows hepatomegaly, mild dilation of the intrahepatic ducts, and normal gallbladder and common bile duct. What test will best establish this patient's diagnosis?

### Complications

- **Steatorrhea/fat-soluble vitamin deficiency:** Treat with bile acids, digestive enzymes, and vitamins A, D, E, and K.
- **Metabolic bone disease:** Treat with  $\text{Ca}^{++}$  and bisphosphonates.
- **Recurrent bacterial cholangitis and dominant strictures:** Treat with antibiotics and biliary stent and drainage.
- **Other:** Biliary stones, **cholangiocarcinoma**, portal hypertension, end-stage liver disease.

### PRIMARY BILIARY CHOLANGITIS (FORMERLY PRIMARY BILIARY CIRRHOSIS)

A chronic cholestatic disease that primarily affects primarily **middle-aged women of all races**. Prevalence is 19 to 240 cases in one million; 90% to 95% are women. Age of onset is 30 to 70 years; often associated with **autoimmune** disorders such as Sjögren syndrome, RA, thyroid disease, celiac sprue, and CREST syndrome.

### Symptoms/Exam

May be asymptomatic (50%-60% at the time of diagnosis) or present with fatigue, **severe and intractable pruritus** prior to jaundice, and malabsorptive diarrhea.

### Differential

Biliary obstruction (stones, benign or malignant masses), autoimmune hepatitis, primary and secondary sclerosing cholangitis, drug-induced cholestasis (phenothiazines, steroids, TMP-SMX, tolbutamide), infiltrative diseases (sarcoidosis, lymphoma, TB).

### Diagnosis

- Triad of unexplained cholestasis (can see isolated ↑ serum alkaline phosphatase), **⊕ antimitochondrial antibodies (AMA)**, and compatible **histology** on liver biopsy.
  - AMA are detected in 95% of cases. ANA (70%), SMA (66%), RF (70%), and antithyroid antibodies (40%) are also seen.
  - **Other:** ↑ serum IgM, total cholesterol, HDL.
- **Liver biopsy:** Important for diagnosis, staging, and prognosis. The pathognomonic finding is the “**florid**” **duct lesion** (duct degeneration with periductular granulomatous inflammation), which is uncommon.

### Management

- Disease-modifying therapy has limited efficacy. Symptom control and prevention and treatment of complications are most important in management.
- **Ursodeoxycholic acid:** Promotes endogenous bile acid secretion and may also have immunologic effects. Colchicine and methotrexate are less commonly used.
- **Liver transplantation:** The most effective treatment for decompensated primary biliary cholangitis.



### KEY FACT

Antimitochondrial antibody (present in 95% of patients) and ↑ serum IgM are the best laboratory diagnostic tools for primary biliary cirrhosis.



### ANSWER

Cholangiography. This patient has primary sclerosing cholangitis. This will best be seen on cholangiogram, which would show the classic **“beads on a string”** appearance of the biliary tree. Although serology could be used to aid in the diagnosis, p-ANCA and ANA are not specific or sensitive enough to confirm the diagnosis.

### Complications

- **Malabsorption:** Treat with fat-soluble vitamins (A, D, E, and K) and pancreatic enzymes.
- **Metabolic bone disease:** Osteopenia (affects 33%) and osteoporosis (affects 10%). Manage with calcium, vitamin D, and bisphosphonates.
- **Cirrhosis:** Late.

## Hepatitis

### HEPATITIS A AND HEPATITIS E

Spread by fecal-oral transmission; cause acute (**not chronic**) hepatitis. More common in developing countries. The annual incidence of hepatitis A virus (HAV) in the United States is 70,000, whereas **hepatitis E virus (HEV)** is rare and limited to **travelers of endemic regions** (Southeast and Central Asia, the Middle East, Northern Africa, and, to a lesser extent, Mexico). HAV is typically asymptomatic, benign, and self-limited in children but can range from mild to severe acute hepatitis in adults. The rate of fatal acute liver failure from HAV is <4% in patients <49 years of age but can be as high as 17% in those >49 years of age. **HEV is more severe than HAV, particularly in pregnancy**, a setting in which **mortality is approximately 20%**.

#### Symptoms/Exam

- Presents with flulike illness, malaise, anorexia, weakness, fever, RUQ pain, jaundice, and pruritus. Children are typically asymptomatic.
- Atypical presentations include acute liver failure, cholestasis (prolonged, deep jaundice), and relapsing disease (2-18 weeks after initial presentation).
- Figure 7.18 illustrates the typical course of HAV.

#### Diagnosis

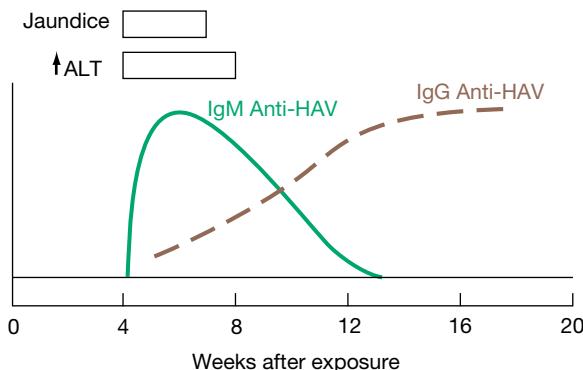
- **History:** Inquire about ill contacts, substandard water supply, travel (HEV), and contaminated food (**shellfish and green onions**).
- **Labs:** Check for **anti-HAV IgM** and **anti-HEV IgM** to diagnose acute infection. IgG levels indicate prior exposure or vaccination.

#### Management

- Supportive care. No specific drug treatment is available for HAV or HEV.
- Consider early delivery for pregnant women with HEV (no proven benefit).

#### Prevention

- **Vaccination:** The HAV vaccine is safe and effective, but no vaccine for HEV is currently available. Travelers to endemic regions, men who have sex with men, IV drug users, Native Americans, those with chronic liver disease (**all HCV**  $\oplus$ ), food handlers, day care center workers should be vaccinated.
- **HAV immunoglobulin:** Effective for postexposure prophylaxis. Indicated within 2 weeks of known contact (eg, through sex, day care, contaminated food), or for those



**FIGURE 7.18. Typical course of acute HAV.** (Modified with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 298-2.)

#### KEY FACT

HAV and HEV cause variably severe acute hepatitis but do not typically cause chronic hepatitis.



#### QUESTION

A 50-year-old man from China presents to his new physician with a history of hepatitis B. His labs reveal that he is HBsAg  $\oplus$ , anti-HBs  $\ominus$ , HBeAg  $\oplus$ , and anti-HBc  $\oplus$  and has an HBV DNA level of 2000 IU/mL. He has no stigmata of liver disease, and INR, albumin, and transaminase levels are all normal. In addition to ensuring that sexual and household contacts are vaccinated, what measures would constitute appropriate surveillance for hepatocellular carcinoma (HCC) in this patient?

traveling immediately to endemic areas in <2 weeks, supplement with the first HAV vaccine shot.

### HEPATITIS B AND HEPATITIS D

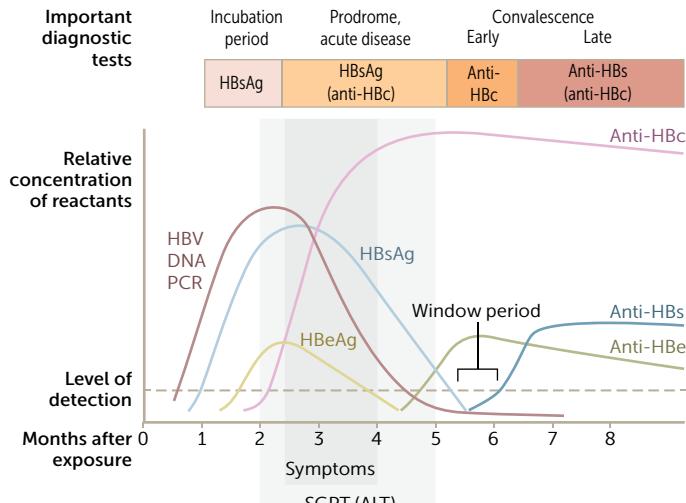
About 400 million people worldwide have chronic hepatitis B virus (HBV) infection, including >1 million in the United States. Transmission can be perinatal (the most common cause worldwide), sexual, or percutaneous. Age at infection is **inversely related** to the risk of chronic infection (younger age = higher risk of chronic infection). Of all patients with chronic HBV, cirrhosis develops in 15% to 20% and HCC develops in 10% to 15%. Hepatitis D virus (**HDV**) infection requires HBV coinfection. In the United States, HDV is found primarily among IV drug users and hemophiliacs.

#### Symptoms/Exam

- **Acute HBV:** Presents with flulike illness, malaise, weakness, low-grade fever, serum sickness-like symptoms (arthritis, urticaria, angioedema), and RUQ pain followed by jaundice (Figure 7.19). Acute liver failure is possible.
- **Chronic HBV:** Can be asymptomatic, but later can progress to sequelae of cirrhosis.
- **Extrahepatic manifestations:** Serum sickness, polyarteritis nodosa, glomerulonephritis, cryoglobulinemia.

#### Diagnosis

- **HBsAg:** Surface antigen indicates **active** infection (Table 7.15).
- **Anti-HBs:** Antibody to HBsAg indicates past viral infection or immunization.
- **Anti-HBc:** IgM is an early marker of infection; IgG is the best marker for prior HBV exposure. IgM may also become detectable in reactivation of HBV.
- **HBeAg:** Proportional to the quantity of intact virus and therefore infectivity. Some HBV variants (called **precore mutants**) cannot make HBeAg. Precore mutants have



A

#### ANSWER

Abdominal CT or ultrasound every 6 months. Hepatitis B **does not need to progress to cirrhosis before HCC can arise**; therefore, this patient with active HBV needs active surveillance. AFP can also be measured but is not required, and by itself it is insufficient as a screening test for HCC.

**FIGURE 7.19. Course of acute HBV infections with resolution.** After the infecting event (time 0) follows a lag phase without detectable markers. Thereafter HBV DNA (within the virus) and HBsAg ↑ exponentially in the serum. HBV DNA is detected earlier because its assay is much more sensitive. HBV DNA and HBsAg peak before outbreak of the acute disease and ↓ after the onset of clinical symptoms. Initially, the HBV DNA decreases faster because it has a shorter half-life time in serum than HBsAg. HBsAg finally disappears whereas HBV DNA may remain detectable in traces. Antibodies against the HBV core antigen (anti-HBc) appear with the onset of symptoms, the protective antibody against HBsAg (anti-HBs) appears very late, usually several weeks or months after disappearance of HBsAg. Disappearance of HBsAg is considered to be a sign of resolution but the virus often remains in occult form in the liver. (Reproduced with permission from USMLE-Rx.com; modified from Gerlich, WH. Medical virology of hepatitis B: how it began and where we are now. *Virol J*. 2013;10:239, Fig. 5.)

**TABLE 7.15.** Serologic Patterns in HBV Infection and Their Interpretation

HBSAG	ANTI-HBS	ANTI-HBC	HBEAG	ANTI-HBE	INTERPRETATION
+	-	IgM	+	-	Acute hepatitis B
+	-	IgG <sup>a</sup>	+	-	Chronic hepatitis B with active viral replication
+	-	IgG	-	+	Chronic hepatitis B with low viral replication
+	+	IgG	+ or -	+ or -	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)
-	-	IgM	+ or -	-	Acute hepatitis B
-	+	-	-	-	Vaccination (immunity)
-	-	IgG	-	-	False-positive; less commonly, infection in remote past

<sup>a</sup>Low levels of IgM anti-HBc may also be detected.

(Modified with permission from McPhee SJ, et al. *Current Medical Diagnosis & Treatment 2010*. New York: McGraw-Hill, 2010, Table 16-5.)

lower spontaneous remission, are less responsive to treatment, and are associated with a higher risk of cirrhosis and HCC. Precore mutants are diagnosed by their high HBV DNA and  $\ominus$  HBeAg.

- **HBV DNA:** Indicates active replication. A level of  $>10^5$  copies/mL is considered active;  $>10^2$  copies/mL are detectable by new assays.
- **Anti-HDV:** Indicates past or present HDV infection. **Does not indicate immunity.**
- **Liver biopsy:** Not routinely needed prior to treatment. Indicated if the diagnosis is in question or to determine the degree of inflammation or fibrosis/cirrhosis.



#### KEY FACT

HBsAg, HBeAg, and HBV DNA suggest active viral replication.

### Management

- **Acute hepatitis B:** Supportive treatment. Start antiviral medication if evidence of acute liver failure.
- **Chronic hepatitis B:** The decision to treat depends on HBeAg status, ALT level, HBV DNA level, and the presence of cirrhosis.
  - In general, treatment is reserved for patients with evidence of active hepatic inflammation (ALT  $>2$  times the upper limit of normal or at least moderate inflammation on liver biopsy) with moderate levels of detectable HBV virus ( $>2000$  IU/mL in HBeAg-negative patients and  $>20,000$  IU/mL in HBeAg-positive patients).
  - If there is evidence of cirrhosis (radiographically or histologically), treatment with oral agents is generally recommended in the setting of any detectable HBV virus regardless of the degree of hepatic inflammation. Interferon is contraindicated in patients with cirrhosis and HBV infection.
- **Nucleoside analogs:** Given PO; generally well tolerated. **Tenofovir** and **entecavir** are first-line therapy; other agents include **lamivudine**, **adefovir**, and **telbivudine**.
- **Pegylated interferon  $\alpha$ -2a:** Given SQ; associated with many side effects (eg, constitutional, psychiatric, bone marrow toxicity, flare of autoimmune disease, hepatic decompensation). **Contraindicated in cirrhosis.** The best responses to treatment are obtained with active hepatic inflammation ( $\uparrow$  ALT) and  $\downarrow$  HBV DNA levels.
- **Liver transplantation:** The treatment of choice for decompensated cirrhosis.

### Prevention

- **Acute exposure/needlestick prophylaxis:** The CDC recommends that hepatitis B immune globulin (HBIG) be given **within 24 hours along with vaccine** if the patient was not previously immunized.
- **Pregnancy:** Treatment is indicated in women with high levels of viremia,  $>200,000$  IU/mL and starts at 28 to 32 weeks' gestation. In addition, the infant should receive HBIG and HBV vaccination.



#### KEY FACT

Needlestick transmission rates follow the rule of 3's: HBV 30%, HCV 3%, HIV 0.3%.

## HEPATITIS C

### KEY FACT

Both HCV and HBV can cause cryoglobulinemia and glomerulonephritis.

Transmission of hepatitis C virus (HCV) is by percutaneous or mucosal blood exposure. Risk factors include blood transfusions before 1992, IV drug use, and occupational exposure (needlesticks). Spontaneous resolution occurs in 15% to 45% of patients, with the highest rates of resolution in children and young women. Chronic infection occurs in the remainder of patients. Cirrhosis occurs in 20% within 20 to 30 years. The risk of carcinoma is 1% to 4% per year after cirrhosis.

### Symptoms/Exam

- **Acute HCV:** Presents with flulike illness, malaise, weakness, low-grade fever, myalgias, and RUQ pain followed by jaundice. Only 30% of patients are symptomatic in acute disease.
- **Chronic HCV:** Often asymptomatic, or may present with cryoglobulinemia associated with a vasculitic skin rash (**leukocytoclastic vasculitis**), **arthralgias**, sicca syndrome, and **glomerulonephritis**. In the setting of cirrhosis, presents with fatigue, muscle wasting, dependent edema, and easy bruising.

### Diagnosis

- **Screening:** One-time screening for all adults born 1945 to 1965, as well as any patients at ↑ risk (dialysis, HCV-infected mother, incarceration, tattoo, high-risk sexual behavior), is recommended. Check **HCV antibody** (⊕ 4-6 weeks after infection). If positive, test for **HCV RNA**.
- **Prognostic:** Liver biopsy or transient elastography to measure liver stiffness.

### Management

- Antiviral therapy for HCV is rapidly evolving and specific regimens depend on **genotype** and **patient factors**. The goal of treatment is to eradicate HCV RNA to prevent complications of chronic HCV infection.
- **Cryoglobulinemia:** Treatment of acute flares includes plasmapheresis ± steroids. Long-term effectiveness is seen with interferon plus ribavirin, and data on rituximab appear promising.

### Prevention

**Acute infection/needlestick prophylaxis:** After known exposure, serial testing for HCV antibody, HCV PCR, AST, and ALT is recommended both immediately and at 4, 8, and 12 weeks.

## AUTOIMMUNE HEPATITIS

Characterized by hypergammaglobulinemia, periportal hepatitis, and autoimmune markers. Autoimmune hepatitis is typically chronic, but 25% of cases are characterized by acute onset and rare fulminant hepatic failure. Prevalence depends on gender and ethnicity; women are affected three times more often than men. The main prognostic factors are severity of inflammation/fibrosis on liver biopsy and HLA type. Associated with other autoimmune diseases.

### Symptoms/Exam

Fatigue (85%), jaundice, RUQ pain. **Pruritus** suggests an alternate diagnosis such as **primary biliary cholangitis** or **primary sclerosing cholangitis**.

## Diagnosis

- International Autoimmune Hepatitis Group criteria:** A definite or probable diagnosis of autoimmune hepatitis requires the following three criteria:
  - Magnitude of hypergammaglobulinemia.
  - Autoantibody expression (**ANA, anti-smooth muscle, p-ANCA, or anti-LKM I**).
  - Certainty of exclusion of other diagnoses (Table 7.16).
- Extrahepatic associations** (present in 10%-50% of cases): Frequent—autoimmune thyroid disease, ulcerative colitis, synovitis. **Uncommon**—RA, DM, CREST syndrome, vitiligo, alopecia.

## Management

- Treatment is generally delayed until patients have active symptoms and/or biochemical evidence of inflammation (AST/ALT >3 times normal). The best treatment responses are obtained in the setting of active hepatic inflammation ( $\uparrow$  ALT).
- Treat with **corticosteroids, including budesonide and/or azathioprine**.
- Liver transplantation:** Should be considered in the presence of decompensated liver disease, severe inflammation, and necrosis on liver biopsy with treatment failure or no biochemical improvement during the first 2 weeks of therapy.

## DRUG-INDUCED LIVER INJURY

Ranges from subclinical disease with abnormal LFTs to fulminant hepatic failure. Accounts for 40% of acute hepatitis cases in US adults >50 years of age, 25% of cases of fulminant hepatic failure, and 5% of jaundice cases in hospitalized patients. Drug-induced hepatitis can be characterized as intrinsic (direct toxic effect) or idiosyncratic (immunologically mediated injury) and as necroinflammatory (hepatocellular), cholestatic, or mixed. Risk factors include advanced age, female gender, use of an  $\uparrow$  number of prescription drugs, underlying liver disease, renal insufficiency, and poor nutrition.

## Symptoms/Exam

May present with constitutional symptoms, jaundice, RUQ pain, and pruritus. Often asymptomatic.

TABLE 7.16. Differential Diagnosis of Immunologic Disease of the Liver

DISEASE	GENDER	LFTS	OTHER LABS	DIAGNOSIS	ASSOCIATION	TREATMENT
Primary sclerosing cholangitis	M > F	AP >1.5 times ULN	p-ANCA	ERCP or MRCP reveals "beads on a string"	Ulcerative colitis in 70%	Liver transplant
Primary biliary cholangitis	F >> M	AP >3-4 times ULN; total bilirubin $\uparrow$	AMA (95%), IgM	Biopsy reveals paucity of bile ducts and granulomatous cholangitis	Autoimmune (thyroiditis, CREST, sicca in 50%)	Ursodeoxycholic acid $\rightarrow$ liver transplant
Autoimmune hepatitis	F > M	$\uparrow$ AST/ALT	ANA, ASMA, anti-LKM antibody, $\uparrow$ IgG	Biopsy reveals interface hepatitis and plasma cell infiltrate		Prednisone, azathioprine

anti-LKM antibody = anti-liver/kidney microsome antibody; AP = alkaline phosphatase; ASMA = anti-smooth muscle antibody; ULN = upper limit of normal.

### KEY FACT

Autoimmune hepatitis is associated with a high rate of anti-HCV false-positives, so the diagnosis must be confirmed by checking a PCR assay for HCV viremia.

### KEY FACT

Advanced liver disease is a poor prognostic sign for treatment response but not a contraindication to the treatment of autoimmune hepatitis.

### KEY FACT

The decision to treat autoimmune hepatitis depends on the severity of hepatic inflammation, not hepatic dysfunction.

### KEY FACT

$\uparrow$  serum LDH suggests drug-induced hepatitis over viral hepatitis.

### KEY FACT

When ALT is >1000 U/L, consider drug/toxic, ischemic, congestive, autoimmune hepatitis, and viral hepatitis.

### Diagnosis

- **History:** Take a detailed drug history that includes dosage, duration, and use of concurrent OTC, alternative (herbs/supplements), and recreational drugs. Commonly implicated drugs:
  - **Intrinsic** (dose dependent, direct toxic effect hours to days after ingestion): Acetaminophen, carbon tetrachloride, alcohol, *Amanita phalloides*, aflatoxins.
  - **Idiosyncratic** (dose independent, immune-mediated toxicity weeks to months after starting drug): NSAIDs, INH, sulfonamides, valproic acid, phenytoin, ketoconazole.
- **Exclude other causes:** Obtain a liver ultrasound with duplex (to evaluate for acute hepatic vasculature thrombosis) and viral hepatitis serology.
- **Labs:** ↑ serum LDH; transaminases typically range from 2 to 4 times normal (sub-clinical) to 10 to 100 times normal.
- **Drug withdrawal:** Most drug-induced hepatitis will improve with discontinuation of the toxic agent.
- **Liver biopsy:** Most useful for **excluding** other etiologies. Eosinophilic inflammatory infiltrate suggests drug-induced hepatitis; histologic patterns can implicate drug classes.

### Management

- Discontinue the implicated drug.
- **Liver transplantation:** Drug-induced fulminant hepatic failure has a low likelihood of spontaneous recovery.

### Acetaminophen Toxicity

The most common cause of drug-induced liver injury and drug-induced fulminant hepatic failure. Risk of acetaminophen toxicity increases in patients with alcohol use, malnutrition, chronic use, or dieting.

- **Symptoms/Exam:** Nausea/vomiting are common early symptoms. Patients can quickly progress to acute liver failure and death.
- **Diagnosis:** Maintain a high clinical suspicion with marked elevation of transaminases. Check an **acetaminophen level** and predict toxicity using the Rumack-Matthew nomogram (assesses acetaminophen concentration, time after ingestion, and risk for toxicity).
- **Management:** Start **N-acetylcysteine** PO or IV empirically. If patient is presenting within 4 hours of ingestion, give **activated charcoal**. Otherwise, provide supportive treatment. **Liver transplantation** should be considered in fulminant liver failure.

#### KEY FACT

Acetaminophen in modest doses (eg, <2 g/day) is much safer than NSAIDs for patients with cirrhosis.

#### KEY FACT

Alcoholic hepatitis is not a prerequisite to alcoholic cirrhosis.

#### KEY FACT

Discriminant function (DF) measures the severity of alcoholic hepatitis. A DF >32 predicts one-month mortality as high as 50% and warrants consideration of treatment with corticosteroids in patients without contraindications (active GI bleeding, active infection, serum creatinine >2.3 mg/dL).

$$DF = [4.6 \times (\text{patient's PT} - \text{control PT})] + \text{serum bilirubin}$$

### Alcoholic Liver Disease

Alcohol accounts for 100,000 deaths per year in the United States, and 20% of these deaths are related to alcoholic liver disease, which carries a risk of progressive liver disease.

#### Symptoms/Exam

- **Alcoholic steatosis:** Asymptomatic or mild RUQ pain.
- **Acute alcoholic hepatitis:** Fever, anorexia, RUQ pain, jaundice, nausea, vomiting.
- **Alcoholic cirrhosis:** Patients may be asymptomatic or may present with anorexia, fatigue, and ↓ libido. Associated with an ↑ risk of variceal hemorrhage.

#### Diagnosis

- Diagnosis is **clinical** and can be confirmed by **liver biopsy**.
- **Alcoholic steatosis:** Modest elevation of AST > ALT in a 2:1 ratio; liver biopsy shows small (microvesicular) and large (macrovesicular) fat droplets in the cytoplasm of hepatocytes.

- **Alcoholic hepatitis:** Marked leukocytosis, modest elevation of AST > ALT in a 2:1 ratio (typically <300), and markedly ↑ serum bilirubin. Liver biopsy shows steatosis, hepatocellular necrosis, **Mallory bodies** (eosinophilic hyaline deposits), ballooned hepatocytes, and **lobular PMN inflammatory infiltrate**.
- **Alcoholic cirrhosis:** Liver biopsy shows micro- or macronodular cirrhosis and peri-venular fibrosis that is not usually seen in other types of cirrhosis.

### Management

- The mainstays of treatment are alcohol abstinence and improved nutrition. Social support (eg, AA) and medical therapy (eg, disulfiram, naltrexone) can assist with abstinence.
- **Alcoholic steatosis:** Can resolve with abstinence and improved nutrition.
- **Alcoholic hepatitis:** Treatment is based on **severity**, which can be judged using the **discriminant function (DF)**, which is a function of PT/INR and total bilirubin. **Corticosteroids improve survival** when DF is >32 and there are no contraindications (active GI bleeding, active infection, serum creatinine >2.3 mg/dL).
- **Alcoholic cirrhosis:** Hepatic function can significantly improve with abstinence and improved nutrition.
- **Liver transplantation** is often precluded by active or recent alcohol abuse or use. Recidivism rates are high. Most transplant centers require at least 6 months of documented abstinence prior to listing for liver transplant.

### NONALCOHOLIC FATTY LIVER DISEASE

The spectrum of nonalcoholic fatty liver disease (NAFLD) ranges from benign steatosis (fatty liver) to nonalcoholic steatohepatitis (NASH) (hepatic inflammation). Patients who have NASH can progress to cirrhosis and worsening fibrosis. Risk factors for NASH include female gender, age >45 years, BMI >30, AST/ALT >1, and type 2 DM.

#### Symptoms/Exam

Presents with fatigue, malaise, and, to a lesser extent, RUQ fullness or pain. Asymptomatic in >50% of patients. On exam, may have evidence of hepatomegaly or stigmata of chronic liver disease.

#### Differential

- Alcoholic liver disease.
- **Nutrition:** TPN, kwashiorkor, rapid weight loss.
- **Drugs:** Estrogens, corticosteroids, chloroquine.
- **Metabolic:** Wilson disease, abetalipoproteinemia.
- **Viral:** Hepatitis B and C.
- **Iatrogenic:** Weight reduction surgery with jejunoileal bypass, gastroplasty, or small bowel resection.

#### Diagnosis

Exclude other causes of liver disease, as above. Expect to see transaminitis, generally with **ALT > AST** though normal levels don't exclude steatosis. Ultrasound or CT may show patterns consistent with fatty infiltration, but diagnosis of NASH can only be made by **liver biopsy**.

#### Management

- Gradual weight loss with diet and exercise, aggressive management of diabetes, hypertension, and hyperlipidemia. **Statins** are safe and may even directly improve NAFLD.

#### KEY FACT

Nonalcoholic fatty liver disease can occur in the absence of obesity.

#### KEY FACT

Nonalcoholic fatty liver disease is the most common cause of chronic liver disease.

#### KEY FACT

Normal LFTs do not exclude nonalcoholic fatty liver disease.



#### QUESTION

A 37-year-old man is being evaluated for ↑ AST/ALT over 1 year. He has hypertension and DM but denies using acetaminophen, supplements, or other medications not prescribed for his known medical conditions. On exam, BMI is 32; lab results show ALT/AST at 200% of ULN. Workup for hepatitis is ⊖, including serology for hepatitis A, B, and C as well as ANA, AMA, ceruloplasmin, ferritin, and transferrin. An ultrasound shows a diffusely hyperechoic liver with patent vessels. What interventions are likely to improve his symptoms?

- No FDA-approved therapy is available.
- **Vitamin E** and **pioglitazone** have shown benefit in histologically proven NASH with reduction in hepatic steatosis and inflammation, though safety profile is unclear.

## Metabolic Liver Disease

### HEREDITARY HEMOCHROMATOSIS

#### KEY FACT

A transferrin saturation of >45% with an ↑ ferritin suggests but does not confirm the diagnosis of hemochromatosis. Perform HFE gene testing.

#### KEY FACT

Suspect hemochromatosis with type 2 DM, degenerative arthritis, or unexplained hypogonadism, heart failure, or liver disease.

An **autosomal recessive** disease associated with a major mutation in chromosome 6, the **HFE** gene resulting in ↑ absorption of iron and subsequent iron deposition in multiple organs (liver, pancreas, heart, joints, thyroid gland, hypothalamus). Patients have a normal life expectancy if there is no cirrhosis and the patient is adherent to treatment; survival is lower if the patient has cirrhosis at the time of diagnosis. Cirrhosis with hereditary hemochromatosis carries a high risk of HCC. The classic triad is cirrhosis, DM, and skin hyperpigmentation.

- **Symptoms/Exam:** Can be asymptomatic. Arthritis (pseudogout), skin color change, RUQ pain, symptoms of chronic liver disease.
- **Diagnosis:** Suspect hereditary hemochromatosis with an unexplained ↑ serum ferritin or iron saturation even with normal LFTs. If **transferrin saturation is >45%** and ferritin is ↑, hereditary hemochromatosis is suggested; check **HFE genotype**. This is helpful if ⊕ but can be nondiagnostic. **Liver biopsy** is the best way to make a definitive diagnosis (hepatic Prussian blue stain with **iron index of >1.9**). Order liver biopsy if you have a ⊖ HFE genotype but elevated transferrin saturation and ferritin >1000 ng/mL, or to determine severity of disease in a patient with known hemochromatosis and abnormal LFTs.
- **Management:** Treatment is indicated if patients are symptomatic or have evidence of end-organ damage (ie, liver, endocrine organs, heart). **Phlebotomy** is the treatment of choice. Perform weekly or biweekly until serum ferritin is <50 ng/mL; then three to four times per year indefinitely. Alternatively, if a patient can't tolerate phlebotomy, can use **deferoxamine (iron chelator) SQ**. Additionally, avoid high-dose vitamin C, screen first-degree family members, and screen for HCC in setting of cirrhosis. Liver transplantation is appropriate for decompensated liver disease.

### $\alpha_1$ -ANTITRYPSIN DEFICIENCY

#### A

#### ANSWER

Weight loss and good control of BP and diabetes. This man likely has nonalcoholic fatty liver disease given his metabolic profile and overall ⊖ workup. There is no established treatment for this condition aside from improving predisposing conditions such as weight, hypertension, triglyceridemia, and diabetes.

$\alpha_1$ -antitrypsin protects tissues from protease-related degradation. The deficiency is encoded on chromosome 14 and has an **autosomal codominant** transmission.  $\alpha_1$ -antitrypsin deficiency is severe when homozygous (eg, PiZZ) and is intermediate when heterozygous (eg, PiMZ). Liver disease can be seen in the neonatal period but can also manifest later in adulthood. There is a high incidence of HCC in those with cirrhosis.

- **Symptoms/Exam:** Neonatal cholestasis, occult cirrhosis, shortness of breath/dyspnea on exertion, panniculitis. Exam reveals signs of cirrhosis (spider angioma, palmar erythema, gynecomastia) and emphysema (clubbing, barrel chest).
- **Diagnosis:** Test for serum  $\alpha_1$ -antitrypsin concentration. If low, confirm with serum  $\alpha_1$ -antitrypsin phenotyping (isoelectric focusing), which is the gold standard. Genotyping and gene sequencing can also be done. **Liver biopsy** is diagnostic for  $\alpha_1$ -antitrypsin liver disease.
- **Management:** Avoid cigarette smoking and alcohol; weight loss if the patient is obese. **IV augmentation** therapy (infusion of pooled  $\alpha_1$  proteinase inhibitor) is used in patients with high-risk phenotype, very low AAT level, and evidence of airflow obstruction, however this does not treat liver disease (because liver disease is related

to hepatic accumulation of abnormal protein, not loss of enzyme activity). **Liver and lung transplantation** is reserved for patients with advanced disease. **Transplant corrects the deficiency.**

### WILSON DISEASE

An uncommon **autosomal recessive** disease. ↓ biliary copper excretion results in toxic copper deposition in tissues.

#### Symptoms/Exam

- Classically presents with abnormal behavior, personality change, psychosis, choreiform movements, tremor, dyskinesia, arthropathy (pseudogout), and jaundice.
- **Organ involvement** (in descending order of frequency): Hepatic, neurologic, psychiatric, hematologic, renal (Fanconi syndrome), other (ophthalmologic, cardiac, skeletal, endocrinologic, dermatologic).
- Exam may reveal **Kayser-Fleischer rings** (Figure 7.20), icterus, slowed mentation, hypophonia, and tremor.

#### Diagnosis

Start by sending **serum ceruloplasmin concentration**, which should be low, but can be nonspecific. Additionally, expect **elevated 24-hour urine copper** and **Kayser-Fleischer rings** on slit-lamp exam. Ultimately, **liver biopsy** is the gold standard, which should show ↑ hepatic copper concentration.

#### Management

- Prognosis with treatment is excellent, and without treatment, it is fatal.
- For both symptomatic and asymptomatic patients identified through screening, treat with **D-penicillamine or trientine** (copper chelators). **Zinc** is an alternative. Copper levels should be monitored regularly through 24-hour urine collection.
- For patients presenting with acute liver failure from Wilson disease or medically refractory disease, **liver transplantation** is indicated.

### Liver Disease in Pregnancy

An approach to thinking about liver disease in pregnancy is to ask the following:

- Is it **coincidental to pregnancy**? Think viral hepatitis, gallstone disease, drug-induced, Budd-Chiari.
- Is it **underlying liver disease**? Consider any of the liver diseases mentioned in the previous sections.
- Is it **unique to pregnancy**? Think hyperemesis gravidarum (first trimester), intrahepatic cholestasis of pregnancy (second/third trimester), preeclampsia (third trimester), HELLP syndrome (third trimester), and acute fatty liver of pregnancy (third trimester).

### HYPEREMESIS GRAVIDARUM

- Characterized by intractable vomiting during the first trimester, sometimes requiring IV hydration.
- **Diagnosis:** Clinical and half of patients have elevated LFTs; rule out viral hepatitis.
- **Management:** Treatment is supportive with antiemetics, rehydration, and nutritional support.

#### KEY FACT

Suspect Wilson disease in patients 3 to 40 years of age with unexplained LFTs or liver disease associated with neurologic or psychiatric changes, Kayser-Fleischer rings, hemolytic anemia, and a  $\oplus$  family history.

#### KEY FACT

The classic biochemical pattern of Wilson disease consists of ↓ alkaline phosphatase, marked hyperbilirubinemia, and modest aminotransaminase elevation (AST > ALT).



**FIGURE 7.20. Kayser-Fleischer ring.**  
(Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

An elevated alkaline phosphatase can be normal in pregnancy.

#### QUESTION

An 18-year-old woman with recent-onset depression and "bizarre" behavior (as described by her family) presents to the ED in an altered state. She has normal vital signs, but lab results reveal ↓ hematocrit, ↑ total bilirubin level (with ↑ unconjugated fraction), and AST/ALT ratio five times ULN. Toxicology screen is normal; blood smear shows active hemolysis. What tests would help make the diagnosis?

### INTRAHEPATIC CHOLESTASIS OF PREGNANCY

- Characterized by **intense pruritus**, lack of abdominal pain, and elevated bilirubin and alkaline phosphatase in the second half of pregnancy, without hemolysis or thrombocytopenia.
- **Diagnosis:** Clinical, and it is important to ensure absence of hemolysis, thrombocytopenia, or DIC that would suggest an alternative diagnosis. Serum bile acid levels are typically elevated.
- **Management:** Treatment is supportive (**ursodeoxycholic acid** for pruritus) and close monitoring and early delivery of the fetus; maternal outcomes are generally good. Symptoms and liver dysfunction resolve immediately after delivery.

### PREECLAMPSIA

Preeclampsia includes the triad of hypertension, edema, and proteinuria in the third trimester of pregnancy; liver involvement suggests severe preeclampsia with significant perinatal morbidity and mortality. This is the **most common** cause of RUQ tenderness and liver dysfunction in pregnancy. Treatment is immediate delivery to avoid eclampsia (seizures), hepatic rupture, and necrosis. Please see Women's Health chapter under the heading Hypertension in Pregnancy for additional details.

### HELLP SYNDROME

HELLP is characterized by hemolysis, elevated liver enzymes, and low platelets. DIC may also be present. This is a laboratory diagnosis and mothers may have progression of disease and sudden deterioration. Multiparous and older patients are at higher risk for HELLP. Treatment includes **hospitalization**, **seizure prophylaxis**, close fetal monitoring, and **immediate delivery**. For most patients, HELLP resolves quickly after delivery. Please see the Women's Health chapter under the heading Hypertension in Pregnancy for additional details.

### ACUTE FATTY LIVER OF PREGNANCY

- Often sudden in onset. Acute fatty liver of pregnancy can lead to rapid deterioration and is more commonly seen in **nulliparous** women. Characterized by microvesicular fatty infiltration.
- **Symptoms/Exam:** Symptoms include nausea, vomiting, anorexia, RUQ pain, and headaches; encephalopathy and liver failure can ensue. Labs reveal elevated transaminases and ↑ INR.
- **Diagnosis:** Based on clinical and laboratory features; definitive diagnosis is by **liver biopsy**.
- **Management:** Treatment relies on early diagnosis and **immediate delivery or termination of pregnancy**, along with aggressive supportive care to manage complications of liver failure. Symptoms and labs typically improve in the days to weeks following delivery.



### ANSWER

Ceruloplasmin, urinary copper excretion, a slit-lamp exam, and liver biopsy. This patient has many features of Wilson disease, including hemolytic anemia, new psychiatric changes, and ↑ LFTs. Although there is no highly sensitive and specific test for Wilson disease, the aforementioned tests can be useful in a setting where suspicion is high. If there are no neurologic symptoms, the slit-lamp exam may not be as useful.

## Acute Liver Injury and Failure

Acute liver injury and failure fall on a spectrum and both are characterized by new liver dysfunction (within 26 weeks) and coagulopathy (INR >1.5). **Failure** is defined by the presence of hepatic encephalopathy. Sometimes, the term **fulminant liver failure** is used to describe patients with acute liver failure within 8 weeks. As many as 17% of patients with acute liver failure will have no identifiable cause.

## Differential

- Drugs and toxins: Acetaminophen, *Amanita phalloides*, halothane, herbal medications, others (see the Drug-Induced Liver Injury section) are most common (70%-80%).
- Viral infections: Hepatitis A, B, D, and E, HSV, CMV, EBV.
- Other: Wilson disease, shock liver (ischemia), Budd-Chiari syndrome, malignancy from metastasis, lymphoma, acute fatty liver of pregnancy, *Leptospira* infection, cryptogenic.

### KEY FACT

Ammonia levels can be helpful in prognosis for acute liver failure. This is not the case in end-stage liver disease, where ammonium levels are often elevated and are not correlated to symptoms or prognosis.

## Management

- For any patient with acute liver injury, monitor for hepatic encephalopathy.
- For any patient who has progressed to acute liver failure, treatment is **supportive** and directed at treating the underlying cause. Mortality from acute liver failure is high and **liver transplantation** should be considered. If a patient is a candidate, they are listed as **status 1A** to get emergency transplant.
- In addition to hemodynamic monitoring:
  - Monitor neurologic status closely. The most common cause of death from acute liver failure is **cerebral edema** leading to intracranial hypertension and herniation.
  - Perform frequent **glucose checks** given risk of hypoglycemia (from reduced gluconeogenesis by the liver and depletion of hepatic glycogen stores) and start dextrose drip if needed.
  - Perform serial **CBCs, PT/PTT, and fibrinogen** and monitor for bleeding, transfuse as needed.
  - Start **PPI** for prophylaxis against UGIB.
  - Monitor **electrolytes** given risk of multiple electrolyte derangements and replete as needed; start enteral nutrition as early as possible.
  - Monitor **renal function** and monitor closely for **infection**.

### KEY FACT

The most common cause of death from acute liver failure is cerebral edema leading to intracranial hypertension and herniation.

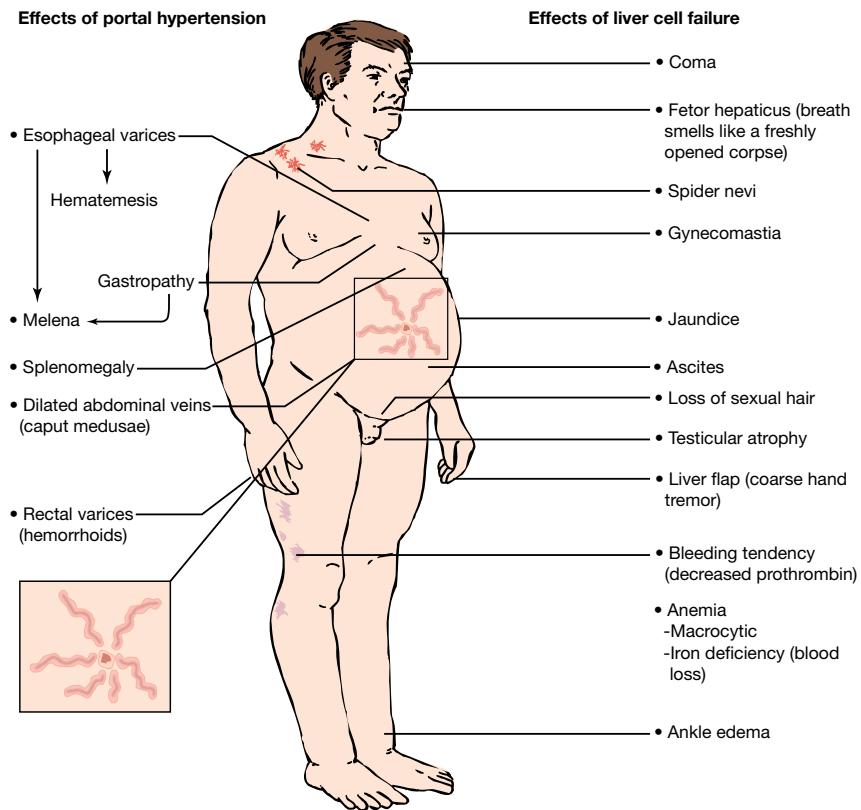
## Advanced Liver Disease

### CIRRHOSIS

The final common pathway of many liver diseases that cause hepatocellular injury leading to fibrosis and nodular regeneration. Reversal may occur with treatment of some chronic liver diseases (eg, HBV, HCV).

#### Symptoms/Exam

- Fatigue, anorexia, muscle wasting, loss of libido, impotence, dysmenorrhea.
- Decompensation associated with GI bleeding, encephalopathy (sleep-wake reversal, ↓ concentration), ascites.
- **Platypnea** (dyspnea induced by sitting upright and relieved by recumbency) and **orthodeoxia** (low Pao<sub>2</sub> when sitting upright that is relieved by recumbency). Both seen in hepatopulmonary syndrome.
- Exam reveals the **stigmata of chronic liver disease** (Figure 7.21):
  - Palmar erythema, spider telangiectasia.
  - **Dupuytren contractures**, gynecomastia, testicular atrophy, bilateral parotid enlargement, **Terry nails** (white, opaque nails).
  - **Portal hypertension**: Caput medusae, splenomegaly, ascites.
  - **Hepatic encephalopathy**: Fetor hepaticus, asterixis, confusion, sleep-wake cycle disturbance.



**FIGURE 7.21. Clinical effects of cirrhosis.** (Modified with permission from Chandrasoma P, Taylor CE. *Concise Pathology*, 3rd ed. Originally published by Appleton & Lange. Copyright © 1998 by The McGraw-Hill Companies, Inc.)

### KEY FACT

The Model for End-Stage Liver Disease (MELD) score is more accurate than the Child-Turcotte-Pugh score at predicting mortality with cirrhosis. MELD is based on three serum laboratory tests: INR, total bilirubin, and creatinine.

### KEY FACT

Whenever cirrhosis is diagnosed, search for an underlying etiology and treat to slow progression.

### Diagnosis

Often suspected based on clinical (stigmata of chronic liver disease) and laboratory findings (evidence of synthetic dysfunction), as well as characteristic imaging features (eg, nodular liver on abdominal ultrasound or CT). However, **liver biopsy** is necessary for definitive diagnosis, and can also help determine underlying etiology. Severity of cirrhosis is graded based on Child-Turcotte-Pugh Scoring (Table 7.17) and Model for End-Stage Liver Disease (MELD) score. All patients with cirrhosis should be screened for complications of ESLD.

- **Labs:** Thrombocytopenia (splenic sequestration); ↑ INR and low albumin (↓ hepatic synthetic function); ↑ alkaline phosphatase, serum bilirubin, and GGT (cholestasis); normal or ↑ transaminases.

**TABLE 7.17. Child-Turcotte-Pugh Score for Cirrhosis Severity**

	1 POINT	2 POINTS	3 POINTS
Ascites	Absent	Nontense	Tense
Encephalopathy	Absent	Grades 1-2	Grades 3-4
Bilirubin (mg/dL)	<2.0	2-3	>3.0
Albumin (mg/dL)	>3.5	2.8-3.5	<2.8
PT (seconds over normal)	1-3	4-6	>6

- Imaging:** Ultrasound with duplex (ascites, biliary dilation, hepatic masses, vascular patency), CT (more specific than ultrasound for cirrhosis and masses, portal hypertension, Figure 7.22), MRI (excellent specificity for hepatic masses).

### Management

- Treatment is based on the underlying cause, prevention of further liver injury, monitoring and treating for complications of cirrhosis (see below sections).
- Avoid alcohol, iron supplements (except in iron deficiency), NSAIDs, and benzodiazepines; minimize narcotics; limit acetaminophen to <2 g/day.
- Fluid restriction is not necessary (unless serum Na is <125 mEq/L), and protein restriction should not be recommended.
- Administer pneumococcal and influenza vaccines.
- HAV and HBV vaccination.
- Screen for HCC with ultrasound and serum AFP every 6 months.
- Screen, prevent, and treat sequelae of liver disease (see below).
- Liver transplantation:** Refer to a transplant center when there is clinical evidence of decompensated liver disease (portal hypertensive bleeding, hepatic encephalopathy, ascites), evidence of HCC, a Child-Turcotte-Pugh score of >6, or a MELD score of >15.

### Complications

Varices, ascites and spontaneous bacterial peritonitis, hepatorenal syndrome (see below).

#### VARICES

- Esophageal variceal hemorrhage accounts for one-third of all deaths in cirrhotic patients. **Mortality with each episode is 30% to 50%.** Alcoholic cirrhotic patients are at highest risk. Patients with cirrhosis should be **screened** for varices with serial EGDs and provided prophylaxis:



**FIGURE 7.22. Cirrhosis.** Transaxial image from contrast-enhanced CT shows a nodular liver contour (arrowheads) and the stigmata of portal hypertension, including splenomegaly (S) and perisplenic varices (arrow). (Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

Vaccination for HAV and HBV is indicated for all nonimmune patients with chronic liver disease, including patients with cirrhosis.

#### KEY FACT

Protein restriction is **not** indicated for hepatic encephalopathy.

#### KEY FACT

Refer to a liver transplant center when minimal listing criteria are present.

**KEY FACT**

Do not overtransfuse in the setting of variceal bleed. A hematocrit >30% is associated with ↑ portal pressures and risk of rebleeding.

**KEY FACT**

Endoscopic variceal band ligation is the endoscopic treatment of choice for 2° prophylaxis of variceal bleeding.

**KEY FACT**

While TIPS may ↓ rebleeding and improve ascites, there is ↑ risk of hepatic encephalopathy with TIPS procedures.

**KEY FACT**

A SAAG  $\geq 1.1$  g/dL is 96% accurate in detecting portal hypertension as the cause of ascites.

- 1° prophylaxis once varices are identified: Treat with nonselective β-blockers (nadolol, propranolol) with a goal HR of 55 bpm if blood pressures can tolerate.
- 2° prophylaxis after an episode of variceal bleeding: Includes endoscopic ablation (banding or sclerotherapy), nonselective β-blockers ± long-acting nitrates, and consideration of portacaval shunt (TIPS or surgical) if recurrent. Gastric and rectal varices are not treatable with endoscopic band ligation.

**Management:**

- Treatment of acute variceal bleeding requires **early endoscopy** with **banding**. Until then, treat medically with resuscitation (goal hematocrit of 28%, platelets >50, INR <1.6), **PPI**, **octreotide drip**, and **empiric antibiotics** (ceftriaxone).
- **Portal hypertensive gastropathy** is a less common source of bleeding. Treat with portacaval shunt (TIPS or surgical) or liver transplantation.

**ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS**

In the United States, >80% of ascites cases are due to chronic liver disease (cirrhosis or alcoholic hepatitis). In 10% to 30% of cirrhotic patients with ascites, spontaneous bacterial peritonitis (SBP) develops every year. Infection-related mortality is 10%, but the overall in-hospital mortality rate is 30%.

**Symptoms/Exam**

Characterized by shifting dullness, fluid wave, and bulging flanks (low sensitivity, moderate specificity). Imaging (ultrasound, CT) is superior to examination. **SBP is often asymptomatic**, but patients may have fever, abdominal pain, and sepsis. Risk factors for SBP include: ascites protein < 1 g/dL, history of variceal bleed, prior episode of SBP.

**Differential**

The serum-ascites albumin gradient (**SAAG**) is helpful (Table 7.18). High SAAG indicates portal hypertensive causes of ascites; low SAAG indicates the opposite.

**Diagnosis**

- **Diagnostic paracentesis** is indicated in the presence of new-onset ascites, ascites present at hospital admission, and ascites with symptoms or signs of infection. Routine studies include cell count and differential, culture, albumin, and total protein.
- **SBP is diagnosed with ascites PMN >250 cells/mL, WBC >500 cells/mL, or a single organism on culture.**
- **2° peritonitis** is suggested by the presence of multiple organisms on ascites culture or ascites WBC >10,000 cells/mL.

**TABLE 7.18. Significance of SAAG Values**

HIGH SAAG ( $\geq 1.1$ )	LOW SAAG ( $< 1.1$ )
Cirrhosis, HCC	Spontaneous or secondary bacterial peritonitis
Alcoholic hepatitis	Peritoneal carcinomatosis
Heart failure	Peritoneal TB
Vascular (Budd-Chiari, portal vein thrombosis)	Nephrotic syndrome
Myxedema	Bowel infarction
Fulminant hepatitis	Serositis

## Management

- **Ascites:** Treatment includes diuresis with furosemide and spironolactone (give doses in a 4:10 ratio—eg, 40 mg to 100 mg, 80 mg to 200 mg) and dietary sodium restriction (<2 g/day). Initiate fluid restriction **only if** serum Na <125 mEq/L. For refractory ascites, consider **large-volume paracentesis and portacaval shunt (TIPS)**.
- **SBP prophylaxis:** Indicated for cirrhotic patients hospitalized with GI bleed (3 days), ascites with albumin <1 g/dL; ascites total protein <1.5 g/dL along with creatinine >1.2, BUN >25 mg/dL, or Na <130 mEq/L; or prior SBP (if the patient has ascites). Prophylaxis is with **fluoroquinolone or TMP-SMX**.
- **SBP treatment:** Do not wait for culture results to begin treatment. Give cefotaxime or ceftriaxone IV  $\times$  5 days and IV albumin on days 1 and 3.

## HEPATIC ENCEPHALOPATHY

- Neuropsychiatric changes in the setting of liver disease constitute hepatic encephalopathy until proven otherwise.
- **Diagnosis:** Look for precipitating factors, including infection, GI bleeding, dehydration, and noncompliance with hepatic encephalopathy treatment. Hepatic encephalopathy is graded from 0 to IV (Table 7.19).
- **Management:** Correct precipitating factors and anticipate treatment-related adverse effects. Administer **lactulose** with a goal of three to four bowel movements a day. For patients who are intolerant or refractory to lactulose, add **rifaximin (nonabsorbable antibiotic)**.

## HEPATORENAL SYNDROME

- For any patient with end-stage liver disease and new renal failure, hepatorenal syndrome should be considered and is a diagnosis of exclusion. Rule out precipitants of renal failure, particularly infection, blood loss, or dehydration. There are two types of hepatorenal syndrome:
  - **Type 1** is defined by doubling of serum creatinine  $>2.5$ , or 50% reduction in 24-hr CrCl in <2 weeks, and is usually after a precipitating event such as infection.
  - **Type 2** is less rapid decline in renal function, mainly from refractory ascites. For both, survival without treatment is on the order of weeks.
- **Diagnosis:** Exclude other cause of renal failure. Urine sodium is <10 mEq/L. Discontinue diuretics and then perform a plasma volume expansion trial. If serum creatinine  $\downarrow$ , suspect another diagnosis.
- **Management:** Identify and treat precipitants. Treatment includes **albumin, midodrine, and octreotide**. Renal failure from hepatorenal syndrome reverses with liver transplantation.

## LIVER TRANSPLANTATION

Liver transplantation is a standard operation with excellent survival rates (80%-90% at 1 year and 60%-80% at 7 years). The scarcity of available cadaveric donor livers is reflected in the high mortality rates (up to 20% per year) in those awaiting liver transplantation. Typical waiting times are **8 months to 3 years** but varies by blood type and region. Living-donor liver transplants constitute a promising alternative but comprise <5% of all liver transplants.

## KEY FACT

Of cirrhotic patients presenting with ascites, 90% will respond to sodium restriction of <2 g/day along with furosemide and spironolactone (at maximum doses of 160 mg and 400 mg, respectively).

## KEY FACT

For SBP treatment, the addition of IV albumin to IV antibiotics significantly  $\downarrow$  renal impairment and mortality. Albumin repletion is also known to improve mortality when performing therapeutic paracentesis.

## KEY FACT

Hepatic encephalopathy is a clinical diagnosis. In cirrhotic patients, diagnosis and treatment should **not** be based on blood ammonia levels.

**TABLE 7.19. Grades of Hepatic Encephalopathy**

GRADE	SYMPTOMS/SIGNS
Grade 0	No change in mental status
Grade I	Changes in behavior, sleep cycle reversal, hyperreflexia
Grade II	Disorientation, lethargy, asterixis
Grade III	Marked confusion, obtundation
Grade IV	Comatose, unresponsive, loss of reflexes

### The Process

- Determine the presence of viruses (HAV, HCV, mononucleosis/EBV, CMV, HSV).
- Refer to a transplant center (often the rate-limiting step).
- There are no minimal listing criteria, yet an indication for transplant should be identified.
- Assess indications and contraindications (see below).
- Perform a psychosocial and financial evaluation.
- Present to a selection committee, where a decision is made on whether to place patient on wait list.
- Priority is determined by the MELD score, a function of INR, total bilirubin, and serum creatinine; the higher the score, the higher the priority. For HCC, a MELD score is assigned independent of the calculated MELD score.

### KEY FACT

Liver graft allocation in the United States is a "sickest-first" system that is based on the MELD score (serum creatinine, total bilirubin, INR).

### Indications

- **Acute hepatic failure:** Acetaminophen overdose, idiosyncratic drug injury, toxins (A *phalloides* ingestion), HAV, HBV flare, acute Budd-Chiari syndrome, Wilson disease, acute fatty liver of pregnancy, others. As high as 17% have an indeterminate (nonidentifiable) cause.
- **Cirrhosis with decompensation:** HBV/HCV, alcohol, NAFLD/cryptogenic, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis.
- **HCC:** Not exceeding stage 2 ( $\leq 3$  lesions  $\leq 3$  cm in size or one lesion  $\leq 5$  cm with no extrahepatic metastasis). Liver biopsy is not required if two radiographic studies are supportive of the diagnosis.
- **Metabolic liver disease:** Hemochromatosis,  $\alpha_1$ -antitrypsin deficiency, Wilson disease, tyrosinemia, glycogen storage diseases.
- **Extrahepatic metabolic disease:** Urea cycle enzyme deficiency, hyperoxaluria.

### Contraindications

- Compensated cirrhosis without complications (too early).
- Extrahepatic malignancy (excluding skin cancers).
- HCC exceeding stage 2 (see above).
- Active substance abuse and alcohol abuse (generally defined as occurring within the last 6 months); some centers include active smoking.
- Active untreated sepsis.
- Advanced untreatable cardiopulmonary disease.
- Uncontrolled psychiatric disease.

### Complications

- **Operative:** Biliary complications (25%), wound infections, death.
- **Immunosuppression:** Opportunistic infections (CMV, HSV, fungal, PCP, others), drug-related effects (hypertension, renal insufficiency, DM, cytopenias, tremor, headaches, nausea/vomiting, seizures, others), malignancies (lymphoma, others).
- **Recurrent disease** (in descending order): HCV ( $>99\%$  if viremic at transplantation), **alcoholism**, HBV, primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis.
- **Acute rejection:** Occurs in up to 30% within the first 3 months after transplant; usually treatable, and rarely results in graft loss.

## CHAPTER 8

# Geriatric Medicine

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## Epidemiology and Aging

The population of older adults is rapidly growing. Average life expectancy is highest for white women (81 years) > black women (78 years) > white men (76.5 years) > black men (72 years).

The leading causes of death for older adults are:

- Heart disease.
- Cancer.
- Chronic lower respiratory diseases.
- Cerebrovascular disease (stroke).
- Alzheimer disease.
- Diabetes mellitus.

## Comprehensive Geriatric Assessment

Comprehensive geriatric assessment is a multifaceted approach to the care of older adults conducted in the outpatient and inpatient settings, and includes assessment of physical, cognitive, mental, and social health, with the goal of developing a care plan to promote health and independence.

Geriatric assessment is most effective with an interprofessional team (ie, physicians, nurse practitioners, social workers, dieticians, physical and occupational therapists).

### FUNCTIONAL ASSESSMENT

Ask patients and/or their caregivers whether they complete daily activities independently or with assistance. Clarify the degree of assistance needed.

Activities of daily living (ADLs): Feeding, dressing, bathing, toileting, transferring, and grooming. Bathing is the ADL with the highest prevalence of disability.

Instrumental ADLs: Transportation, medication and financial management, shopping, housework, and using a telephone.

### GAIT EVALUATION

Ask and assess for use of and need for assistive devices for mobility.

The “**timed up and go**” test is a helpful screening test to identify patients with impaired mobility (Figure 8.1). Patients rise from a chair, walk 10 feet, turn around, and walk back to the chair and sit down. Results are as follows:

- <12 seconds: Normal.
- ≥12 seconds: Abnormal. Requires further evaluation.

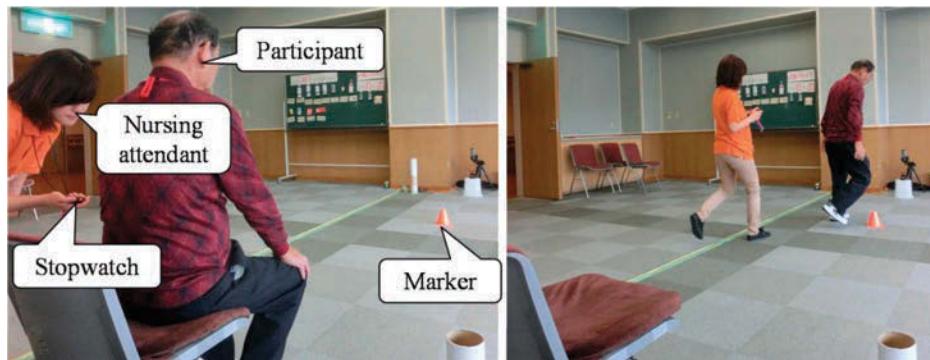
## Sensory Impairment

Consider sensory impairment in the differential diagnosis of older adults with falls, depression, **cognitive impairment**, or ↑ social isolation.



### KEY FACT

Gait speed is an important predictor of future disability and death. Gait speeds below 0.8 m/s, and particularly below 0.6 m/s are associated with poor health and function.



**FIGURE 8.1. Timed up and go test.** (Source: Yorozu A, et al. Improved leg tracking considering gait phase and spline-based interpolation during turning motion in walk tests. *Sensors (Basel)*. 2015;15(9):22451-22472.)

## VISUAL DISORDERS

- Common causes of vision loss in older adults include age-related macular degeneration, glaucoma, cataracts, and diabetic retinopathy (see the Ophthalmology section in the Ambulatory Medicine chapter).
- Arcus senilis (Figure 8.2), defined as loss of pigment in the periphery of the iris, is a common nonpathologic finding in older adults and does not interfere with vision.

## HEARING LOSS

By age 80 years, approximately 80% of adults will experience some degree of hearing loss. During an office examination, a whisper or finger rub test is sufficient to screen; audiology can confirm the type of hearing loss and qualify patients for hearing aids.

**Presbycusis**, a form of sensorineural hearing loss that is most often associated with aging, is due to loss of hair cells in the cochlea and neurons in CN VIII, leading to a **high-frequency, bilateral, symmetric** hearing loss.

For further detail, see the discussion of hearing loss in the Ambulatory Medicine chapter.

## Nutritional Recommendations

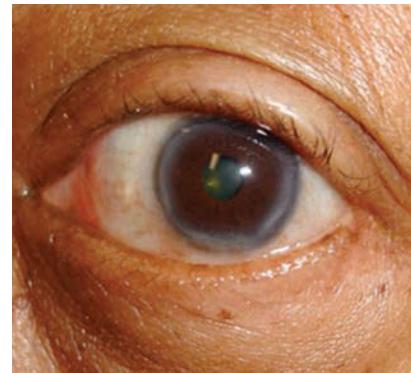
In general, nutritional guidelines for older adults are similar to those for the general population. Patients >75 years of age who are on restricted diets are at risk for protein-calorie malnutrition and inadequate intake of folate, vitamin B<sub>12</sub>, calcium, and vitamin D.

## VITAMIN D

- Older adults are at higher risk for vitamin D deficiency because of:
  - ↓ ability of the skin to produce vitamin D.
  - ↓ sun exposure.
  - ↓ synthesis of 1,25-vitamin D due to a higher prevalence of renal dysfunction.
  - ↓ vitamin D intake.

## KEY FACT

Age-related macular degeneration, the most common cause of permanent vision loss in older adults, is characterized by central vision loss and retinal drusen (yellow spots on the macula).



**FIGURE 8.2. Arcus senilis.** Note the gray ring in the corneal margin. (Reproduced with permission from USMLE-Rx.com.)



## QUESTION 1

An 87-year-old man is brought into clinic for behavioral changes. He has trouble following conversations, no longer wants to go out to social events, and is turning the volume of his TV and radio up to extremely loud levels because he "can't hear." What is the most likely diagnosis?



## QUESTION 2

What vaccines should a healthy 69-year-old man receive?

- Maintaining adequate vitamin D levels can be hard to achieve by diet and sun exposure alone. Vitamin D improves bone mineral density (BMD) and muscle function and may ↓ the risk of falls and fractures. Recommendations include:
  - Oral vitamin D<sub>3</sub> (cholecalciferol) can be taken as a daily supplement (800-2000 IU/day). Generally, the goal 25(OH)D level in older adults is ≥30 ng/mL.
  - Treat severe vitamin D deficiency (<20 ng/mL in older adults) with high-dose PO ergocalciferol 50,000 IU weekly for 8 to 12 weeks.

## CALCIUM

Calcium intake should be 1000 to 1200 mg per day. Most healthy individuals do not require supplementation unless they have intestinal malabsorption or calcium-deficient diets. Dietary and supplemental calcium lead to small increases in BMD.

## VITAMIN E

There is no evidence that vitamin E is effective in cancer prevention, in the treatment of coronary artery disease (CAD), or in prevention of dementia. **High-dose vitamin E (>400 IU/day)** may ↑ all-cause mortality.

## Immunizations

See the Ambulatory Medicine chapter for vaccination guidelines. In older adults, give special consideration to the following:

- **Influenza vaccine:** Efficacy declines with age, but vaccination is still important in this high-risk group. Should be done yearly, use high-dose flu vaccine in adults ≥65 years.
- **Pneumococcal vaccine:** ↓ the risk of pneumococcal **bacteremia** but has no significant effect on outpatient pneumonia or hospitalizations for pneumonia. Use if the patient is unvaccinated or if the patient's previous vaccination history is unknown. Patients ≥65 years ideally should receive PCV13 first, followed by PPSV23 one year later.
- **Tetanus vaccine:** Clinical tetanus is rare in the United States but commonly occurs in unvaccinated or underimmunized older adults or in those who have skin ulcers. Patients ≥65 years should receive a Td booster every 10 years. Tdap should be substituted for Td once.



## ANSWER 1

Presbycusis.



## ANSWER 2

Influenza (yearly), Td booster (every 10 years, with Tdap given once), varicella series if not immune by history or labs, zoster/shingles (once). Give an initial 13-valent pneumococcal conjugate vaccine (PCV13), followed 1 year later by a dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23).

## Dysphagia

Swallowing can be divided into three phases: oral (voluntary), pharyngeal, and esophageal (involuntary). Dysphagia can occur due to disease at any phase. See the Gastroenterology and Hepatology chapter for further discussion of esophageal dysphagia.

### Symptoms/Exam

- **Oral dysphagia:** Difficulty with the voluntary transfer of food from the mouth to the pharynx. Can have absent or continuous chewing with tendency to pocket or spit food. The most common cause of oral dysphagia is **dementia**.
- **Pharyngeal dysphagia:** Difficulty with protecting the airway due to delayed initiation of swallowing and transferring food from the pharynx to esophagus. May notice coughing or choking, which can lead to aspiration pneumonia. Associated with cerebrovascular accident (CVA), neurologic disease (eg, amyotrophic lateral sclerosis [ALS], myasthenia gravis, Parkinson disease), or mechanical obstruction (eg, malignancy).

- Depression can lead to a disinterest in food. Important to distinguish from true dysphagia.

### Diagnosis

Swallowing can be assessed by speech therapists through bedside evaluation, fiberoptic endoscopic evaluation of swallowing, or modified barium swallow.

### KEY FACT

In older adults with dementia and dysphagia, feeding tubes do **not** reduce aspiration, mortality, or improve function. Careful hand feeding is recommended.

### Management

Management of oral and pharyngeal dysphagia involves swallow therapy (such as exercises or head positioning) and altering the consistency of foods.

## Weight Loss

Aging is associated with changes in body composition, including ↑ in body fat and ↓ in bone mass, lean mass, and water content. This shift affects pharmacokinetics for water-soluble and fat-soluble drugs differently. However, unintended weight loss (>10 pounds or 5% of body weight over 6 months) is **not a normal part of aging**. Although the cause cannot be identified in 25% of cases, known etiologic factors include the following:

- Medical:** Chronic heart disease, chronic lung disease, dementia, poor dentition, xerostomia, changes in taste or smell (from aging or medication side effect), chronic constipation, dysphagia, mesenteric ischemia, cancer, diabetes, hyper- or hypothyroidism.
- Psychosocial:** Alcoholism, depression, social isolation, homelessness, limited funds, difficulty shopping for or preparing food, need for assistance with feeding, executive dysfunction from cognitive impairment.
- Pharmacologic:** Antiepileptics, digoxin, selective serotonin reuptake inhibitors (SSRIs), bupropion, metformin, and opiates may ↓ appetite or slow gut transit time leading to weight loss.

### Symptoms/Exam

- Evidence of change in clothing size, reports of poor appetite, history from family or friend. Confirmation of weight loss on exam.
- Mini Nutritional Assessment is a validated tool to help measure nutritional risk.

### QUESTION

A 90-year-old man with a chronic deep sacral ulcer suddenly developed involuntary muscle tightening (can't open his mouth or swallow). What vaccine could have prevented this?

### Diagnosis

- Identify treatable medical, psychological, and social causes. Lab tests might include CBC, basic metabolic panel, LFTs, TSH, CRP, ESR, LDH, prealbumin/albumin, and UA.
- Perform age-appropriate cancer screening (eg, colon, breast, lung), **matched to a patient's risk profile, prognosis, and preferences**.

### KEY FACT

Loss of lean body mass and ↑ in % body fat are normal age-related changes; unintentional weight loss is not.

### Management

- Discontinue any offending drugs.
- Appetite stimulants and dietary supplements may ↑ weight but do not improve mortality. The adverse effects of appetite stimulants often outweigh the benefit, particularly in older adults.
- Tube feeding has complications (aspiration, pneumonia, pain) and does **not** ↓ mortality or ↑ life expectancy in patients with dementia.

### Complications

Associated with high morbidity, including falls, isolation, skin breakdown, and nursing home placement.

**KEY FACT**

Urge incontinence is common in both men and women. The hallmark is “overactive” bladder symptoms: urinary urgency, frequency, nocturia.

**A****ANSWER**

Tetanus vaccine (either Td or Tdap).

**Urinary Incontinence**

See Table 8.1 and the mnemonic **DIAPPERS** for an overview of urinary incontinence.

**Differential**

Consider factors outside the lower urinary tract, including medical conditions (eg, diabetes mellitus, congestive heart failure (CHF), constipation, peripheral venous insufficiency), medications, and functional etiologies (ie, physically unable to get to the bathroom). **Lower urinary tract** causes are discussed in Table 8.1. Mixed incontinence with components of stress and urge symptoms is common.

**TABLE 8.1. Overview of Urinary Incontinence**

Type of Incontinence	Mechanism	Characteristics	Treatment Options
Urge (“overactive bladder”)	Uninhibited bladder contraction (detrusor overactivity) caused by bladder irritation or loss of inhibitory neurological control of bladder contractions	Most common cause in older adults Abrupt urgency with moderate to large leakage (“can’t make it to the bathroom in time”)	Behavioral therapy (bladder training, ie, timed voiding, biofeedback): Goals include frequent voluntary voiding and training of CNS and pelvic mechanisms to inhibit detrusor contractions  If unsuccessful, add an antimuscarinic agent (eg, oxybutynin, tolterodine, trospium); can take several weeks to take effect  Beware of anticholinergic side effects
Stress	Intra-abdominal pressure overcomes sphincter closure mechanisms due to urethral sphincter and/or pelvic floor weakness	Primarily affects women Involuntary leakage on exertion such as sneezing or coughing	Pelvic floor exercises (Kegels), pessaries, bladder suspension surgery
Overflow (“underactive bladder”; urinary retention)	Overdistended bladder due to impaired detrusor activity and/or outlet obstruction	5% of patients with chronic incontinence Associated with obstruction (men with prostatic enlargement), neurologic conditions (sacral spinal cord injuries, radical pelvic surgery, DM), antihistamines and anticholinergic drugs  Incomplete voiding: Leakage of small volumes, slow stream, dribbling, hesitancy  May have reduced sensation on filling High postvoid residuals (>200 mL) Recurrent UTIs can occur	BPH: $\alpha$ -adrenergic antagonists (reduce urethral smooth muscle), 5 $\alpha$ -reductase inhibitors, transurethral resection of prostate (see Ambulatory Medicine chapter)  Intermittent or continuous catheterization

## Diagnosis

Although a history, physical exam, and UA are often sufficient to provide a working diagnosis, a minority of patients require referral or specialized testing (eg, to urology for urodynamic testing). In general, do **not** order urodynamic testing because outcomes are not improved compared to clinical evaluation alone.

## Management

- Table 8.1 lists treatment options for the different types of urinary incontinence.
- Urinary catheter use: Indwelling or intermittent in-and-out urinary bladder catheters may be considered in some patients with refractory incontinence; however, they are associated with a high risk of infection. Four indications for temporary catheter placement are:
  - Inability to void: Usually due to outlet obstruction (eg, BPH), neurogenic bladder with retention, or medications.
  - Incontinence **and** open wounds needing protection (pressure ulcers), critical illness requiring close monitoring of urine output, and end-of-life care and patient preference.
  - After anesthesia (short-term only).
  - Severe cases of gross hematuria or pyuria with concerns for obstruction, monitoring, and/or irrigation.

## Fecal Incontinence

Fecal incontinence, the continuous or recurrent uncontrolled passage of fecal material for at least 1 month, and urinary incontinence, are common **causes of nursing home placement**.

Loss of continence is often multifactorial, including functional, structural, and medical factors. Causes may include history of vaginal delivery (anal sphincter tears and trauma to pudendal nerve), DM (autonomic neuropathy), and fecal impaction.

## Diagnosis

- Do a rectal exam to assess for fecal impaction, sphincter tone, pelvic floor tone, and any masses.
- Inspection of the distal colon and anus with flexible sigmoidoscopy and anoscopy can exclude mucosal inflammation or masses.

## Management

Management of underlying medical or structural disorders is key. For symptomatic management of both constipation and diarrhea, first remove contributing medications.

- For constipation:
  - Osmotic laxatives, such as polyethylene glycol, can be used. Avoid long-term use of stimulant laxatives (eg, bisacodyl, senna).
  - Bulking agents (eg, supplemental fiber) must be used with caution in older adults, since inadequate fluid intake with fiber can make constipation worse.
- For diarrhea: Loperamide is more effective than diphenoxylate for reducing urgency. Neither should be used long term.



## MNEMONIC

**Reversible/2° causes of urinary incontinence—**

### DIAPPERS

#### Delirium

Infection (acute UTI can cause detrusor instability)

#### Atrophic vaginitis/urethritis

Pharmaceuticals (alcohol, alpha-adrenergic agonists/antagonists, anticholinergics, cholinesterase inhibitors, diuretics, opiates, sedative-hypnotics)

#### Psychological

Excess urine output (hypercalcemia, hyperglycemia, diuretics, caffeine, nocturnal mobilization of peripheral edema)

#### Restricted mobility

#### Stool impaction



## KEY FACT

Asymptomatic bacteriuria is common in older adults. Do not treat unless symptoms of UTI are present.



## KEY FACT

Urinary catheter placement causes more harm in the long term; consider only as a short-term bridge to a different solution.



## KEY FACT

Fecal impaction due to ↓ gut motility and medication side effects is a common cause of fecal incontinence in older adults.



## QUESTION

A 76-year-old woman has worsening of sudden urges to urinate and often leaks urine. She is started on a medicine and develops confusion. What is the most likely cause?

**KEY FACT**

Urinalysis is important when determining the underlying cause of lower urinary tract symptoms. UA should assess for the presence of blood, leukocytes, bacteria, protein, or glucose.

**KEY FACT**

Rapid onset of ED suggests psychogenic causes or medication side effects. More gradual onset is associated with medical conditions.

**KEY FACT**

Medications associated with ED:

- Antihypertensives (thiazides,  $\beta$ -blockers, clonidine, methyldopa)
- Antiandrogens (spironolactone, H<sub>2</sub>-blockers, finasteride)
- Antidepressants (TCAs, SSRIs), antipsychotics
- Benzodiazepines, opiates

**KEY FACT**

Oral PDE5 inhibitors are effective for all types of ED, including those related to DM, psychiatric issues, prostatectomies, and spinal surgeries. Make sure your patient is not concomitantly taking nitrates and does not have unstable cardiac issues.

**ANSWER**

Anticholinergic side effects (dry mouth, dry eyes, confusion) of antimuscarinic drugs (eg, oxybutynin, trospium) used for urge incontinence.

**Erectile Dysfunction**

Erectile dysfunction (ED) is defined as an inability to acquire or maintain an erection sufficient for sexual intercourse in >75% of attempts. Evaluation is directed at distinguishing organic from psychogenic causes.

Conditions that are associated with ED:

- Medical: Obesity, DM, peripheral vascular disease, endocrine disorders (hypogonadism, hyperprolactinemia, thyroid problems).
- Pelvic surgery (eg, TURP) or injury (eg, bicycle riding).
- Spinal cord injury and other neurologic disorders.
- Medications: Antihypertensives, antidepressants, antipsychotics, antiandrogens.
- Drugs of abuse: Amphetamines, cocaine, marijuana, alcohol, tobacco.

**Diagnosis**

- **Rule out an organic etiology:** Look for a history of medical conditions associated with ED; perform a physical exam focusing on evidence of endocrine abnormality (gynecomastia, testicle size), GU abnormalities (Peyronie disease, prostate size), and peripheral neurovascular abnormalities. Screening labs should include glucose, cholesterol, TSH, and total testosterone.
- If total testosterone is abnormal, check morning serum free or bioavailable testosterone, as well as prolactin, FSH, and LH to rule out a pituitary abnormality.

**Management**

- Correct the underlying disorder (testosterone replacement for hypogonadism); eliminate drug-related causes.
- Assess for cardiovascular disease (CVD) given risks of PDE5 inhibitors in patients with unstable/refractory angina, heart failure, recent myocardial infarction (MI), hypertrophic cardiomyopathy, or severe valve disease.
- **Oral phosphodiesterase inhibitors** (sildenafil, vardenafil, tadalafil) are first-line therapy if there is no suspected organic etiology but are **contraindicated with nitrates or active cardiac disease**, including active coronary ischemia and heart failure with low blood pressure (can cause hypotension and sudden death). Efficacy is about 70% (lower in DM).
- Second-line therapies include intraurethral alprostadil suppositories (especially helpful for neurologic ED), vacuum constrictive pumps, and penile prostheses.

**Sleep Disorders**

Sleep disorders are disruptions in the two sleep states: non-rapid eye movement (NREM) and rapid eye movement (REM). A typical night of sleep begins with NREM; REM occurs after 80 minutes. Both sleep states then alternate, with REM periods ↑ as the night progresses. NREM includes four stages:

- **Stages 1 and 2:** Classified as light sleep. Stage 1 is a transition from wakefulness to sleep.
- **Stages 3 and 4:** Classified as deep, restorative sleep.

**Symptoms/Exam**

Changes in sleep occur as a normal part of aging. Such changes may affect sleep pattern (the amount and timing of sleep), sleep structure (stages), or both. Specifically, stages 1 and 2 may ↑, while stages 3 and 4 ↓. Typical complaints from older adults include the following:

- Difficulty falling asleep.
- Midsleep awakening and ↑ arousal during the night.

- Nonrestorative sleep (may be perceived as ↓ sleep time).
- Earlier bedtime and earlier morning awakening.
- Daytime napping or reversal of the sleep-wake cycle.

### Differential

- Dementia.
- 1° sleep disorders: Circadian rhythm disorders, sleep apnea, restless leg syndrome, REM behavior disorder.
- Psychiatric (eg, depression, anxiety) and medical conditions (eg, pain, CHF, nocturia) often account for insomnia.
- Medications (eg, diuretics, theophylline, β-agonists, antidepressants, corticosteroids).



### KEY FACT

Age-related sleep changes include: ↓ sleep efficiency, ↑ daytime napping, and ↓ deep sleep.

### Diagnosis

Polysomnography is indicated when a sleep-related breathing disorder or narcolepsy is suspected, or if there are violent behaviors during sleep.

### Management

- **General measures:**
  - Diagnose and treat **obstructive sleep apnea**.
  - Identify any contributing comorbid medical or psychiatric conditions.
  - Encourage good sleep hygiene, such as adhering to regular bedtimes, limiting daytime napping, exercising in daytime, and avoiding caffeine/alcohol/nicotine at night.
- **Medications:** If medications must be used, they should be administered short term, in the lowest effective dose. Use of the following medications should be actively discouraged:
  - Benzodiazepines and sedative-hypnotics: ↑ the likelihood of falls, leading to hip fracture and motor vehicle accidents as well as ↑ the risk of cognitive impairment.
  - Antihistamines (eg, diphenhydramine) and TCAs: Anticholinergic effects.

### Complications

Untreated sleep disorders result in poor memory, impaired concentration, ↑ numbers of accidents and falls, and chronic fatigue.



### KEY FACT

Use of benzodiazepines, sedative-hypnotics, antihistamines, and TCAs are discouraged in older adults.

## Cognitive Impairment

**Mild cognitive impairment (MCI)** is defined as a decline in one or more cognitive domains (memory, language, visuospatial, executive), beyond that expected for age alone, but **not** to a degree that causes functional impairments. The **risk of conversion of MCI to dementia is about 10% per year**.

### DEPRESSION

Depression is underdiagnosed and undertreated in older patients. Older adults may be more likely to present with somatic or cognitive complaints (change in **eating or sleeping** habits, change in function, anxiety) and are less likely to report depressed mood. Older men and older African American/Hispanics are at even greater risk of underdiagnosed depression.

Risk factors for depression in older adults include:

- A prior episode of depression, family history of depression, alcohol or substance use, Parkinson disease, cognitive impairment.

**KEY FACT**

Management of depression in older adults is driven more by side effect profile of the antidepressant than in younger adults.

Mirtazapine (which has a potentially helpful side effect of appetite stimulation, among others) or SSRIs are often first line. Beware of GI side effects of SSRIs (anorexia, ↓ appetite, nausea, and weight loss). Use caution with TCAs due to anticholinergic side effects.

**KEY FACT**

The side effects of mirtazapine (a noradrenergic and serotonin antagonist)—somnolence, appetite stimulation, and weight gain—may actually help older adults who have depression associated with sleep problems or unintentional weight loss.

- Recent MI, history of CVA, multiple comorbid conditions, uncontrolled pain or insomnia.
- Lack of social support, loss of autonomy, presence of functional impairment.

**Management**

Mainstay of treatment for major depression consists of medications ± psychotherapy.

- **Pharmacotherapy:** Medications for older patients are chosen largely on the basis of their side effect profiles (eg, anxiety, insomnia, pain, weight loss). See Table 8.2.
- **Psychotherapy:** Cognitive-behavioral therapy, problem-solving therapy, and interpersonal psychotherapy are effective either alone or in combination with pharmacotherapy.
- **Electroconvulsive therapy:**
  - Associated with response rates of 60% to 70% in patients with refractory depression. **Can be very effective for older adults** and may have fewer side effects than medications, although does carry a risk of confusion and retrograde amnesia.
  - First-line therapy for patients who are severely depressed, for those who are at high risk for suicide, and in other situations when a rapid response is urgent (eg, when a medical condition is severely compromised by depression). Also an option for patients who are not eligible for pharmacotherapy as a result of hepatic, renal, or cardiac disease.

**T A B L E 8 . 2 . Pharmacotherapy for Depression in Older Adults**

CLASS/MEDICATION	USES	SIDE EFFECTS
SSRIs (sertraline, fluoxetine, citalopram, escitalopram)	First-line medications; equally efficacious and <b>usually initiated at half the listed starting dose in older adults</b>	Nausea and sexual dysfunction are most common; paroxetine has the most anticholinergic side effects Fluoxetine is rarely used because of its long half-life and inhibition of cytochrome P-450 If SSRIs are discontinued abruptly, patients can experience withdrawal (flulike symptoms, dizziness, headache) There is an ↑ risk of serotonin syndrome in patients taking SSRIs and/or MAOIs
2° amine TCAs (nortriptyline)	May offer added benefit in patients with neuropathic pain, detrusor instability, or insomnia	<b>Anticholinergic side effects</b> are common; also associated with conduction abnormalities Lethal in overdose and should be avoided in patients with suicidal ideation
Mirtazapine	Beneficial for depression with sleep abnormalities and in patients with <b>unintentional weight loss</b> due to the side effect profile	Somnolence, ↑ appetite, modest weight gain, dizziness
Trazodone	Not as efficacious as other antidepressants Used to treat insomnia	Associated with <b>priapism</b> Also causes somnolence and anticholinergic effects
SNRIs (duloxetine, venlafaxine)	In addition to antidepressant effects, also used to treat anxiety and neuropathic pain	Dizziness, nausea, BP increases
Bupropion	Also reduces cravings in smoking cessation; lowest risk of sexual side effects	Seizure risk that is dose and titration related
Psychostimulants (dextroamphetamine, methylphenidate)	Sometimes used in patients with predominantly vegetative symptoms	Commonly associated with tachycardia, insomnia, and agitation

## DEMENTIA

**Dementia** is an acquired syndrome involving a decline in memory plus at least one other cognitive domain—language (aphasia), motor function (apraxia), visuospatial capacity (agnosia), or executive function (abstract thinking, organization, problem solving)—that leads to impairments in occupation, social activities, or relationships and represents a change from a prior level of function. Risk factors are listed in Table 8.3.

### Symptoms/Exam

Normal aging involves mild decline in memory, requiring more effort and time to recall new information. Signs of dementia include:

- Getting lost in familiar places.
- Personality changes such as poor impulse control or behavioral disturbance.
- ↓ ability to plan and problem solve.
- Trouble with complex or routine tasks (eg, balancing the checkbook, making meals).
- Difficulty learning new things.
- Impaired or poor judgment.
- Language problems (eg, word finding difficulty).

See Table 8.4 for descriptions of specific types of dementia.

### Diagnosis

- The Mini-Mental Status Exam (MMSE) is the best-studied instrument for screening for dementia. Accuracy depends on age, language proficiency, and highest educational level completed.
- The Montreal Cognitive Assessment (MoCA) has higher sensitivity than the MMSE for detecting mild cognitive impairment and tests a wider range of cognitive domains.
- The Mini-Cog, which is a brief test consisting of three-item recall and clock draw, is a rapid screening tool that is useful in 1° care settings. Abnormal results on any of these screening tests merits further investigation.
- Workup includes CBC, electrolytes, creatinine, LFTs, calcium, TSH, vitamin B<sub>12</sub>, RPR, and HIV.
- Neuroimaging by noncontrast CT or MRI is indicated for patients with a new diagnosis of dementia.
- Neuropsychiatric testing, an in-depth evaluation of cognitive performance in multiple domains, is indicated if the diagnosis is uncertain. For example, if a patient has significant functional deficits but performs well on screening cognitive tests or if there is a concern that a comorbid psychiatric condition, such as anxiety or depression, is contributing to poor cognitive performance.
- Lumbar puncture if any of the following are present: Onset <60 years of age, immunosuppression, history of cancer or paraneoplastic disorders, concern for infection, positive syphilis or Lyme serology, autoimmune disease, or concern for CNS inflammatory disorder.

TABLE 8.3. Risk Factors for Dementia

STRONG RISK FACTORS	OTHER RISK FACTORS
Age (particularly for Alzheimer disease)	Head trauma with loss of consciousness
A family history in first-degree relatives	A history of depression, particularly late in life
Apolipoprotein E ε4 genotype	Low educational achievement
Cardiovascular disease and risk factors (DM, HTN, smoking, HLD)	

### KEY FACT

Alzheimer disease is characterized by an insidious, progressive course without waxing and waning. Patients experience early loss of short-term memory. Physical activity and high level of intellectual achievement are protective and can delay the onset of dementia.

### KEY FACT

Patients with Lewy body dementia classically have a dramatic worsening of extrapyramidal symptoms when given antipsychotic medications (eg, haloperidol).

### KEY FACT

Normal pressure hydrocephalus presents in this order: wobbly (magnetic, shuffling gait) → wet → wacky. This should be distinguished from urinary incontinence that can occur with dementia.

### KEY FACT

Frontotemporal dementia leads to progressive alterations in behavior and personality (eg, apathy, disinhibition, stereotyped behaviors). Age of onset is 50 to 70 years.

### KEY FACT

Lewy body dementia can be distinguished from Alzheimer disease by three characteristics not prominently seen in Alzheimer: (1) fluctuations in attention and alertness (looks like delirium), (2) visual hallucinations (can be seen in late Alzheimer), and (3) parkinsonism (gait/postural instability).

### KEY FACT

An MMSE score of >26 is considered normal; 24 to 26 is suggestive of cognitive impairment; and <24 is suggestive (but not diagnostic) of dementia. Note that attention may be preserved until the late stages of Alzheimer disease, and MMSE may not pick up dementia in patients with high baseline IQ. Similarly, a MoCA score of <26 is abnormal.

TABLE 8.4. Subtypes of Dementia

TYPE OF DEMENTIA	CLINICAL PRESENTATION	TREATMENT CONSIDERATIONS
Alzheimer disease (the most common cause of dementia)	<p><b>Progressive loss of cognitive skills, eg, memory, language, judgment, and orientation.</b></p> <p><b>Early stage:</b> Starts with short-term memory loss; leads to progressive memory loss, personality changes, delusional thinking, and functional impairment.</p> <p><b>Late stage:</b> Aphasia, agnosia, apraxia; assistance is needed for all ADLs.</p> <p>↑ risk is associated with apolipoprotein E genotype ε4 allele (affected patients have more amyloid plaques, neurofibrillary tangles, Figure 8.3), but testing is considered optional.</p>	<p><b>Mild to moderate disease:</b> Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine).</p> <p><b>Late stage:</b> Memantine (blocks NMDA glutamate receptors); small ⊕ effect.</p> <p><b>Behavioral symptoms (delusions, hallucinations, agitation/sundowning):</b> Atypical antipsychotics are often used but are associated with ↑ mortality.</p> <p><b>Physical and cognitive activity.</b></p>
Vascular/multi-infarct dementia	<p>Frequently characterized by <b>sudden</b> onset and <b>stepwise</b> decline due to multiple small strokes.</p> <p>Neurologic deficits on exam and imaging correlate with previous stroke location.</p> <p>Commonly coexists with Alzheimer disease.</p>	<p>Treat any underlying causes of cerebral infarction, 2° prevention for CVA.</p> <p>Physical and cognitive rehabilitation.</p>
Lewy body dementia	<p>Includes dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD). The sequence of symptoms differs between the two, but the symptoms and underlying pathology are very similar.</p> <p><b>PDD:</b> If Parkinson disease has been diagnosed or has been present for ≥1 year before cognitive symptoms are seen.</p> <p><b>DLB:</b> If Parkisonian (motor) symptoms are present after or &lt;1 year before the onset of cognitive symptoms.</p> <p>Patients have <b>parkinsonism</b> (gait instability and postural instability), <b>visuospatial impairment and hallucinations</b>, and REM sleep disorder. <b>Fluctuations in attention and alertness</b> are also seen.</p> <p>Intracytoplasmic Lewy body inclusions are found in the brainstem (Figure 8.4).</p>	<p><b>Acetylcholinesterase inhibitors</b> (donepezil, galantamine, rivastigmine).</p> <p>Patients have ↑ sensitivity to antipsychotic medications (vs Alzheimer patients).</p> <p><b>Dopaminergic medications can be used for motor symptoms, but with caution</b>, as these medications can worsen psychotic symptoms.</p>
Frontotemporal dementia	<p>Characterized by impaired executive function (initiating activity, planning), poor self-awareness of one's deficits, and <b>disinhibited behavior</b>.</p> <p>Pick disease is one type (Pick bodies are found in the neocortex and the hippocampus).</p> <p>A family history in a first-degree relative is a major risk factor.</p>	Monitor patients for the development of ALS.
Pseudodementia	<p>Depression presenting as dementia.</p> <p>Associated with an ↑ likelihood that the patient will develop dementia.</p>	SSRIs, or other medication ± psychotherapy for treatment of depression.
Creutzfeldt-Jakob disease	<p>A rare, infectious, rapidly progressive dementia that is usually fatal within 1 year of onset.</p> <p>Presents with rapid cognitive impairment accompanied by motor deficits and seizures, ataxia, myoclonus.</p>	Diagnosis is made by autopsy; there is no treatment.

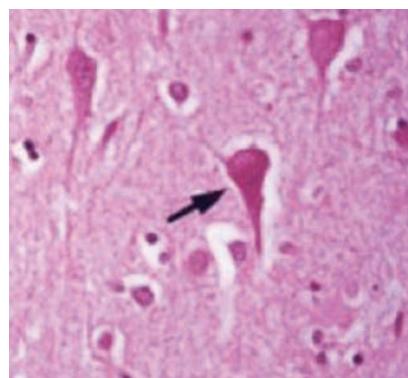
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**TABLE 8.4. Subtypes of Dementia (continued)**

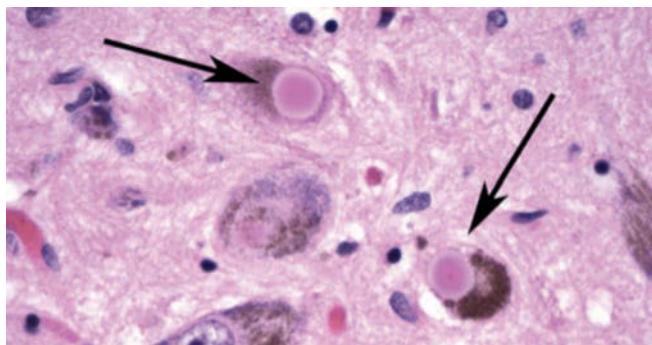
TYPE OF DEMENTIA	CLINICAL PRESENTATION	TREATMENT CONSIDERATIONS
Normal pressure hydrocephalus	The classic presentation is, in this order, "WOBBLY → WET → WACKY"—gait apraxia, urinary incontinence, and dementia. Gait is typically shuffling and is the first symptom, and is unresponsive to antiparkinsonian medications.	Diagnosis is confirmed by ventriculomegaly on CT/MRI. CNS drainage (ventricular shunt) may improve symptoms.
Other causes of cognitive impairment	<b>Medications:</b> Analgesics, anticholinergics, antipsychotics, sedatives. <b>Metabolic disorders:</b> Thyroid disease, vitamin B <sub>12</sub> deficiency, hyponatremia, hypercalcemia, hepatic and renal insufficiency. <b>Other:</b> Alcohol, HIV, encephalitis, syphilis, Parkinson disease, trauma, Huntington disease.	

### Management

- Alzheimer disease will progress despite treatment. There is controversy about the effectiveness and goals of treatment for currently available pharmacologic therapies.
- The mainstays of management are physical and cognitive activity, and environmental and behavioral interventions.
- Medications have a limited role in dementia and are used for **symptom control**. The following agents can be tried and discontinued if no improvement:
  - **Cholinesterase inhibitors (donepezil, rivastigmine, galantamine):** The most evidence is for use in **mild to moderate** Alzheimer disease, but there is some evidence of benefit in other dementias (including Lewy body, mixed, and vascular). Benefits include improvement or stabilization on neuropsychiatric scales, but benefits appear to be modest at 2 years. May also help treat behavioral symptoms of dementia.
  - **NMDA antagonists (memantine): Proposed to be neuroprotective.** For **moderate to severe** Alzheimer disease with or without concomitant cholinesterase inhibitor use.
- The following can be used to treat neuropsychiatric symptoms of dementia (depression, agitation, delusions, hallucinations), unresponsive to behavioral or environmental interventions.



**FIGURE 8.3. Neurofibrillary tangles in Alzheimer disease.** Intracellular, hyperphosphorylated tau protein; number of tangles correlates with degree of dementia. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 8.4. Lewy bodies.** These round eosinophilic cytoplasmic inclusions are seen in the remaining pigmented neurons of the substantia nigra and locus ceruleus in Parkinson disease and in the cortex in patients with dementia. Lewy bodies are composed of a fine filament called  $\alpha$ -synuclein. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

For Alzheimer disease, treatment only helps symptoms and does not stop progression. Trial a cholinesterase inhibitor (eg, donepezil, rivastigmine) for mild to moderate symptoms and consider changing to or adding memantine for more severe symptoms.



### QUESTION

A 60-year-old woman has emotional lability with frequent outbursts of crying and laughing for 1 year, new hoarding behavior, and sexual disinhibition. Her short-term memory is intact. What is the most likely diagnosis?

**KEY FACT**

No clear benefit has been shown for gingko biloba, selegiline, vitamin E, or estrogen in slowing the progression of dementia.

**KEY FACT**

Comorbidities and functional status are more important than age alone as risk factors for iatrogenic complications.

**KEY FACT**

Delirium is an independent risk factor for ↑ morbidity and mortality, and predicts poor outcomes after discharge.

**KEY FACT**

Minimize or eliminate use of physical restraints in the hospital setting, which do not prevent falls and lead to ↑ mortality, ↑ hospital lengths of stay, pressure ulcers, nosocomial infection, and emotional distress.

**A****ANSWER**

Frontotemporal dementia.

- **Atypical antipsychotics** (eg, olanzapine, quetiapine): Use with caution per the FDA's black box warning for ↑ CVA and mortality risk in this population.
- **Antidepressants** (eg, SSRIs).
- Medications to help address sleep and pain: Trazodone or melatonin can be used for sleep, and scheduled acetaminophen can be helpful, particularly if unmanaged pain could be contributing to the behavior.

**DELIRIUM**

Delirium is common in older adults, especially among hospitalized patients. Although covered in detail in the Hospital Medicine chapter, it is mentioned here because it is a common mimicker of dementia and depression. Delirium is an acute or subacute confusional state characterized by fluctuations in cognition and attention, with disturbances in behavior, memory, thought, and alertness. Usually has a multi-factorial etiology, with many risk factors:

- Preexisting cognitive impairment (especially dementia).
- Advanced age.
- Severe underlying illness, number and severity of comorbid conditions.
- Functional impairment.
- Visual or hearing impairment.
- Malnutrition and dehydration.
- Unmanaged pain or sleep disturbance.
- Always consider drug-drug interactions due to polypharmacy and adverse drug reactions due to changes in medication distribution, metabolism, and clearance as a cause of delirium.

**Falls**

Complications from falls are the leading cause of death from injury in adults >65 years. History is key to determine the etiology and risk factors for the fall.

**Risk factors:**

- Gait instability (ie, poor balance, deconditioning). See the Comprehensive Geriatric Assessment section in this chapter for gait evaluation.
- Cardiovascular conditions (eg, orthostatic hypotension).
- Neurologic disease (eg, CVA, Parkinson disease).
- Medications (eg benzodiazepines, sedatives, neuroleptics, antihistamines, opiates) and alcohol use.
- Vision impairment.
- Incontinence.
- Fear of falling.
- Environmental hazards (ie, loose rugs, stairs, poor footwear).

**Prevention:**

- Environmental modifications: Installation of handrails, removal of rugs, use of shower rails and seats, use of ramps, and first-floor setup (placement of the bed, commode, and bath on the same floor, preferably on the main level of the residence). Improve lighting, remove environmental hazards (eg, rugs), and address visual deficits.
- Reduce or eliminate psychotropic or other known offending medications.
- Older adults with low vitamin D levels are at higher risk for loss of muscle mass, strength, and hip fracture. Vitamin D and exercise are recommended to reduce risk of falls.
- Exercise and use of assistive devices. Risk of injurious falls ↓ with strength/balance exercise training (eg, tai chi).

## Complications

- Traumatic injuries: Fractures, intracranial hemorrhage.
- Prolonged time on the floor can lead to rhabdomyolysis, dehydration, and hypothermia.
- Associated with nursing home placement and functional decline.

## HIP FRACTURES

The 1-year mortality rate following a hip fracture is up to 25%; half of older patients are unable to continue to live independently after the fracture.

### Symptoms/Exam

- Hip or groin pain after a fall. Patients are often unable to bear weight.
- Leg shortening and external rotation when the patient is supine. Tenderness on palpation or internal/external rotation may be seen. Look for other fall-related trauma, such as head injury or rib fractures.

### Diagnosis

Radiographic studies generally establish the diagnosis, usually on AP pelvis or hip series. Rarely, an MRI is needed to diagnose a subtle fracture or to confirm avascular necrosis (Figure 8.5).

### Management

The major components of therapy are as follows (see also the mnemonic O-ROT):

## Ulcers

## PRESSURE ULCERS

The most common chronic ulcer, and a marker of quality of care in hospital and long-term care settings. Commonly occur over bony areas (Figure 8.6). Causes may be extrinsic and/or intrinsic:

- **Extrinsic causes:** Sustained pressure, primarily over bony prominences (eg, sacrum, ischium, heels, trochanters), combined with shearing forces, friction, and/or moisture.



**FIGURE 8.5. Hip fracture.** Frontal radiograph of the pelvis shows an intertrochanteric fracture of the right femur (arrows). (Reproduced with permission from USMLE-Rx.com.)



## MNEMONIC

### Treatment of hip fracture—

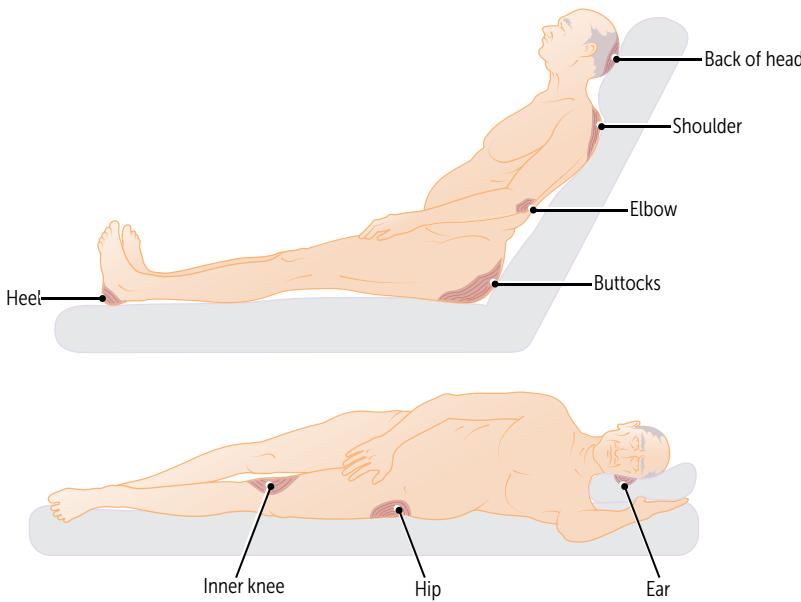
#### O-ROT

Orthopedic management (ideally occurs within 24-72 hours of fracture; prophylactic anticoagulation until ↑ mobility)

Rehab (begin immediately or as soon as allowed by surgeon)

Osteoporosis treatment (consider starting bisphosphonate; hip protectors may slightly ↓ fracture risk but do not prevent falls)

Tertiary fall prevention



**FIGURE 8.6. Common sites of pressure ulcers.** Bony areas, such as back of the head, ears, shoulders, elbows, buttocks, hips, inner knees, and heels are most commonly affected. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 8.7. Pressure ulcer. Stage III.** (Reproduced with permission from Wolff K, et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill, 2009, Fig. 16-17.)

- **Intrinsic causes:** Immobility; cognitive dysfunction; impaired wound healing (may be due to diabetes, peripheral vascular disease, venous stasis, or poor nutritional status); changes in skin structure and integrity associated with aging.

#### Diagnosis

- **Stage I:** Nonblanching erythema over intact skin.
- **Stage II:** Partial-thickness skin loss (epidermis  $\pm$  dermis).
- **Stage III:** Full thickness tissue loss; subcutaneous fat can be visible, but bone, tendon or muscle is not exposed (Figure 8.7).
- **Stage IV:** Full-thickness tissue loss with exposed muscle, tendon, or bone. Associated undermining and tunneling may also be present.
- **Unstageable:** Full-thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) in the wound bed. Slough and/or eschar should be removed to expose the base of the wound, and stage can be determined.
- **Suspected deep tissue injury:** A localized purple or maroon area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear.

#### Management

Prevention techniques include:

- **Pressure relief:** Pressure-relieving mattresses and seat cushions; physical therapy and out of bed activity; frequent repositioning (every 2 hours). Do not use “donut” cushions.
- **Debridement of dead or infected tissue:** Sharp, mechanical, or enzymatic debridement may be used.
- **Selection of topical dressing:** The goal is maintenance of a moist wound bed to promote healing. Hydrocolloid dressings are preferred over wet-to-dry gauze dressings, as wet-to-dry dressings do not promote healing since they pull off healing new tissue with each application.

- **Management of bacterial load:** Not all wounds are infected! There is no need for systemic antibiotics unless there are signs of cellulitis (erythema, pain, warmth, or ↑ drainage/odor) or systemic infection.
- For malnourished patients, correct protein and caloric intake and consider nutritional supplementation.

### VENOUS, ARTERIAL, AND DIABETIC ULCERS

See Figure 8.8 for venous, arterial, and diabetic ulcers.

- **Venous ulcers:** Irregular and shallow ulcers occurring along the lower medial calf to just below the medial malleolus (Figure 8.8A). These can be painful. Generally associated with chronic venous stasis changes on legs. Management includes compression, elevation, local wound care, pentoxifylline.
- **Arterial ulcers:** Painful, punched-out appearance, over bony prominences in lower extremities (Figure 8.8B). Caused by underlying peripheral arterial disease. Management includes revascularization and management of risk factors for arterial disease. Compression is not recommended as can further compromise blood supply.
- **Neuropathic ulcers:** Usually painless, and located on plantar surface of feet in patients with DM or neuropathy (Figure 8.8C). Management is generally with offloading pressure, local wound care, and management of diabetes.
- For full healing, wounds that develop in setting of arterial insufficiency usually require surgery to correct local blood flow.



### QUESTION

A 92-year-old woman is admitted with pain due to a compression fracture. Medications include lorazepam, alendronate, and cyclobenzaprine. She is started on IV morphine as needed for pain. On hospital day 1, she appears intermittently lethargic, apathetic, and incoherent. She refuses medication and food and has disturbed sleep. What is the most likely diagnosis?



A



B



C

**FIGURE 8.8. Venous, arterial, and diabetic ulcers.** (A) Two coalescing ulcers with a necrotic base in an area of atrophie blanche, lipodermatosclerosis, and stasis dermatitis. Scratch marks indicate itchiness of surrounding skin, while the ulcers are painful. (B) Chronic arterial insufficiency with a sharply defined, “punched out” ulcer with irregular outlines; the extremity was pulseless, and there was massive ischemia on the toes. (C) Diabetic, neuropathic ulcer on the sole. A large ulcer overlying the second left metacarpophalangeal joint. The patient, a 60-year-old man with DM of 25 years’ duration, has significant sensory neuropathy of the feet and lower legs as well as peripheral vascular disease, which resulted in the amputation of the fourth and fifth toes. (Reproduced with permission from Wolff K, et al. *Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology*, 7th ed. McGraw-Hill, 2013, Figs. 17-11A, 17.13, and 15-5.)

## Clinical Pharmacology and Aging



### KEY FACT

When an older adult presents with a new symptom, always check the medication list first for culprit medications.



### ANSWER

Delirium due to polypharmacy.

Polypharmacy typically refers to use of multiple medications; however, there is no standard criterion for number of medications. Adverse medication effects and interactions are a significant cause or contributor to hospitalizations in older adults. Changes in physiologic function and pharmacokinetics in the older patient promote ↑ sensitivity to medications and hence ↑ the possibility of complications and adverse drug events. Specific changes include the following:

- **Altered medication distribution:**

- ↓ protein binding of some drugs (eg, warfarin, phenytoin) due to low serum albumin.
- Water-soluble drugs become more concentrated (due to lower volume of distribution) and fat-soluble drugs have longer half-lives (↑ volume of distribution).

- **Metabolism:** ↓ hepatic blood flow, size and mass reduces the metabolic clearance of drugs.

- **Excretion:** Renal function ↓ by as much as 50% by age 85 years. Serum creatinine is not an accurate reflection of creatinine clearance in older adults, the Cockcroft-Gault equation should be used to estimate CrCl (taking into account age and weight).

#### Symptoms/Exam

- Delirium can result from many drugs. Common offenders include benzodiazepines, opiates, and anticholinergics.
- Other common symptoms/signs of adverse drug reactions include nausea, anorexia, weight loss, parkinsonism, constipation, hypotension, gait imbalance, and acute renal failure.

#### Management

- Try nonpharmacologic interventions before drugs.
- Improve adherence by keeping the dosing schedule simple (once daily is best), the number of pills low, and medication changes infrequent.
- Continually review the drug list for potential discontinuations and interactions.
- Consider dose reduction or discontinuation of medications rather than treating an adverse drug effect with another medication.

## Elder Abuse

Elder abuse is widespread but often underreported. The abuser is usually a caregiver or family member.

#### Symptoms/Exam

Patients should initially be interviewed alone. Ask about their perceived safety and dependency on family/caregivers. Table 8.5 details the types and clinical characteristics of elder abuse.

#### Management

- The goal is to protect the safety of the older adult while simultaneously respecting that person's autonomy.
- Always refer to Adult Protective Services, regardless of capacity (see below).
- If the patient is cognitively impaired, and **does not have the capacity to accept or refuse intervention**, the physician should collaborate with a clinical social worker

**TABLE 8.5. Types and Characteristics of Elder Abuse**

TYPE	DESCRIPTION
Domestic	Maltreatment of an older adult living at home or in a caregiver's home
Institutional	Maltreatment of an older adult living in a residential facility
Self-neglect	Behavior of an older adult who lives alone that threatens his or her own health or safety
Physical abuse	Intentional infliction of physical pain or injury
Financial abuse	Improper or illegal use of the resources of an older adult without his/her consent, benefiting a person other than the older adult
Psychological abuse	Infliction of mental anguish (eg, humiliation, intimidation, threats)
Neglect	Failure to fulfill a caretaking obligation to provide goods or services (eg, abandonment; denial of food or health-related services)
Abandonment	Desertion of an older adult by someone who has assumed responsibility for providing care to that person
Sexual abuse	Nonconsensual sexual contact of any kind

or case manager for assistance with conservatorship, surrogate decision making, and financial management.

### REPORTING REQUIREMENTS

Reporting requirements for elder abuse vary, but in nearly all states, health care providers are mandated reporters, and should report any suspected cases to their local Adult Protective Services agency. Health care providers must be familiar with their state reporting laws.

In many states, the suspicion of abuse constitutes grounds for reporting, and physicians making reports in good faith are immune from legal liability. Often the reporter remains anonymous.

## Palliative and End-of-Life Care

Palliative care aims to maximize quality of life for patients with serious or life-limiting illness. It can be provided concurrently with curative care. Goals can include:

- To continue to treat potentially **reversible** disease.
- To **alleviate suffering**, including physical, psychological, social, and spiritual distress.
- To help the patient and loved ones **prepare for the end of life**.
- Hospice care is available for patients with a terminal condition and an estimated prognosis of 6 months or less. Hospice care focuses on the patient and family, in addition to the disease, and stresses the management of symptoms, provision of comfort, pain relief and quality of life, rather than curing illness or prolonging life.
  - Associated with ↑ **patient satisfaction**, ↓ **family anxiety**, and ↑ **life expectancy in some clinical scenarios**.
  - Patients may be treated at home, an assisted living or board and care facility, or an inpatient hospice care facility.
  - To qualify per Medicare guidelines, two physicians must estimate a prognosis of ≤6 months.



### QUESTION

An 80-year-old man with advanced COPD on hospice complains of breathlessness. In addition to supplemental oxygen and bronchodilators, adding what medication would be most helpful?

## ETHICAL CONSIDERATIONS

**Ethical considerations** near the end of life may include the following:

- The concept of futile medical interventions, which may lead to conflicts between provider, patient, or family. Can often be resolved through discussions to clarify the purpose and utility of ongoing medical interventions, and the hopes and wishes of the patient and family.
- The individual has the right to refuse or withdraw medical treatments. Ethically, there is no difference between *withdrawal* of life-sustaining treatment (eg, a mechanical ventilator) and *refusing to initiate* such an intervention.
- The potential to hasten death is permissible if the 1° intention is to provide comfort and dignity and to relieve suffering (ie, it is appropriate to prescribe as much morphine as needed to relieve suffering if congruent with patient goals of care). This is often termed the “ethical principle of **double effect**.”
- **Physician-assisted suicide** involves a physician giving a patient with a terminal illness the information or means to end his or her own life.

### KEY FACT

The ethical principle of double effect allows for treatments that may hasten death if the 1° intention is to relieve suffering.

## ADVANCE DIRECTIVES

Patients can indicate their end-of-life wishes, or advance directives, in several ways. If they have decision-making capacity, then they have the right to change their minds and revise the preferences or surrogates designated in their advance directives. Requests for withdrawal of certain life-sustaining measures (eg, intubation, dialysis) must be respected when received from appropriately informed and competent patients or their surrogates.

**Advance directives** are legal documents completed by competent patients specifying their wishes with the purpose of guiding their care should they become incapacitated. These documents help guide medical providers and family members in medical decision making based on the patient’s previously recorded wishes. Examples include the following:

- **Living will:** A written, legal document that includes preferences for **end-of-life** care, usually in the setting of irreversible illness, such as preferences about life-prolonging therapies or interventions, fluids and nutrition, pain management, and organ donation.
- **Durable power of attorney for health care (DPOA-HC):** The patient designates a surrogate decision maker/proxy. The role of the surrogate is to offer “substituted judgment” such as that which would be offered if the patient could speak for himself/herself. The surrogate defaults to family members if not designated.
- **“Do not resuscitate” (DNR) orders:** Only 15% of all patients who undergo CPR in the hospital survive to hospital discharge. Older adults with chronic illness have a survival rate of <5%; for those with advanced illness (eg, metastatic cancer in patients with poor functional status), survival rate is 0% to 3%. Patients should be informed about likely mortality as well as the potential adverse outcomes of CPR and resuscitation attempts (eg, fractured ribs, neurologic disability, invasive procedures).
- **POLST (Physician Orders for Life Sustaining Treatment):** These forms, also called MOST (Medical Orders for Scope of Treatment) forms, are now used in most states. Completed by patients and their physicians, these forms designate a patient’s wishes regarding resuscitation, extent of medical treatment, and artificial nutrition.

A

### ANSWER

A short-acting opioid as needed, but if chronic symptoms, can also add a long-acting opioid.

## SYMPTOM MANAGEMENT

### Pain

- Use a numeric or visual analog scale to assess, and help the patient set pain management goals (strike a balance between sedation and pain relief).

**Management:**

- First-line for mild to moderate pain is **acetaminophen**. Consider **scheduled dosing for persistent pain**. Maximum is 3 g/24 hours for older adults.
- NSAIDs are helpful for chronic inflammatory pain, but have a high risk of side effects in older adults, including renal failure, GI irritation/bleed, and worsening heart failure.
- Nonopioid, adjuvant therapies, such as antidepressants and antiepileptics, can also be helpful.
- **Opioids** are indicated for **moderate to severe** pain, refractory to nonopioid pain medications.
- Treat **chronic pain** around-the-clock with **long-acting drugs**, and add **short-acting drugs for breakthrough symptoms**.
- Use caution with combining different formulations and agents (ie, IV, PO, transdermal, short and long acting) as effects are cumulative.
- Sedation from opioids typically precedes significant respiratory depression.
- Always add a bowel regimen to prevent constipation in patients receiving opioids.

**Dyspnea**

- Identify and treat the underlying cause where possible (eg, treat COPD or CHF as you would normally to alleviate dyspnea from these causes).

**Management:**

- Opioids are highly effective to ↓ the sensation of breathlessness.
- Nonpharmacologic measures include O<sub>2</sub> (if hypoxic), fresh air, and using fans to keep air moving.
- Benzodiazepines treat the associated anxiety but not the dyspnea itself.
- In patients with excessive secretions, a scopolamine patch or atropine drops may alleviate dyspnea and “choking” sensations.

**Nausea and Vomiting****Management:**

- First always address potentially reversible causes and stop contributing medications.
- If opioid-related, consider a sustained-release formulation, a different agent at an equianalgesic dose, or the addition of a dopamine antagonist antiemetic.
- If due to an intra-abdominal process (constipation, gastroparesis, gastric outlet obstruction), try small food portions, NG tube aspiration, laxative/bowel regimens, prokinetic agents, high-dose corticosteroids, or 5-HT<sub>3</sub> antagonists (eg, ondansetron).
- If related to elevated ICP, use corticosteroids or palliative cranial irradiation as indicated.
- If due to vestibular disturbance, treat with anticholinergic or antihistaminic agents (eg, scopolamine, diphenhydramine, promethazine).
- Consider around-the-clock dosing of antiemetics.
- Benzodiazepines and dronabinol may also be effective.

**Constipation**

**Management:** Start stool softeners and bowel stimulants prophylactically for patients on opioids, and add enemas and other treatments as needed.

**KEY FACT**

The use of opioids for end-of-life care is **not** associated with the development of addiction or abuse.

**Confusion and Agitation**

- Many patients experience confusion before death. Consider the psychoactive effects of current medications and usual reversible causes of delirium (see the Delirium section in this chapter). Treat if indicated.
- **Management:** Haloperidol or atypical antipsychotics may be used if reversible causes are not identified and behavioral management is unsuccessful.

**KEY FACT**

For patients with irreversible conditions, such as advanced dementia, tube feeding has not been shown to improve mortality and comfort but has been shown to lead to complications including infection, pain, and restraint use.

**NUTRITION AND HYDRATION**

- Dying patients who have stopped eating or drinking rarely experience hunger or thirst.
- Dry mouth can be managed with swabs and good oral care.
- IV hydration can lead to dyspnea (pulmonary edema) and pain (lower extremity edema) and is **not** recommended at the end of life.

**PSYCHOLOGICAL AND SOCIAL ISSUES**

- Patients and families rank emotional support as one of the most important aspects of good end-of-life care.
- Clinicians can provide listening, assurance, and support as well as coordination with psychotherapy and group support.

# CHAPTER 9

## Hematology

Pierce Stewart, DO

Derek Galligan, MD

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**MNEMONIC****Causes of Macrocytosis—****FAT RBC**

- Folate**
- Alcohol**
- Thyroid (hypothyroid)**
- Reticulocytosis**
- B<sub>12</sub> deficiency**
- Cirrhosis**

**KEY FACT**

Five complications other than anemia due to iron deficiency:

- Alopecia
- Pica
- Plummer-Vinson syndrome
- Reactive thrombocytosis
- Restless legs syndrome

**KEY FACT**

Iron deficiency plus dysphagia suggests

**Plummer-Vinson syndrome.** The esophageal webs and dysphagia will disappear once iron is replaced.

**KEY FACT**

Iron deficiency is the most common cause of reactive thrombocytosis and the most common presentation of celiac disease.

**KEY FACT**

The total iron-binding capacity (TIBC) is often the simplest test to differentiate ACD from iron deficiency. TIBC is low in ACD and high in iron deficiency.

**KEY FACT**

The most common presentation of celiac disease is iron deficiency anemia that is refractory to oral iron therapy.

**KEY FACT**

A ferritin <30 µg/L is highly suggestive of iron deficiency.

**Anemia****APPROACH TO ANEMIA**

The best first steps in evaluation are measurement of the absolute **reticulocyte count** (Figure 9.1) and review of the **peripheral smear**. Reticulocyte count categorizes anemias into **hypoproliferative** (Table 9.1) versus **hyperproliferative**.

**IRON DEFICIENCY ANEMIA**

Think of the three categories of iron deficiency:

- **Chronic blood loss:** GI tract, Genital tract (eg, menses), GU tract.
- **Reduced absorption:** Reduced intake, **celiac disease**.
- ↑ **need for iron:** From pregnancy, lactation, CKD due to low erythropoietin.

**Differential of Microcytic Anemia**

- **Anemia of chronic disease (ACD):** Table 9.2 distinguishes ACD from iron deficiency.
- **Lead poisoning:** Presents with ↑ RBC protoporphyrin, basophilic stippling, and lead lines on the gums.
- **Thalassemia.**

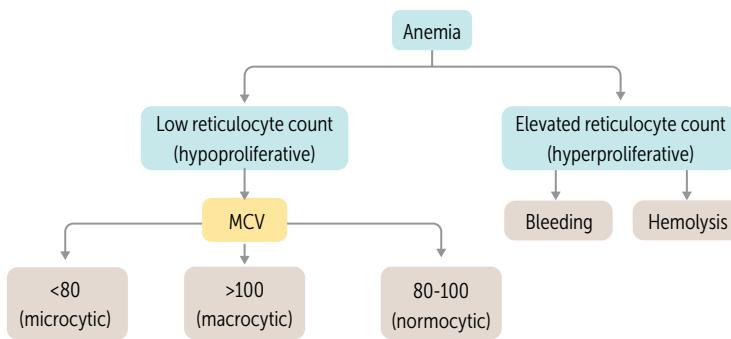
**Diagnosis**

- Peripheral smear: Microcytic, hypochromic RBCs with marked anisocytosis (Figure 9.2).
- **Serum ferritin** is the most useful screen for iron deficiency. Values <30 µg/L are highly suggestive of iron deficiency. Although normal values do not rule it out, values of >100 µg/L make iron deficiency unlikely.
- Bone marrow biopsy is rarely indicated but is still considered the gold standard.

**Management**

Do not treat until first identifying the underlying cause. Iron replacement:

- Oral elemental iron, approximately 300 mg per day; can cause constipation.
- Parenteral iron indicated for oral iron intolerance, malabsorption, and significant chronic blood loss. Note: Older formulations (iron dextran) carried risk of anaphylaxis.



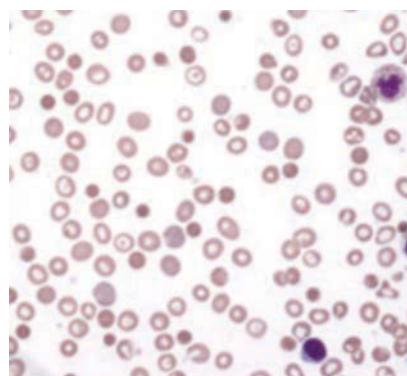
**FIGURE 9.1. Algorithm for categorizing anemias.** (Reproduced with permission from USMLE-Rx.com.)

**TABLE 9.1.** Classification of Hypoproliferative Anemias

MICROCYTIC (MCV <80)	MACROCYTIC (MCV >100)	NORMOCYTIC (MCV 80-100)
<b>"TAIL":</b>	Main causes:	ACD
Thalassemia	■ $B_{12}$ , folate deficiency	Aplastic anemia
Anemia of chronic disease (ACD)	■ Myelodysplasia	Myelodysplasia
Iron deficiency	■ Drug-induced bone marrow suppression	Renal insufficiency
Lead toxicity	■ Alcohol	Mixed disorder
	■ Liver disease	
	■ Hypothyroidism	
	Other:	
	■ Myeloma	
	■ Aplastic anemia	
	■ Pure red cell aplasia	

**KEY FACT**

Unexplained iron deficiency, especially in someone >50 years, is an absolute indication for colon cancer screening.

**ANEMIA OF CHRONIC DISEASE**

ACD is caused by sequestration of iron in the reticuloendothelial system as a result of an underlying inflammatory disorder. ACD is the **most common cause of anemia in the elderly population**.

- **Diagnosis:** A diagnosis of exclusion: must be differentiated from iron deficiency anemia (see Table 9.2); peripheral smear is nonspecific.
- **Management:** Treat the underlying cause; high doses of erythropoietin (30,000-60,000 U/wk) may be tried in patients with serum erythropoietin levels of <100 to 500 IU/L.

**FIGURE 9.2. Iron deficiency anemia.**  
Note the microcytic RBCs of variable size (anisocytosis) with central pallor and targeting indicative of iron deficiency.  
(Reproduced with permission from USMLE-Rx.com.)

**ANEMIA ASSOCIATED WITH CHRONIC KIDNEY DISEASE**

Erythropoietin is produced by the kidneys, and patients with chronic kidney disease (CKD) often produce inadequate amounts. The anemia is usually normocytic and normochromic.

- **Diagnosis:** If workup for other causes of anemia are unrevealing and estimated GFR <30 mL/min/1.73 m<sup>2</sup>, the anemia can be treated as anemia associated with CKD. Measurement of serum erythropoietin levels is generally not indicated.
- **Management:** Treatment with **subcutaneous erythropoietin** is recommended if hemoglobin <10 g/dL, to target hemoglobin of 10 to 12 g/dL. Iron supplementation is usually required to maintain adequate iron stores.

**TABLE 9.2.** Anemia of Chronic Disease Versus Iron Deficiency Anemia

VARIABLE	ACD	IRON DEFICIENCY
MCV	Normal/low	Low
RDW	Normal	Normal or ↑
Ferritin	Normal/high	Low
TIBC	↓	↑
Soluble transferrin receptor	Normal	↑

**KEY FACT**

In developed countries, the most common cause of vitamin B<sub>12</sub> deficiency is pernicious anemia.

**KEY FACT**

The neurologic changes associated with B<sub>12</sub> deficiency are not always reversible with B<sub>12</sub> replacement.

**KEY FACT**

MMA is a more sensitive test than B<sub>12</sub> level to evaluate for serum B<sub>12</sub> deficiency. In patients with borderline B<sub>12</sub> levels, ↑ MMA is diagnostic of B<sub>12</sub> deficiency.

**KEY FACT**

Use RBC folate—not serum folate—level when looking for folate deficiency. RBC folate is more reflective of long-term folate levels than serum folate.

**KEY FACT**

In a patient with B<sub>12</sub> deficiency, anti-intrinsic factor antibodies are virtually diagnostic for pernicious anemia as the cause of B<sub>12</sub> deficiency.

**KEY FACT**

In patients with pernicious anemia, be on the lookout for other commonly associated autoimmune diseases, such as vitiligo, thyroid disease, and Addison disease.

**VITAMIN B<sub>12</sub>/FOLATE DEFICIENCY**

The absorption of vitamin B<sub>12</sub> requires many factors, including the secretion of intrinsic factor (IF) from the stomach and an intact terminal ileum. Vegans are at high risk for B<sub>12</sub> deficiency as B<sub>12</sub> comes solely from animal products, whereas folate is derived from green, leafy vegetables.

**Symptoms and Signs**

- In either B<sub>12</sub> or folate deficiency may see: glossitis; mild icterus due to ineffective erythropoiesis, causing intramedullary hemolysis.
- Atrophic gastritis may be seen in pernicious anemia.
- **Neurologic findings** are present in B<sub>12</sub> deficiency (less common in folate deficiency) and are not always reversible with B<sub>12</sub> replacement. Neurologic changes include:
  - Peripheral sensory neuropathy: Paresthesias in the distal extremities.
  - Posterior column findings: Loss of vibratory sensation and proprioception; gait instability.
  - Dementia or more subtle personality changes may occur at any time (“megabolastic madness”).

**Differential**

The causes of B<sub>12</sub> and folate deficiency are further outlined in Table 9.3.

**Diagnosis**

- Suspect in anemic patient with MCV > 100 and look for low serum B<sub>12</sub> level or RBC folate levels. May also see ↑ LDH and ↑ indirect bilirubin due to intramedullary hemolysis. Pancytopenia is seen in severe cases.
- When B<sub>12</sub> level is borderline low, obtain homocysteine or methylmalonic acid (**MMA**) levels, which will be elevated, distinguishing B<sub>12</sub> deficiency from folate deficiency (Table 9.4).
- Smear: Macro-ovalocytes and hypersegmented neutrophils—any neutrophil with ≥ 6 lobes or the majority with ≥ 4 lobes (Figure 9.3).
- Bone marrow: Megaloblastic (hypercellular, ↓ myeloid/erythroid ratio, enlarged RBC precursors with relatively immature nuclei); may mimic the blastic appearance of acute leukemia.
- Schilling test to establish cause of B<sub>12</sub> deficiency. This test is rarely done now.
- Antibodies: **Anti-intrinsic factor antibodies are highly specific—close to 100%—for pernicious anemia as the cause of B<sub>12</sub> deficiency.** Antiparietal cell antibodies have limited role: while they are more sensitive for pernicious anemia, they lack specificity.

**TABLE 9.3. Causes of B<sub>12</sub>/Folate Deficiency**

B <sub>12</sub> DEFICIENCY	FOLATE DEFICIENCY
Dietary deficiencies—very rare; typically found in strict vegans	<b>Inadequate intake:</b> <ul style="list-style-type: none"> <li>■ Malnutrition</li> <li>■ Alcoholism</li> <li>■ Malabsorption (eg, tropical sprue)</li> </ul>
↓ IF—the most common cause; typically from pernicious anemia (autoimmune destruction of parietal cells)	<b>↑ Demand:</b> <ul style="list-style-type: none"> <li>■ Pregnancy</li> <li>■ Hemodialysis (folate lost in dialysate)</li> <li>■ Chronic hemolytic anemia</li> <li>■ Psoriasis</li> </ul>
Gastrectomy	
Ileal resection	
Crohn disease	
Tapeworm infestation ( <i>Diphyllobothrium latum</i> )	
Bacterial overgrowth of terminal ileum	

**TABLE 9.4. Serum MMA and Homocysteine Levels in B<sub>12</sub> and Folate Deficiency**

	B <sub>12</sub> DEFICIENCY	FOLATE DEFICIENCY
MMA	↑	<b>Normal</b>
Homocysteine	↑	↑

### Management

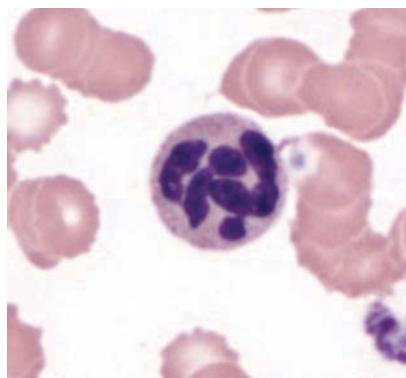
- Parenteral B<sub>12</sub>: Recommended for the initial treatment of B<sub>12</sub> deficiency in case the patient cannot absorb oral B<sub>12</sub>.
- Replacement: Give 1000 µg IM daily × 1 week, then every week × 1 month, then 1000 µg IM every month as maintenance.
- Oral B<sub>12</sub>: Equally effective to parenteral as long as the patient is capable of absorbing. The recommended dose is 1 to 2 mg PO daily.
- Oral folate: A dose of 1 mg PO daily is adequate for folate deficiency.

### HEMOLYTIC ANEMIA

Laboratory findings in hemolytic anemias are: ↑ LDH, ↑ indirect bilirubin, ↑ reticulocytes, and ↓ haptoglobin. Hemolysis is classically categorized as either extravascular or intravascular, as shown in Table 9.5; peripheral smear findings are shown in Figure 9.4 (A and B). Table 9.6 lists other tests useful in identifying the cause of hemolysis.

**TABLE 9.5. Extravascular Versus Intravascular Hemolytic Anemia**

FEATURE	EXTRAVASCULAR	INTRAVASCULAR
Site of RBC destruction	Spleen	Bloodstream, liver
Peripheral smear findings	Spherocytes	Depends on underlying cause: <b>Spherocytes</b> imply autoimmune hemolysis (see Figure 9.4A) <b>Schistocytes</b> indicate microangiopathic cause (see Figure 9.4B)
Serum haptoglobin	Normal or mildly ↓	Markedly ↓
Urine hemosiderin	Unchanged	↑
Examples	Warm antibody immune hemolysis Hypersplenism Delayed transfusion reaction	Cold antibody immune hemolysis Acute transfusion reaction Microangiopathic hemolysis Oxidative hemolytic anemia (eg, G6PD deficiency) Paroxysmal nocturnal hemoglobinuria Hemoglobinopathies (sickle cell anemia) Infection related (malaria, <i>Clostridium</i> , <i>Babesia</i> )



**FIGURE 9.3. Megaloblastic anemia.** Note the macro-ovalocytes and hypersegmented neutrophil. (Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

Any chronic hemolytic anemia should be treated with folate supplementation and vaccinations for encapsulated bacteria.

#### KEY FACT

If a patient with CLL or SLE develops a new anemia with microspherocytes on peripheral blood smear, suspect warm antibody autoimmune hemolytic anemia. A direct antiglobulin (Coombs) test will typically be + for IgG, and initial treatment is corticosteroids.

#### QUESTION

A 60-year-old woman with chronic lymphocytic leukemia treated with chemotherapy 3 months ago complains of weakness and dark urine. Exam reveals scleral icterus, cervical lymphadenopathy, and splenomegaly. Laboratory results: Hb, 6.5 g/dL; platelets, 200,000/µL; reticulocytes, 13%; total bilirubin, 6.0 mg/dL; LDH, 357 U/L; and direct antiglobulin (Coombs) test, + for IgG. What is the most likely diagnosis?

RBC Forms						
Spherocytes (A)	Schistocytes (B)	Target cell (C)	Teardrop cell (D)	Burr cell (echinocyte) (E)	Howell-Jolly bodies (F)	Spur cell (acanthocyte) (G)
Associated Conditions						
Extravascular hemolysis, hereditary spherocytosis	Microangiopathy, intravascular hemolysis (eg, DIC)	Liver disease, hemoglobinopathy (ie, $\beta$ -thalassemia)	Myelofibrosis, thalassemia	Uremia	Postsplenectomy, functional asplenia (ie, sickle cell disease)	Liver disease

**FIGURE 9.4.** Summary of Peripheral Smear Morphology—RBCs. (Images A, B, C, and G reproduced with permission from USMLE-Rx.com; Images D and E reproduced with permission from USMLE-Rx.com; courtesy of Dr. Kristine Krafts; Image F reproduced from the CDC.)

### KEY FACT

If a patient develops hemolytic anemia soon after starting a new medication—especially sulfas or dapsone—suspect G6PD deficiency and look at peripheral smear for bite cells, spherocytes, and Heinz bodies (the latter requires a special stain to see).

### Differential

- Immune hemolysis:** Divided into warm and cold antibodies, referring to the temperature at which the responsible autoantibody will bind erythrocytes and thus predict several other characteristics (Table 9.7).
- Microangiopathic hemolytic anemias (intravascular):** Characterized by schistocytes (see Figure 9.4B) and  $\ominus$  Coombs test. Almost all are associated with thrombocytopenia.
- G6PD deficiency:** erythrocytes have  $\downarrow$  ability to withstand oxidative stress. Classic triggers include medications (eg, **dapsone**, **sulfonamides**, antimalarials, and nitrofurantoin), and dietary factors (eg, fava beans). Peripheral smear shows bite cells, spherocytes (see Figure 9.4A), and Heinz bodies (the latter requires a special stain to see).

**TABLE 9.6.** Tests Associated With Various Etiologies of Hemolytic Anemia

TEST	ASSOCIATED CONDITION	COMMENT
Direct antiglobulin (Coombs) test	Autoimmune hemolytic anemia	More commonly warm antibody than cold antibody
G6PD level	G6PD deficiency	Level may be normal during a crisis (all the deficient cells are killed; remaining cells have adequate G6PD)
Osmotic fragility	Hereditary spherocytosis	Reduced surface area to volume ratio increases susceptibility to lysis in hypotonic solution
Hemoglobin electrophoresis	Hemoglobinopathies (ie, HbS, HbC)	Separates normal hemoglobins (HbA, HbF, HbA2), as well as variants (HbS, HbC)
Cold agglutinins	Cold agglutinin associated hemolytic anemia	Most commonly IgM; often associated with <i>Mycoplasma</i> infections
Flow cytometry	Paroxysmal nocturnal hemoglobinuria	Look for abnormalities in CD55 and CD59 expression (often $\downarrow$ or absent expression)

A

### ANSWER

Warm antibody-mediated hemolytic anemia. Autoimmune hemolytic anemias may be idiopathic or result from drugs, lymphoproliferative disorders, collagen vascular diseases, or malignancies. CLL is a common cause.

**TABLE 9.7. Immune Hemolysis Categories**

	WARM ANTIBODY	COLD ANTIBODY
Autoantibody	IgG	IgM
Direct antiglobulin test	⊕ for IgG	⊕ for IgM, complement
Peripheral smear	Spherocytes	Red cell agglutination
Associated conditions	Autoimmune diseases; CLL, lymphoma; α-methyldopa	<i>Mycoplasma</i> infection, EBV, CLL, lymphoma
Treatment	Corticosteroids, splenectomy, immunosuppression	Warming extremities, plasmapheresis, alkylator medications, rituximab

to see). Lab tests: G6PD activity (remember that measuring this during an acute hemolytic episode may result in a false-negative test).

- **Paroxysmal nocturnal hemoglobinuria (PNH):** A rare clonal stem cell disorder caused by defective expression of RBC membrane proteins (CD55 and CD59) which normally function to protect the cell against complement-mediated destruction. Characterized by the classic triad of pancytopenia, intravascular hemolysis, and thrombosis. Diagnosis established by **flow cytometry for CD55 and CD59**. Associated with pancytopenia, thromboses (especially Budd-Chiari), and progression to myelodysplasia or AML. Can also cause massive hemoglobinuria, resulting in acute renal failure. Treatment options are allogeneic hematopoietic stem cell transplantation (HSCT) or eculizumab (monoclonal antibody targeting complement C5).
- **Sickle cell anemia:** This subtype is covered in the Hemoglobinopathy section below.

## Microangiopathies

Table 9.8 outlines the distinguishing features and treatment of microangiopathies.

### THROMBOTIC THROMBOCYTOPENIC PURPURA

Rare, often related to autoantibody against, or deficiency of, ADAMTS13. Characterized by microangiopathy, ↑ LDH, and neurologic changes. The **classic pentad**—fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic changes, and renal failure—is seen in <10% of cases.

#### Symptoms/Exam

- Typically presents with anemia, bleeding, or neurologic abnormalities.
- Neurologic changes may be subtle and include personality changes, headache, confusion, lethargy, or coma.

#### Differential

Associated conditions include:

- **Medications:** Cyclosporine, tacrolimus, quinine, ticlopidine, clopidogrel, mitomycin C, estrogens.
- **Pregnancy:** Overlaps with eclampsia and HELLP.
- **Autoimmune disorders:** SLE, antiphospholipid antibody syndrome, scleroderma, vasculitis.
- **HIV.**
- **Bone marrow transplantation:** Autologous or allogeneic.

#### KEY FACT

The classic triad for PNH is hemolysis, pancytopenia, and thrombosis. Flow cytometry for CD55 and CD59 is the diagnostic test of choice.

#### KEY FACT

The classic pentad for TTP is fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic changes, and renal failure—but rarely are all five seen together.

#### KEY FACT

PT, PTT, d-dimer, and fibrinogen levels are normal in HUS and TTP and abnormal in DIC.

#### QUESTION

A 44-year-old woman presents with 3 days of ↑ confusion and fevers. She has no medical problems, takes no medications, and is not sexually active. Temperature is 38.6°C (101.5°F); BP, 136/72 mm Hg; HR, 92 beats per minute; and RR, 18 breaths per minute. She appears confused; neurologic exam is otherwise nonfocal. Remaining exam findings are normal except for petechiae at the sites of her BP cuff. Lab results: WBC count, 12,000/ $\mu$ L; Hb, 8.5 g/dL; and platelet count, 22,000/ $\mu$ L. Creatinine, 1.4 mg/dL; LDH, 1250 IU/L; PT and PTT are normal, as are radiographs and UA. Peripheral smear demonstrates 2⊕ schistocytes. Empiric antibiotics are started. Over the next 2 days, her platelet count and hemoglobin continue to drop while her creatinine rises. Blood and urine cultures remain ⊖ and LP results are normal, but she continues to spike intermittent fevers. On the third hospital day, she has a seizure. Brain MRI is normal. What do you suspect and how would you treat this condition?

TABLE 9.8. Differential and Treatment of Microangiopathies

CAUSES OF MICROANGIOPATHY	DISTINGUISHING FEATURES	TREATMENT
DIC	Associated with severe infection, sepsis, malignancy, and intravascular thrombus Consumptive coagulopathy; ↑ PT and PTT; low fibrinogen	Treat the underlying condition; cryoprecipitate (FFP if indicated)
TTP	↑ LDH, neurologic symptoms, normal coagulation tests (unless concomitant DIC), ADAMTS13 activity <10%	<b>Plasma exchange with FFP;</b> corticosteroids; <b>no platelet transfusions</b>
HUS	↑ LDH, renal insufficiency, normal coagulation tests (unless concomitant DIC); seen in setting of shiga-toxin producing bacteria	Hemodialysis if necessary; may be self-limited; avoid antibiotics
Atypical HUS	Diagnosis of exclusion Features similar to HUS, but history absent of a diarrheal illness and ⊖ shigatoxin assay	Eculizimab (monoclonal antibody directed against complement C5)
Preeclampsia	Peripartum period; hypertension	Early delivery; diuretics, antihypertensives
HELLP syndrome	Peripartum period; ↑ liver enzymes; probably a variant of eclampsia	Early delivery
Malignant hypertension	Hypertension	Antihypertensives
Vasculitis	Features of specific vasculitis	Treat the underlying condition
Miscellaneous (metastatic cancer, mechanical heart valve, severe burns)		Treat the underlying condition

**A****ANSWER**

The combination of anemia and thrombocytopenia with schistocytes in this previously healthy woman raises suspicion for a microangiopathic hemolytic anemia; the ↑ LDH further supports this diagnosis. Of this anemia type, thrombotic thrombocytopenic purpura (TTP) is most likely based on the normal PT and PTT (ruling out DIC) and the presence of fever, neurologic findings, and acute renal failure. HUS less likely given lack of diarrheal illness. Treatment is plasma exchange with FFP and should NOT be withheld while awaiting confirmatory testing with ADAMTS13 activity assay (<10% indicates TTP). Atypical HUS is diagnosis of exclusion.

**Diagnosis**

- Peripheral smear shows thrombocytopenia with microangiopathy (ie, schistocytes). **PT/PTT should be normal unless disseminated intravascular coagulation (DIC) is also present.**
- **ADAMTS13 activity**, von Willebrand factor (vWF) cleaving protease: <10% activity is diagnostic of TTP.
- **LDH is almost always ↑.**
- **Unusual for platelets <20,000/ $\mu$ L unless concomitant disorder.**

**Management**

- **Plasmapheresis:** Plasma exchange (PLEX) with fresh frozen plasma (FFP) has a high response rate. Daily treatment continued until neurological symptoms resolve and LDH is normal.
- If PLEX is unavailable, treatment can be temporized with FFP infusion.
- Rituximab for cases refractory to PLEX.
- Platelet transfusion is contraindicated unless serious bleeding is present.

**HEMOLYTIC-UREMIC SYNDROME**

- Hemolytic-uremic syndrome is similar to TTP, but **without neurologic changes and with more prominent renal failure.**
- **Diagnosis:** Associated with diarrheal illnesses with shiga toxin-producing bacteria (eg, *E coli* O157:H7, O154:H4, *Shigella*, *Campylobacter*) but may be associated

**KEY FACT**

Hemolytic anemia with schistocytes, thrombocytopenia, normal coagulation tests, and ↑ LDH should make you suspicious for TTP or HUS.

with the same medications and conditions as TTP. Characterized by microangiopathy, ↑ LDH, and renal failure.

- **Management:** Supportive care and renal replacement therapy as needed for uremic symptoms.
- **Atypical HUS** has clinical features similar to HUS but without diarrheal illness and is shiga toxin–negative. The pathophysiology of atypical HUS—complement-mediated destruction—differs from typical HUS, and so does the treatment. Atypical HUS is treated with eculizimab, a monoclonal antibody that inhibits complement.

## Hemoglobinopathies

### THALASSEMIA

- In normal patients, adult hemoglobin (HbA) is primarily (97%-99%) composed of two  $\alpha$  chains plus two  $\beta$  chains ( $\alpha_2\beta_2$ ). In thalassemia, there is a ↓ amount of either  $\alpha$  or  $\beta$  chain, resulting in ↓ HbA. The two general types of thalassemia are:
  - **$\alpha$ -thalassemia:** Affects persons from Southeast Asia and China and African Americans.
  - **$\beta$ -thalassemia:** Affects persons of Mediterranean descent; rarely affects Asians or African Americans.
- **Differential:** The severity of  $\alpha$ -thalassemia depends on the number of  $\alpha$ -globin genes functioning (Table 9.9). Table 9.10 displays two subtypes of  $\beta$ -thalassemia.
- **Diagnosis:** Peripheral smear typically shows microcytosis, hypochromia, and basophilic stippling ( $\beta$ -thalassemia only). With increasing severity, ↑ nucleated RBCs and target cells are seen (Figure 9.5).
- **Management:** Transfusions. Iron chelation may be indicated for iron overload.

### SICKLE CELL ANEMIA

Sickle cell anemia is caused by a defect in the  $\beta$ -globin gene that produces sickle Hb (HbS). Heterozygotes have sickle cell trait and are clinically normal except under extreme stress. Those with HbS are at risk for complications seen in sickle cell disease but at ↓ frequency compared to those with sickle cell anemia (HbSS). Sickling ↑ by dehydration, acidosis, or hypoxia. Peripheral smear shows target cells, Howell-Jolly bodies, and classic sickle cells (Figure 9.6).

#### Symptoms/Exam

Due to unstable sickle cells that hemolyze and aggregate to cause vaso-occlusion resulting in acute and chronic complications (Figure 9.7):

- **Acute vaso-occlusion:** Presents as episodes of pain (eg, pain crises, acute chest syndrome; Table 9.11), priapism, stroke, and splenic sequestration.

TABLE 9.9. Differential Diagnosis of  $\alpha$ -Thalassemia

	SILENT CARRIER	$\alpha$ -THALASSEMIA TRAIT	HEMOGLOBIN H DISEASE	HYDROPS FETALIS
Functional $\alpha$ -globin chains	3	2	1	0
Hematocrit	Normal	28%-40%	22%-32%	N/A
Hemoglobin electrophoresis	<b>Normal</b>	<b>Normal</b>	10%-40% HbH	N/A
Clinical course	Normal	Normal life span	Chronic hemolytic anemia, exacerbated by stress	Universally lethal as neonate

### KEY FACT

Emergent plasma exchange, not corticosteroids, is the treatment of choice for TTP.

### KEY FACT

Be able to recognize thalassemia as the cause of a patient's chronic hypochromic microcytic anemia with normal results of tests for iron deficiency. Suspect  $\alpha$ -thalassemia if a patient is from Southeast Asia, China, or of African descent and  $\beta$ -thalassemia if from the Mediterranean. Also, Hb electrophoresis will be normal in  $\alpha$ -thalassemia trait but will show a ↓ in HbA, ↑ in HbA<sub>2</sub>, and ↑ in fetal Hb in  $\beta$ -thalassemia.

### KEY FACT

$\beta$ -thalassemia is most commonly confused with iron deficiency anemia.  $\beta$ -thalassemia will have normal/high ferritin levels, a high RBC count, Hb electrophoresis with ↑ HbA<sub>2</sub>, and ↑ fetal Hb. One quick way to differentiate iron deficiency anemia from thalassemia is to look at the RDW. Iron deficiency anemia tends to cause quite variable sizing, leading to a high RDW, whereas thalassemia results in more uniform small cells, thus a low RDW.

### KEY FACT

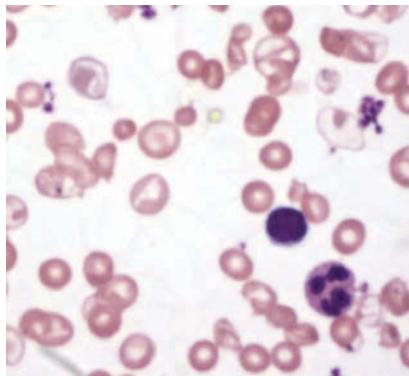
Those with transfusion-dependent anemias (eg,  $\beta$ -thalassemia major) may develop iron-overload and require chelation therapy.

**KEY FACT**

**Asplenia:** Sickle cell patients often undergo autosplenectomy thus are at risk for overwhelming sepsis from encapsulated organisms (ie, *H influenza*, *Neisseria meningitidis*, *S pneumoniae*) and should receive appropriate vaccinations.

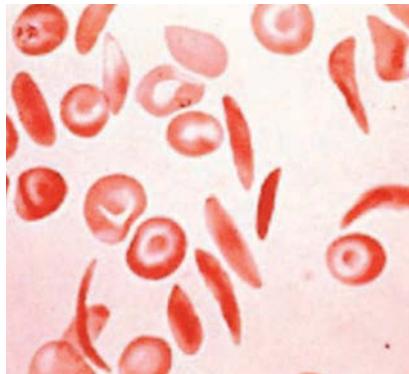
**KEY FACT**

**Transient aplastic crisis:** Infection with parvovirus B19 can cause transient aplastic crisis, which can be severe in patients with sickle cell disease.



**FIGURE 9.5.  $\beta$ -Thalassemia major.**

Peripheral blood smear of a 30-year-old man with the condition shows hypochromia and marked aniso- and poikilocytosis. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 9.6. Sickle cell anemia.**

Multiple sickle forms are characteristic. (Reproduced with permission from USMLE-Rx.com.)

**TABLE 9.10. Differential Diagnosis of  $\beta$ -Thalassemia**

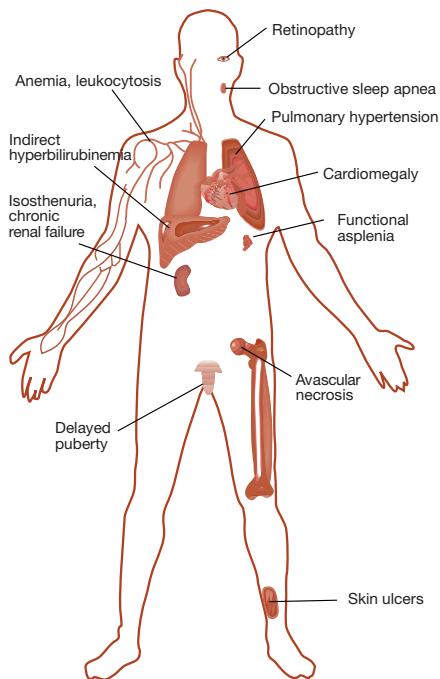
	$\beta$ -THALASSEMIA MINOR	$\beta$ -THALASSEMIA MAJOR (COOLEY ANEMIA)
$\beta$ -globin synthesis	Near normal (heterozygous)	Almost complete absence
Hematocrit	28%-40%	<10% without transfusions
Life span	Normal	20-30 years
Transfusion dependent	No	Yes
Clinical notes	Asymptomatic; mild microcytic anemia	Bony anomalies, hepatosplenomegaly, jaundice, transfusional iron overload

- **Chronic vaso-occlusion:** Manifests as renal papillary necrosis, avascular necrosis, autosplenectomy, retinal hemorrhage, and **chronic hemolytic anemia**—presenting as jaundice, pigment gallstones, and aplastic crisis.

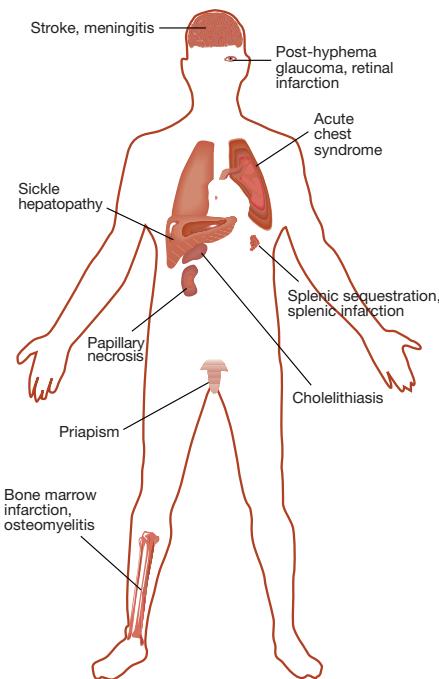
### Management

- **Health maintenance:**
  - Although not universally accepted, folate supplementation may be required.
  - Pneumococcal vaccination.
  - Screen yearly for retinal disease and renal dysfunction.
  - Consider **hydroxyurea** in patients with recurrent pain crises requiring hospitalization or in those with acute chest syndrome. Hydroxyurea is contraindicated in pregnancy and renal failure.
- **Acute episodes of pain:**
  - Treat pain crises with aggressive hydration, opioid analgesics, supplemental O<sub>2</sub>, and incentive spirometry.

### CHRONIC COMPLICATIONS



### ACUTE COMPLICATIONS



**FIGURE 9.7. Chronic and acute complications of sickle cell disease.**

**TABLE 9.11. Manifestations of Acute Pain in Sickle Cell Disease**

	PAIN CRISIS	ACUTE CHEST SYNDROME
System	Any organ or tissue, typically bones	Pulmonary microvasculature
Symptoms/signs	Commonly manifests as pain in the back and long bones that lasts hours to days	Characterized by chest pain, hypoxia, fever; pulmonary infarction or infiltrates on CXR
Diagnostic implications	Triggered by factors that promote sickling: hypoxia, dehydration, and infection	↑ mortality May be impossible to differentiate from PE and pneumonia Repeated episodes can lead to pulmonary hypertension and cor pulmonale
Treatment	Aggressive hydration, opioid analgesics, supplemental O <sub>2</sub> , and incentive spirometry	Same treatment as pain crisis, plus transfusion and antibiotics covering <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria</i> , <i>Mycoplasma pneumoniae</i> , and <i>Chlamydia pneumoniae</i> May require ICU admission

- Transfusions should be minimized given risks of alloimmunization and iron overload. Transfusions are not indicated for routine pain crisis, but may be indicated for severe vaso-occlusive emergencies (acute chest syndrome, priapism, stroke). Transfuse until HbS is <30%; initiate **exchange transfusion**, if necessary, to keep hemoglobin ≤10 g/dL.

## Other CBC Abnormalities

### THROMBOCYTOPENIA

Thrombocytopenia is defined as a platelet count of  $<150 \times 10^9/\text{L}$ . Causes are outlined in Table 9.12.

#### Diagnosis

- To exclude mimickers, first examine peripheral smear:
  - Rule out platelet clumping, which could produce falsely low platelet count on a CBC. Ask for a count/smear done in citrate, as EDTA (the anticoagulant most often employed in tubes used to collect a CBC) can cause clumping of platelets.
  - Look for evidence of microangiopathy (ie, schistocytes), marrow suppression (megaloblastic changes, dysplastic changes), or immature platelets (giant platelets) suggesting ↑ platelet turnover (Table 9.13).
- Take a careful drug history:
  - Acetaminophen, H<sub>2</sub> blockers, sulfa drugs, furosemide, captopril, digoxin, and β-lactam antibiotics are all associated with thrombocytopenia.
  - Never forget HIT (see the discussion of Clotting Disorders below).
- Further testing and evaluation:
  - Consider bone marrow biopsy if other findings suggest marrow dysfunction (eg, pancytopenia).
  - Antiplatelet antibody testing generally should never be sent—not sensitive nor specific for diagnoses such as idiopathic thrombocytopenic purpura (ITP). **Exception:** The specific antiplatelet factor 4 antibody is useful to diagnose HIT.
  - If no other cause identified, ITP is the diagnosis of exclusion.



#### KEY FACT

Acute chest syndrome should be treated with careful hydration, adequate analgesics, O<sub>2</sub>, and either transfusion to a hemoglobin of 10 g/dL or exchange transfusion if the hemoglobin is already ≥10 g/dL. In addition, antibiotics to cover for *S pneumoniae*, *H influenzae*, *Neisseria*, *M pneumoniae*, and *C pneumoniae* should be administered.



#### QUESTION 1

A 30-year-old woman with sickle cell disease presents with left-sided weakness. She has had many episodes of acute chest syndrome. Her medications include folic acid and hydroxyurea. MRI is consistent with an acute infarction in the right MCA territory. How would you prevent stroke in this patient?



#### QUESTION 2

A 65-year-old recently hospitalized woman returns to the hospital with right lower extremity DVT. During her last hospitalization, she was given low-molecular-weight heparin (LMWH). CBC shows a platelet count of 100,000/μL. She is given IV unfractionated heparin (UFH); 10 hours later, her platelet count drops to 20,000/μL. What is the most appropriate next step?

**KEY FACT**

In an otherwise healthy patient (no meds and tests for HIV, HCV, HIV, HCV, SLE, and CLL are  $\ominus$ ) who presents with mucosal bleeding and has isolated thrombocytopenia on CBC, normal coagulation tests, and a normal blood smear (except for a paucity of platelets), suspect ITP.

**KEY FACT**

Not all thrombocytopenia results in bleeding. Antiphospholipid antibody syndrome and HIT are conditions in which platelet count is low but the patient is at risk of clotting.

**TABLE 9.12. Causes of Thrombocytopenia**

CAUSE	EXAMPLES
$\uparrow$ destruction	<b>Immune thrombocytopenia:</b> <ul style="list-style-type: none"> <li>■ <b>1°:</b> Autoimmune (ITP)</li> <li>■ <b>2°:</b> Lymphoid malignancies, HIV, SLE, alloimmunization from prior platelet transfusions</li> <li>■ <b>Drug induced:</b> Gold, abciximab, ticlopidine, quinine, heparin</li> <li>■ <b>Post-transfusion purpura</b></li> </ul> <b>Microangiopathies:</b> <ul style="list-style-type: none"> <li>■ TTP, HUS, eclampsia</li> <li>■ DIC, sepsis</li> <li>■ Severe hypertension</li> </ul> <b>Mechanical:</b> <ul style="list-style-type: none"> <li>■ Artificial heart valves</li> <li>■ Hemangiomas</li> <li>■ Central venous catheters</li> </ul> <b>Hypersplenism</b>
$\downarrow$ production	Essentially any cause of marrow suppression can produce thrombocytopenia in isolation. See the pancytopenia discussion below Probably the most important is drug-induced thrombocytopenia
Other	<b>Dilutional:</b> From massive blood transfusions and fluid resuscitation <b>Pseudothrombocytopenia:</b> From platelet clumping

**Management**

- Treat underlying cause.
- Platelet transfusions in the absence of bleeding are usually unnecessary. Specific guidelines are given in the discussion of transfusion medicine. Platelet transfusions are **contraindicated** in TTP/HUS and HIT.

**A****ANSWER 1**

Exchange transfusion targeting sickle Hb <30% acutely and 30%-50% chronically without allowing Hb >11 g/dL is an appropriate means of preventing stroke in adults with sickle cell disease.

**A****ANSWER 2**

Stop UFH and initiate a direct thrombin inhibitor (eg, argatroban). Heparin-induced thrombocytopenia (HIT) classically occurs 5 to 10 days after initial heparin exposure but may be delayed up to 3 months; reexposure can result in a more rapid  $\downarrow$  in platelet count, as in this case.

**EOSINOPHILIA**

- Eosinophilia is defined as an absolute eosinophil count of  $>0.5 \times 10^9/L$ . May be primary (idiopathic) or secondary.
- **Idiopathic hypereosinophilia syndrome:**
  - Extremely rare and heterogeneous. May be associated with the activating mutation of PDGFR.
  - A prolonged eosinophilia of unknown cause with the potential to affect multiple organs by eosinophil infiltration.

**TABLE 9.13. Associated Peripheral Smear Findings and Possible Etiologies of Thrombocytopenia**

ASSOCIATED PERIPHERAL SMEAR FINDINGS	POSSIBLE ETIOLOGY
Schistocytes	Microangiopathic hemolytic anemia
Spherocytes	Autoimmune hemolysis
Leukopenia and anemia	Bone marrow failure (ie, MDS)
Leukocytosis	Leukemia
Teardrop cells	Myelofibrosis

- Almost all cases have bone marrow infiltration, but heart, lung, and CNS involvement predicts a worse outcome.
- Some cases are treatable with imatinib mesylate (Gleevec) or corticosteroids.
- 2° eosinophilia:** Remember the mnemonic NAACP.

## PANCYTOPENIA

Pancytopenia almost always represents ↓ or ineffective bone marrow activity. Differentiated as follows:

- Intrinsic bone marrow failure:** Aplastic anemia, myelodysplasia (Figure 9.8A), acute leukemia (Figure 9.8B), myeloma, drugs (chemotherapy, chloramphenicol, sulfonamides, antibiotics).
- Infectious:** HIV, post-hepatitis, parvovirus B19 (Figure 9.8C).
- Marrow infiltration** (Figure 9.8D): TB, disseminated fungal infection (especially coccidioidomycosis and histoplasmosis), metastatic malignancy.
- Nutritional deficiency:** B<sub>12</sub>, copper, or folate deficiency (Figure 9.8E).
- Diagnosis:** Peripheral smear morphology is often helpful (Figures 9.4 and 9.8).



## MNEMONIC

### Causes of 2° eosinophilia—NAACP

**NAACP**

- Neoplastic
- Asthma/Allergic
- Addison disease
- Collagen vascular disease
- Parasites

## NEUTROPENIA

Neutropenia is defined as an absolute neutrophil count of  $<1.5 \times 10^9/L$  ( $<1.2 \times 10^9/L$  in African Americans). Causes are outlined in Table 9.14.



## KEY FACT

The most common medication causes of neutropenia or agranulocytosis are NSAIDs, carbamazepine, phenytoin, PTU, cephalosporins, and TMP-SMX.

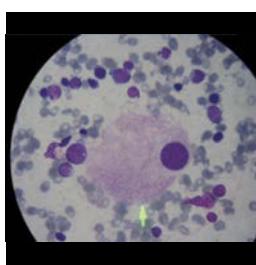
## Bone Marrow Failure Syndromes

### APLASTIC ANEMIA

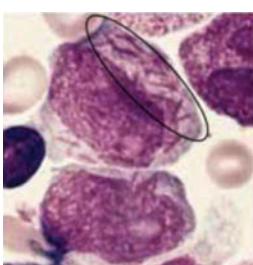
Marrow failure with hypocellular bone marrow and no dysplasia. Typically seen in young adults or elderly patients. Subtypes are: **autoimmune (1°) aplastic anemia—the most common type**—diagnosed when 2° causes have been ruled out, and **2° aplastic anemia**. Causes of 2° aplastic anemia include:

- Toxins:** Benzene, toluene, insecticides.
- Drugs:** Such as gold, chloramphenicol, clozapine, sulfonamides, tolbutamide, phenytoin, carbamazepine, allopurinol; post-chemotherapy or radiation.

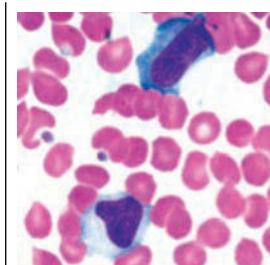
### WBC Form



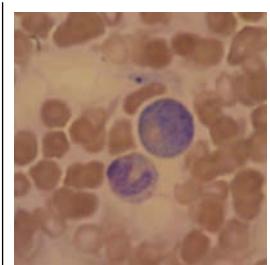
Hypolobulated megakaryocytes (A)



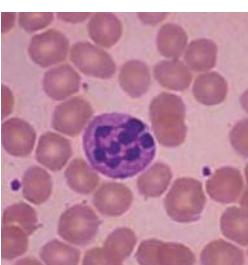
Auer rods (B)



Atypical lymphocytes (C)



Toxic granulations (D)



Hypersegmented neutrophil (E)

### Associated Conditions

Myelodysplasia, congenital

AML

Mononucleosis, toxoplasmosis, CMV, HIV

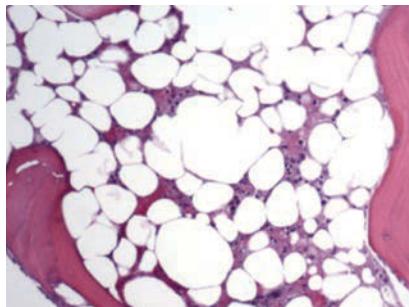
Infections, sepsis

B<sub>12</sub> or folate deficiency

**FIGURE 9.8. Summary of Peripheral Smear Morphology—WBCs.** (Image A reproduced from Acar H, et al. A pediatric myelodysplastic syndrome with chromosome 5q deletion. *J Can Epi Treat*. 2015;1(2):1-4; image B reproduced with permission from USMLE-Rx.com; courtesy of Dr. Robert W. Novak; image C reproduced with permission from USMLE-Rx.com; courtesy of Ed Uthman, MD; image D reproduced from Wikimedia Commons; and image E reproduced with permission from USMLE-Rx.com.)

**KEY FACT**

Suspect aplastic anemia in an otherwise healthy young adult with pancytopenia, no blasts on peripheral smear, and a hypocellular bone marrow. Take a careful history for meds and exposures, and send tests for viruses. For idiopathic aplastic anemia, consider antithymocyte globulin and cyclosporine or allogeneic bone marrow transplant.

**FIGURE 9.9. Aplastic anemia.**

Markedly hypocellular bone marrow (predominantly fat) with rare hematopoietic precursor cells but no atypical cells in a 60-year-old man with pancytopenia. (Reproduced with permission from USMLE-Rx.com.)

**KEY FACT**

Immunosuppressive therapy with antithymocyte globulin and cyclosporine is effective in reducing transfusion requirements in >70% of patients with aplastic anemia.

**KEY FACT**

In a patient with isolated hypoproliferative anemia without another obvious cause, consider pure red cell aplasia, most commonly from parvovirus B19, thymoma (as seen in myasthenia gravis), HIV, SLE, and lymphoma/CLL.

**TABLE 9.14. Causes of Neutropenia**

IMPAIRED PRODUCTION	↑ DESTRUCTION
Cytotoxic chemotherapy and other drugs	Autoimmune neutropenia
Aplastic anemia and other causes of marrow failure	Felty syndrome (RA + splenomegaly + neutropenia)
Congenital	Sepsis
Cyclic neutropenia	HIV
	Acute viral illness
	Rickettsial infection

- **Viral infections:** Post-hepatitis syndrome, parvovirus B19, HIV, CMV, EBV.
- **Other:** PNH, pregnancy.
- **Symptoms/Exam:** Presents with symptoms of pancytopenia (fatigue, bleeding, infections). Adenopathy and splenomegaly generally not seen.
- **Diagnosis: Look for pancytopenia and markedly ↓ reticulocytes:**
  - Peripheral smear is bland—pancytopenia without dysplastic changes.
  - Bone marrow is hypocellular without dysplasia (Figure 9.9).
- **Management:** Supportive care as necessary (transfusions, antibiotics). Hematopoietic growth factors are ineffective.
- **1° aplastic anemia:**
  - Definitive treatment is allogeneic bone marrow transplantation.
  - Antithymocyte globulin and cyclosporine are first-line medications.
- **2° aplastic anemia:** Treat by correcting the underlying disorder.

**PURE RED CELL APLASIA**

Pure red cell aplasia is a rare bone marrow failure in erythroid lineage only, characterized by anemia with severely reduced reticulocytes, but other cell lineages normal. Classic associations include: **thymoma**, CLL, HIV, SLE, RA, **parvovirus B19**, and **anti-erythropoietin antibodies**.

- **Diagnosis:** If the cause is not obvious, obtain parvovirus B19 serology, or PCR, and chest CT to look for thymoma. Bone marrow biopsy will show characteristic giant pronormoblasts in parvovirus B19 infection.
- **Management:** Treat any underlying conditions (eg, remove thymoma if present or stop offending drug). Initial treatment is supportive transfusion and prednisone. If no response, consider addition of cyclosporine or IVIG.

**MYELODYSPLASTIC SYNDROME**

Myelodysplastic syndrome (MDS) is a clonal stem cell disorder that results in ineffective hematopoiesis and cytopenias and exists on a continuum with acute leukemia. **Eighty percent of patients are >60 years of age.** MDS that arises in a patient previously treated with myelotoxic drugs carries higher risk of evolving into AML. Other prognostic features include percentage of blasts, cytogenetics, and the number of cytopenias.

- **Symptoms:** Related to those of cytopenias.
- **Differential:** See section on pancytopenia for causes of cytopenias that need to be excluded before making a diagnosis of MDS.

- Diagnosis:** Peripheral smear and bone marrow may show dysplasia in all three lines:
  - RBCs: Macrocytosis, macro-ovalocytes.
  - WBCs: Hypogranularity, hypolobulation (pseudo-Pelger-Huët).
  - Platelets: Giant or hypogranular.
- Cytogenetics from bone marrow can be normal or abnormal.
- Management:** No survival benefit of treating asymptomatic patients. Treatment is indicated for symptomatic anemia or thrombocytopenia or for recurrent infections secondary to neutropenia. Therapies include transfusions as well as chemotherapy with hypomethylating agents (azacytidine or decitabine) or lenalidomide, or bone marrow transplantation (for younger patients).

## Myeloproliferative Syndromes

Myeloproliferative syndromes are characterized by **clonal ↑ of bone marrow RBCs, WBCs, platelets, or fibroblasts**. Each is defined by the cell lineages predominantly affected. Syndromes have **considerable clinical overlap**—unusual thrombosis, splenomegaly, constitutional symptoms—and variable association with JAK2, a tyrosine kinase, and all carry potential risk of progressing to AML. Table 9.15 compares the various myeloproliferative syndromes.

### ERYTHROCYTOSIS

Erythrocytosis is categorized as 1° (polycythemia vera) or 2° (reactive). Causes of 2° erythrocytosis are listed in Table 9.16.

- Diagnosis:**
  - Hemoglobin >18.5 g/dL in men, >16.5 g/dL in women. Blood volume studies are “gold standard,” but rarely performed.
  - Exclude obvious causes of 2° erythrocytosis (see Table 9.16).
  - Best first test** is serum erythropoietin. Levels should be low to normal in polycythemia vera. **JAK2** mutations are present in 95%-100% of polycythemia vera. See Table 9.17 for additional tests to consider.
  - Note that in patients with chronic hypoxemia (eg, COPD patient), O<sub>2</sub> saturation <92% is sufficient to cause erythrocytosis.
  - Low erythropoietin levels suggest polycythemia vera, but not perfectly sensitive nor specific.
  - Low ferritin and high B<sub>12</sub>/folate levels are associated with polycythemia vera and not with 2° erythrocytosis.
- Management:** No specific treatment of 2° erythrocytosis is necessary, but may need to treat underlying cause (eg, RCC). The treatment of polycythemia vera is covered in the following section.

TABLE 9.15. Differentiation of Myeloproliferative Disorders

	WBC COUNT	HEMATOCRIT	PLATELETS	RBC MORPHOLOGY	COMMENTS
Polycythemia vera	Normal or ↑	↑	Normal or ↑	Normal	JAK2 + in 95%-100% of cases
CML	↑	Normal or ↓	Normal or ↑	Normal	Philadelphia chromosome or BCR-ABL + in >95% of cases
Myelofibrosis	Variable	Usually ↓	Variable	<b>Abnormal</b>	JAK2 + in 40%-60% of cases <sup>a</sup>
Essential thrombocythemia	Normal or ↑	Normal	↑	Normal	JAK2 + in 50%-60% of cases <sup>a</sup>

<sup>a</sup> In JAK2-negative myelofibrosis or essential thrombocythemia, nearly all will be positive for CALR or MPL, which are useful in making the diagnoses.

### KEY FACT

Patients with MDS may present with cytopenias of one, two, or all three cell lines, but isolated macrocytic anemia is most common.

### KEY FACT

**5q deletion syndrome** is a subset of MDS primarily occurring in older women associated with a deletion of the long arm of chromosome 5. The disorder is associated with better prognosis and response to treatment with lenalidomide.

### KEY FACT

In a patient with an ↑ hematocrit who is not dehydrated or hypoxic, a low erythropoietin level is suggestive, but not diagnostic, of polycythemia vera.

### QUESTION

A 70-year-old man presents to his 1° care physician with fatigue. CBC reveals a normal WBC and platelet count, but his Hb level is 8.5 mg/dL with an MCV of 102 fL. He takes no medications or alcohol, and his B<sub>12</sub> and folate levels are normal. What is the most likely diagnosis?

**KEY FACT**

Erythromelalgia presents as erythema, warmth, and pain in the distal extremities, typically after a hot bath. It is often associated with polycythemia vera, and ASA relieves the symptoms.

**FIGURE 9.10. Cutaneous erythromelalgia of polycythemia vera.**

**vera.** A 77-year-old woman with long-standing polycythemia vera experienced increasingly prolonged bouts of redness, swelling, and burning pain in her hand (shown on right) and other extremities. (Reproduced from Herbert L. Fred, MD and Hendrik A. van Dijk. Images of Memorable Cases: Case 151. OpenStax CNX. Dec 4, 2008.)

**ANSWER**

Myelodysplasia, which commonly presents as isolated macrocytic anemia in older adults.

**KEY FACT**

To diagnose polycythemia vera, you must have at a minimum an ↑ hemoglobin level (or RBC mass) **and** no other cause of 2° erythrocytosis. In polycythemia vera, JAK2 is almost always  $\oplus$ , and erythropoietin levels are low.

**KEY FACT**

The JAK2 mutation is seen in all myeloproliferative disorders but is most strongly associated with polycythemia vera.

**TABLE 9.16. Causes of 2° Erythrocytosis**

TYPE	ETIOLOGY
Congenital	High-affinity hemoglobin, congenitally low 2,3-DPG, autonomous high erythropoietin
Arterial hypoxemia	Smokers, high altitude, cyanotic heart disease, COPD, sleep apnea
Renal lesions	Renal tumors, renal cysts, hydronephrosis, renal artery stenosis
Liver lesions	Hepatoma, hepatitis
Tumors	RCC is most common erythropoietin-secreting tumor
Medications	Androgens, surreptitious erythropoietin

**POLYCYTHEMIA VERA**

Polycythemia vera is defined as an abnormal ↑ in all blood cells, predominantly RBCs. The most common of the myeloproliferative disorders, it shows no clear age predominance.

**Symptoms/Exam**

- Splenomegaly is common.
- Symptoms due to higher blood viscosity and expanded blood volume: dizziness, headache, tinnitus, blurred vision, pruritus, and plethora.
- Look for pruritus following warm shower (“aquagenic pruritus”).
- **Erythromelalgia** (Figure 9.10) is frequently associated with polycythemia vera and is characterized by erythema, warmth, and pain in the distal extremities. May progress to digital ischemia. Treatment is ASA.

**Diagnosis**

- Exclude 2° erythrocytosis (see the Erythrocytosis section in this chapter). Evaluate serum erythropoietin and JAK2 mutation status. If erythropoietin level is normal/high and JAK2 negative → PV excluded (see Table 9.17).
- A mutation of **JAK2** is found in 95% to 100%.
- Bone marrow aspirate and biopsy with cytogenetics usually not needed.
- Hemoglobin >18.5 g/dL in men, >16.5 g/dL in women, or other evidence of ↑ red cell volume.
- Low erythropoietin level.

**Management**

- No treatment clearly affects the natural history of the disease, so treatment should be aimed at controlling symptoms.
- All patients should take low-dose (81-mg) ASA unless contraindicated.

**TABLE 9.17. Evaluation of Erythrocytosis**

LABS	IMAGING
Arterial O <sub>2</sub> saturation	RBC mass
Ferritin, B <sub>12</sub> , folate, creatinine, LFTs, uric acid	Abdominal ultrasound or CT scan
Serum erythropoietin	
JAK2 mutation	

- Those without active thromboses and not at risk for thrombosis (age <60 years and no prior thromboses) should receive therapeutic **phlebotomies** with goal hematocrit <45% in men, <42% in women. Patients should not receive Fe supplementation.
- Those at high risk for thrombosis (age >60 years or prior thromboses) should receive **both** phlebotomy as well as hydroxyurea.
- Allopurinol may be added if uric acid is elevated.

### Complications

Predisposes to both clotting (stroke, DVT, Budd-Chiari) and bleeding; may progress to myelofibrosis or acute leukemia.

## CHRONIC MYELOGENOUS LEUKEMIA

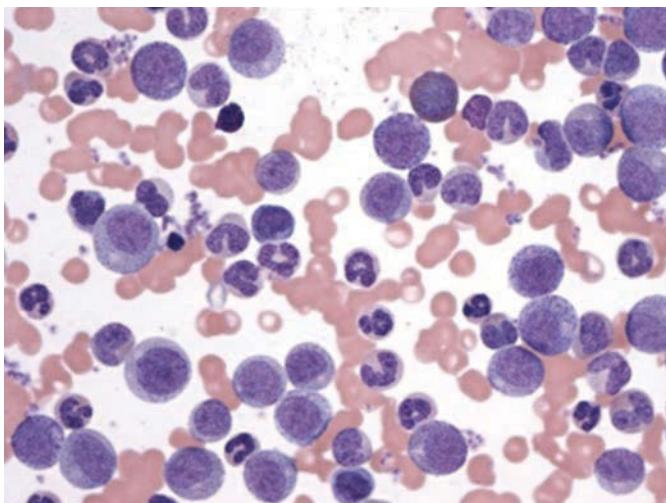
Chronic myelogenous leukemia is an excessive accumulation of neutrophils defined by chromosomal translocation **t(9;22)**, the **Philadelphia chromosome**, producing the fusion protein **BCR-ABL**. Ionizing radiation is the only known risk factor.

### Symptoms/Exam

- Most commonly asymptomatic with ↑ in WBC count or with nonspecific fatigue, night sweats, and hepatosplenomegaly.
- **Leukostasis syndrome** includes visual disturbances, headache, dyspnea, MI, TIA/CVA, and priapism, which are typically seen when the **WBC count is >300,000/µL** (but may occur at lower WBC counts in AML).

### Diagnosis

- Markedly ↑ neutrophil count (~100K).
- **Basophilia** usually present. Eosinophilia and thrombocytosis may also be seen (Figure 9.11).
- The **Philadelphia chromosome** is present in 90% to 95% of cases. Detectable by cytogenetics or by PCR for the BCR-ABL fusion gene, performed on peripheral WBCs.



**FIGURE 9.11. Chronic myelogenous leukemia.** Peripheral blood smear of a 60-year-old man with a WBC count of 150,000/µL demonstrates markedly ↑ WBCs and large numbers of immature myeloid forms, including metamyelocytes, myelocytes, and promyelocytes, as well as a large number of eosinophils and basophils. (Reproduced with permission from USMLE-Rx.com.)



### KEY FACT

CML is associated with the Philadelphia chromosome, t(9;22), in 90% to 95% of cases. First-line treatment is generally imatinib, a tyrosine kinase inhibitor that targets BCR-ABL—the unique gene product of the Philadelphia chromosome.



### QUESTION

A 75-year-old man presents with headache and blurred vision of one week's duration. Neurologic exam, including visual acuity, is normal, and remaining physical findings are unremarkable except for mild splenomegaly. Labs show a WBC count of 322,000/µL, with 85% neutrophils, 7% lymphocytes, 5% basophils, and 3% blasts; Hb level, 12 g/dL; and platelet count, 400,000/µL. The BCR-ABL fusion gene is detected by PCR. What treatment would rapidly ↓ this patient's WBC count?

### Management

- An appropriate tyrosine kinase inhibitor either with the first-generation imatinib or later generation drugs dasatinib or nilotinib (many will be started on a second-generation drug as initial treatment). They are all highly effective and when to use/how to sequence is debated. After 5 years, >80% of patients remain in cytogenetic remission. If resistance develops, can change to another tyrosine-kinase inhibitor with good response. Other treatment options:
  - Only curative therapy is allogeneic HSCT.
  - Hydroxyurea can be used as temporizing therapy to ↓ WBC count.
- The disease progresses through three phases based on the percentage of blasts in peripheral blood:
  - **Chronic phase:** Bone marrow and circulating blasts <10%.
  - **Accelerated phase:** Bone marrow or circulating blasts 10% to 20%.
  - **Blast crisis:** Bone marrow or circulating blasts ≥20%.
- Treatment goal regardless of phase is remission. Accelerated phase and blast phase typically involve consideration of allogeneic HSCT.

### NEUTROPHILIA

- Neutrophilia is defined as an absolute neutrophil count of  $>10 \times 10^9/L$ . The main distinction to be made is between myeloproliferative disorders (**typically CML**) and reactive neutrophilia.
- Reactive neutrophilia usually readily apparent from the history (inflammation, infection, severe burns, glucocorticoids, epinephrine) and from examination of a peripheral smear (Döhle bodies, toxic granulations).

### MYELOFIBROSIS (AGNOGENIC MYELOID METAPLASIA)

Fibrosis of bone marrow leading to **extramedullary hematopoiesis**—marked splenomegaly; bizarre peripheral blood smear—is known as myelofibrosis (agnogenic myeloid metaplasia). Affects adults  $>50$  years of age and can be due to marrow insults, including other myeloproliferative disorders, radiation, toxins, and metastatic malignancies.

- **Symptoms/Exam:** Characterized by symptoms of cytopenias. Fatigue and bleeding are especially common. Abdominal fullness due to **massive splenomegaly** and hepatomegaly.
- **Diagnosis:**
  - CBC shows individual cytopenias or **pancytopenia**.
  - Peripheral smear reveals **teardrop cells**, immature WBCs, nucleated RBCs, and giant degranulated platelets.
  - The presence of the JAK2 mutation is not part of the diagnostic criteria but strongly supports the diagnosis.
  - Bone marrow aspirate is frequently a **dry tap** (**no aspirate can be obtained**); biopsy shows marked fibrosis (Figure 9.12).
- **Management:** Mostly supportive with transfusions as necessary. Other treatments include:
  - Splenectomy or splenic irradiation provides no mortality benefit. Reserve for patients with painful spleen or if transfusion requirements are unacceptably high.
  - $\alpha$ -interferon or thalidomide are occasionally helpful. New agent, **ruxolitinib**, leads to improved symptoms and is favored up-front treatment, but has no overall survival benefit.
  - Allogeneic HSCT for selected patients.
- **Complications:** May evolve into AML with an extremely poor prognosis.



### ANSWER

Leukapheresis can lower WBC counts rapidly. This patient has underlying CML complicated by leukostasis, as evidenced by headache and visual changes, so treatment with imatinib also should be initiated.

## ESSENTIAL THROMBOCYTHEMIA

Essential thrombocythemia is a clonal disorder with ↑ platelet counts and a tendency toward thrombosis and bleeding. Indolent course with **median survival of >15 years**.

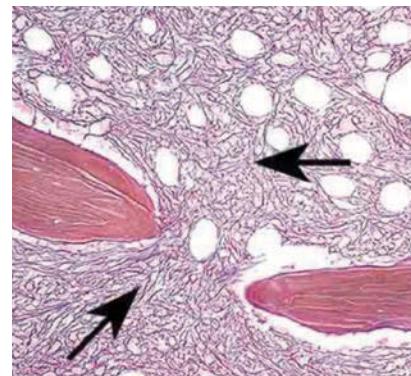
- **Symptoms/Exam:** Usually asymptomatic at presentation, but occasionally presents with symptoms of small vessel occlusion (headache, vision change, erythromelalgia—painful swelling of the extremities often induced by a warm bath) or arterial or venous thrombosis (stroke, MI, miscarriage, DVT).
- **Diagnosis:** Primarily a **diagnosis of exclusion**:
  - **First rule out 2° causes of thrombocytosis** (see Thrombocytosis section in this chapter).
  - Diagnosed by a persistent platelet count of  $>600,000/\mu\text{L}$  with no other cause of thrombocytosis.
  - 50% of essential thrombocythemia are  $\oplus$  for JAK2.
  - Bone marrow biopsy should be performed to make the diagnosis as there are forms of MDS that can present with high platelet counts.
- **Management:**
  - All patients should receive ASA.
  - High-risk patients (age  $>60$  years or history of thromboses) should receive cytoreductive therapy with hydroxyurea or anagrelide.
  - Consider plateletpheresis for elevated platelets with severe bleeding or clotting.
- **Complications:**
  - Blood clots.
  - Bleeding may occur secondary to induced **von Willebrand disease** (vWD) due to consumption of vWF when platelet counts are  $>1000\text{K}$ .
  - ~5% lifetime risk of AML conversion. May also convert to myelofibrosis.

## THROMBOCYTOSIS

Thrombocytosis is defined as a platelet count of  $>450 \times 10^9/\text{L}$ . The main distinction is **reactive thrombocytosis** versus a primary bone marrow disorder such as a **myeloproliferative disorder**. The steps involved in the evaluation of thrombocytosis are outlined in Table 9.18.

**TABLE 9.18. Evaluation of Thrombocytosis**

STEPS IN EVALUATION	COMMENTS
Repeat CBC and examine peripheral smear	↑ platelet count may be spurious or transient; clues to reactive thrombocytosis may be present.
Stratify by degree of thrombocytosis	Platelet count of $<600,000/\mu\text{L}$ is unlikely to be essential thrombocythemia. Platelet count of $>1000\text{K}$ is less likely to be reactive thrombocytosis, but many "platelet millionaires" still have reactive thrombocytosis.
Identify causes of reactive thrombocytosis	Iron deficiency anemia, RA, IBD, infection or inflammatory states, postsplenectomy, active malignancy, sideroblastic anemia.
Rule out other myeloproliferative syndromes	Consider testing for the JAK2 mutation for essential thrombocythemia. BCR-ABL by PCR in CML. Characteristic peripheral smear and splenomegaly in myelofibrosis.
Consider a bone marrow biopsy	Megakaryocyte morphology can suggest essential thrombocythemia. Examination for myelodysplasia, sideroblasts.



**FIGURE 9.12. Myelofibrosis.** Bone marrow core biopsy demonstrating marked fibrosis (arrows). (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Ed Uthman, MD.)

### KEY FACT

Don't be tricked: The most common causes of thrombocytosis are iron deficiency and infection, and a  $\ominus$  JAK2 does not exclude essential thrombocythemia.

### KEY FACT

The most common cause of 2° thrombocytosis is iron deficiency anemia.

**KEY FACT**

Patients with acute leukemias can present with **leukostasis**, which occurs with very high blast counts (typically  $>100,000/\mu\text{L}$ ). Rigid blasts clog the microcirculation, leading to local hypoxemia, which most often causes CNS and pulmonary symptoms. It is considered an oncologic emergency and is treated with hydroxyurea and/or leukapheresis.

**KEY FACT**

In adults, CLL is the most common leukemia, and AML is more common than ALL.

**KEY FACT**

In patients with ALL, CNS prophylaxis with intrathecal chemotherapy is always mandatory regardless of CNS involvement at time of diagnosis. Majority will develop CNS involvement without intrathecal chemotherapy prophylaxis.

**KEY FACT**

Poor prognostic factors in ALL include ↑ age, t(4;11) (the MLL gene), t9;22 (BCR-ABL gene), deletion of chromosome 7, or trisomy 8.

**KEY FACT**

M4 and M5 AML commonly present with infiltration of the bones of the orbits, sinuses, maxilla (gingival changes), and jaw (numb chin).

**KEY FACT**

Key steps in the treatment of AML are to induce remission and then to continue consolidation with further chemotherapy.

## Acute Leukemias

Most common genetic disorders associated with acute leukemia are Down syndrome and Fanconi anemia. Risk factors include chemical exposure (eg, benzene, petroleum products), hair dyes, smoking, and prior chemotherapy or radiation.

- **Symptoms/Exam:** Signs and symptoms include bone pain, symptoms of pancytopenia (fatigue due to anemia, infection due to leukopenia, and bleeding due to thrombocytopenia), evidence of leukemic infiltration such as gingival hyperplasia in M4 and M5 AML or sinus headaches from maxillary bone involvement.

**Diagnosis:**

- CBC with differential and peripheral smear to identify blasts.
- Bone marrow biopsy to evaluate for blasts. Include immunohistochemistry, cytogenetic evaluation (used to group patients into favorable, intermediate, and unfavorable prognoses), and flow cytometry.
- PT, PTT, D-dimer, and fibrinogen to evaluate for DIC, especially high risk in promyelocytic (M3) AML.
- Uric acid, LDH, potassium, creatinine, phosphorus, and calcium to evaluate for tumor lysis.

### ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) may be either B-cell (75%) or T-cell lineage. For T-cell ALL, test for human T-cell leukemia virus (HTLV-1), which is endemic to southern Japan, the Caribbean, the South Pacific, and sub-Saharan Africa. The Philadelphia chromosome, t(9;22), is common and portends a poor prognosis. Adult ALL is more aggressive and less curable than childhood ALL.

- **Management: Combination chemotherapy**—multiple, complicated regimens used. One example includes cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (hyper-CVAD).

**General treatment principles:**

- Initial induction chemotherapy given to restore normal bone marrow and attain complete remission. Significant risk of tumor lysis syndrome during induction (see Tumor Lysis Syndrome under Oncologic Emergencies in the Oncology chapter).
- Without further therapy, most patients will relapse after short period. Goal of post-induction treatment is to eliminate any residual disease.
- Post-remission treatment options include consolidation chemotherapy followed by maintenance therapy, and/or allogeneic HSCT.
- **CNS prophylaxis with intrathecal chemotherapy is mandatory for all patients** regardless of CNS involvement (systemic chemotherapy does not sufficiently penetrate the blood-brain barrier).

### ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia is more common than ALL in adults. Incidence ↑ with age. **Idiopathic AML**, the most common subtype, carries a better prognosis than **treatment-related AML** (which results from prior anticancer therapy such as alkylating agents or topoisomerase inhibitors) or **2° AML** arising from prior MDS.

- **Diagnosis:** Made by bone marrow biopsy with  $>20\%$  marrow blasts. Multiple subtypes, but most useful distinction is between acute promyelocytic versus all other AMLs.

**Management:**

- Induction chemotherapy typically consists of cytarabine plus an anthracycline, so-called “7 + 3” for the typical number of days over which the cytarabine and anthracycline, respectively, are given. Goal is complete remission.

Moderate-high risk of tumor lysis syndrome during induction (see Tumor Lysis Syndrome under Oncologic Emergencies in the Oncology chapter).

- Consolidation therapy dependent upon risk of relapse. High-risk genetics include del(5q), del(7q), and complex abnormal karyotypes. Those with unfavorable risk do best with allogeneic HSCT.
- High risk of infection during induction chemotherapy requires close monitoring and protective isolation while neutropenic (see Neutropenic Fever under Oncologic Emergencies in the Oncology chapter).

### ACUTE PROMYELOCYTIC LEUKEMIA

Acute promyelocytic leukemia (AML-M3, APL) is characterized by heavily granulated promyelocytic blasts (Figure 9.13); associated mutation t(15;17) involving the retinoic acid receptor. DIC often present at time of diagnosis or occurs following start of chemotherapy. High rate of early mortality, but has highest cure rate of AML.

- **Management:** Start *all-trans* retinoic acid (ATRA) as soon as diagnosis is suspected given high mortality rate. ATRA causes terminal differentiation of malignant promyelocytes into mature neutrophils. Treatment course unique from other AML:
  - Induction regimens include ATRA combined with anthracycline plus cytarabine or arsenic trioxide.
  - QTc monitoring required while on arsenic trioxide.
  - Consolidation and maintenance regimens include ATRA plus chemotherapy.
  - **Retinoic acid syndrome** (aka “differentiation syndrome”) is characterized by pulmonary infiltrates, respiratory failure, fever, capillary leak syndrome, and cardiovascular collapse. Treat early with high-dose corticosteroids and temporary cessation of ATRA.

## Chronic Leukemias

### CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia is discussed earlier in this chapter under Myeloproliferative Syndromes.

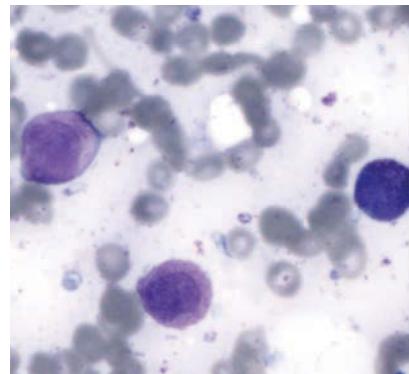
### CHRONIC LYMPHOCYTIC LEUKEMIA

Abnormal accumulation of morphologically mature-appearing lymphocytes with a characteristic immunophenotype (CD5 $\oplus$  CD20 $\oplus$ , and CD23 $\oplus$  B cells) in the blood, bone marrow, or lymphatic tissues. The most common leukemia in adults. Median survival is 10 to 15 years. **Autoimmune phenomena are common.**

- **Symptoms/Exam:** Often identified in the early stage of disease by an  $\uparrow$  lymphocyte count, flow cytometry, and **smudge cells** on peripheral blood smear (Figure 9.14).
- Most patients are asymptomatic.
- Evaluate for lymphadenopathy, cytopenias, organomegaly, flow cytometry of peripheral blood, and bone marrow biopsy (not always done).
- **Evans syndrome** is common in CLL and involves autoimmune hemolytic anemia and thrombocytopenia (ITP).
- Course tends to be very indolent with slow disease progression over many years.
- Progression of CLL is marked by generalized lymphatic and/or splenic enlargement with concomitant pancytopenia. Major causes of death: complications of pancytopenia (ie, hemorrhage or infection)
- **Management:** Treatment is not curative, but relieves symptoms. Thus, **patients who are not symptomatic are generally not treated.** Indications for treatment:
  - Disease-related symptoms.

### KEY FACT

Induction chemotherapy for AML is a high-risk time for the development of tumor lysis syndrome when WBC  $\geq 100K$ .



**FIGURE 9.13. Acute promyelocytic leukemia.** Note the Auer rod present in the cytoplasm of promyelocytes in bone marrow biopsy specimen. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

AML-M3 is unique among AMLs for its propensity to cause DIC and for its high curability when treated with ATRA.

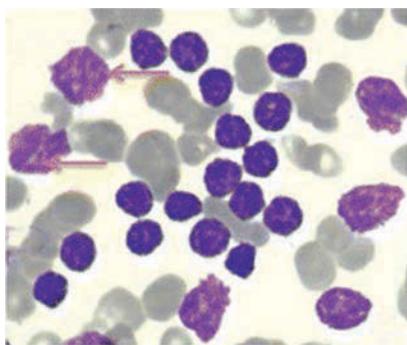
### KEY FACT

Anemia in CLL may be due to warm-antibody autoimmune hemolysis. A direct antiglobulin test (direct Coombs test) is typically  $\oplus$ .



### QUESTION

A 60-year-old woman with myelodysplastic syndrome diagnosed 1 year ago has worsening fatigue, fever, and epistaxis. She has been receiving intermittent blood transfusions, no platelet transfusions. Temperature is 38°C (100.5°F). Exam reveals dried blood around the nares as well as numerous ecchymoses and petechiae, particularly on the extremities. No abdominal tenderness, splenomegaly, or lymphadenopathy. Labs show a Hb, 6.5 g/dL; leukocyte count, 2000/ $\mu$ L; and platelet count, 6000/ $\mu$ L. Peripheral blood smear shows 50% immature myeloid blasts and paucity of platelets. What is the most appropriate next step?



**FIGURE 9.14. Chronic lymphocytic leukemia.** Peripheral blood smear shows typical small lymphocytes, with hypermature clumped chromatin and scanty cytoplasm, and presence of smudge cells (arrows). (Reproduced from Sall A, et al. Characteristics of chronic lymphocytic leukemia in Senegal. *BMC Hematology*. 2016;16:10.)

#### KEY FACT

Treatment for CLL is not curative (rare exception is the younger patient who can receive allogeneic HSCT) and the natural history of CLL is generally indolent, so CLL patients who are not symptomatic are generally not treated.

#### KEY FACT

FNA is often inadequate for diagnosing Hodgkin disease because it does not allow the pathologist to see the lymph node. Excisional biopsy is preferred.

A

#### ANSWER

In addition to blood transfusion and bone marrow aspiration, initiate induction chemotherapy with cytarabine and anthracycline for AML. Severe pancytopenia and circulating myeloid blasts on peripheral smear suggest disease transformation to AML. Patients with AML arising from MDS have poorer response rates and disease-free survival rates than those with de novo AML.

- Rapidly progressive disease.
- Autoimmune hemolytic anemia.
- Thrombocytopenia, infection.
- Treatment options include alkylating agents (chlorambucil, cyclophosphamide), nucleoside analogs (bendamustine, fludarabine, cladribine, pentostatin), and monoclonal antibodies (rituximab, alemtuzumab), and the tyrosine kinase inhibitor ibrutinib. **Allogeneic HSCT**—the only potentially curative treatment for CLL—should be considered in young patients with CLL.
- **Complication: Richter transformation** occurs in 3% to 10% of patients; CLL transforms into a large-cell lymphoma, characterized by fever, a rising LDH, and rapid enlargement of nodal disease. Associated with a very poor prognosis even with treatment.

## Hodgkin Lymphoma

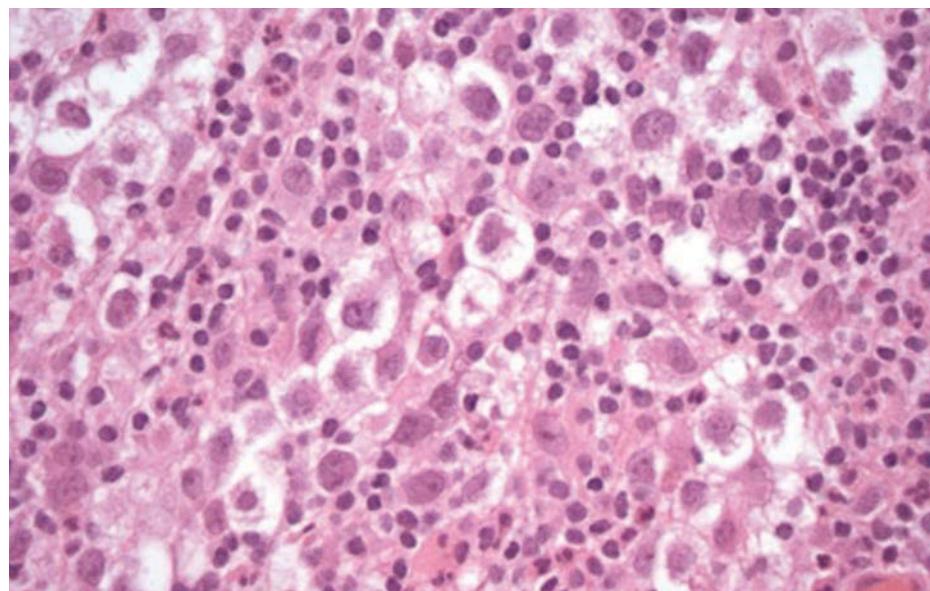
Hodgkin lymphoma has a bimodal age distribution. The malignant cell is the Reed-Sternberg cell (“owl-eye” cell).

#### Symptoms/Exam

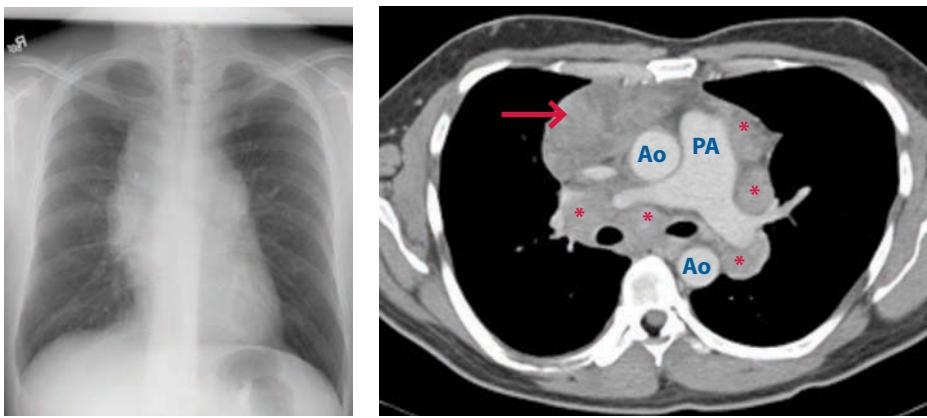
- Forty percent of patients present with systemic symptoms (B symptoms): weight loss, fever, and night sweats.
- Symptoms are also related to the site of involvement.

#### Diagnosis

- **Excisional biopsy** for architecture; FNA is not sufficient (Figure 9.15).
- Staging includes physical examination of lymph nodes; detection of hepatosplenomegaly; CXR and CT of the chest/abdomen/pelvis (Figure 9.16); and measurement of laboratory values, including CBC, LDH, ESR, and alkaline phosphatase.
- Routine staging laparotomy (splenectomy) has fallen out of favor.



**FIGURE 9.15. Nodular sclerosing Hodgkin lymphoma.** This is the most common form of Hodgkin lymphoma. The image shows a nodule containing abundant **lacunar cells** that have folded nuclei lying within a prominent clear space caused by retraction of the cytoplasm during processing of the tissue. (Reproduced with permission from USMLE-Rx.com.)

**A****B**

**FIGURE 9.16. Hodgkin lymphoma.** (A) Frontal CXR showing an abnormal mediastinal contour, with widening of the right paratracheal stripe and bilateral hilar enlargement. (B) Transaxial image from a follow-up contrast-enhanced CT demonstrates conglomerate lymphadenopathy in the anterior mediastinum (arrow) and multiple other enlarged lymph nodes (\*) in the mediastinum and right hilum. Ao = aorta; PA = main pulmonary artery.

(Reproduced with permission from USMLE-Rx.com.)

## Management

- **Early-stage disease (localized lymphadenopathy):**
  - Subtotal nodal irradiation or mantle irradiation.
  - Chemotherapy with ABVD (Adriamycin, bleomycin, vinorelbine, and dacarbazine) followed by radiation of the involved field. More than 75% of newly diagnosed disease is cured with combination chemotherapy ± radiation.
- **Advanced disease:** Combination chemotherapy with ABVD is standard. If the prognosis is unfavorable, the regimen can be escalated to BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, vinorelbine, procarbazine, prednisone).
- **Refractory or relapsed disease:** Patients with refractory disease should be considered for high-dose chemotherapy followed by autologous stem cell transplantation.

## Complications

Long-term complications include myelodysplasia and acute leukemia, 2° cancers (breast cancer in women treated with nodal irradiation), cardiomyopathy (due to doxorubicin), pulmonary toxicity (due to bleomycin), infertility, hypothyroidism, and neuropathy.

## Non-Hodgkin Lymphoma

A heterogeneous group of cancers of B and T cells. The incidence of NHL is ↑ for unknown reasons.

### Symptoms/Exam

Include B symptoms (weight loss, fever, night sweats) and symptoms referable to lymph node masses or extranodal masses.

### Diagnosis

- Diagnosis is based on histology, immunohistochemistry, and flow cytometry.
- Core needle biopsy and excisional biopsy are preferred.
- **Lumbar puncture (LP):** To evaluate for CNS involvement (cytology and flow cytometry) in patients with highly aggressive NHL (eg, Burkitt lymphoma, HTLV-1-



### QUESTION 1

A 35-year-old woman presents for follow-up 15 years after successful treatment for Hodgkin lymphoma with radiation therapy to the chest and abdominal lymph nodes. She never received combination chemotherapy, has never smoked, lacks any family history of cancer, and has no current medical problems. Her exam is normal. What is she at ↑ risk for developing in the future?



### QUESTION 2

A 35-year-old man presents with a rapidly enlarging 4-cm lump on the left side of his neck. He has had no fevers, night sweats, weight loss, recent illness, or any other significant history. The remainder of his exam is normal. CBC, chemistry, and LDH are all normal. Examination of the excised lymph nodes reveals CD20+ diffuse large B-cell lymphoma, an aggressive lymphoma. CT scans of the neck, chest, abdomen, and pelvis as well as a PET scan and bone marrow biopsy all confirm the absence of residual disease. What is the most appropriate treatment?

**KEY FACT**

In lymphomas that express CD20, treatment may include rituximab, a monoclonal antibody against CD20 B cells.

**KEY FACT**

Poor prognostic features in NHL include age >60 years, LDH >1x normal, poor performance status, late stage of disease, and extranodal disease.

**KEY FACT**

Marginal zone B-cell lymphoma is associated with HCV; treatment of the underlying infection may result in remission of the lymphoma.

**A****ANSWER 1**

Hodgkin lymphoma survivors who received extended-field radiation have a 1% risk per year of developing solid tumors. Young women are particularly prone to developing breast cancer, with a lifetime risk of >50% for a 20-year-old patient treated with mediastinal radiation therapy. CAD is also a risk if the heart was in the radiation field.

**A****ANSWER 2**

This patient has early-stage (IA) diffuse large B-cell lymphoma, an aggressive but highly curable type of non-Hodgkin lymphoma. It is considered systemic even when the results of CT and PET scans are  $\ominus$  and requires systemic therapy. The combination of the monoclonal antibody rituximab and CHOP, with or without radiation therapy, is curative for most patients. The disease would most likely recur without any further therapy.

associated T-cell leukemia/lymphomas); HIV-positive NHL; those with epidural, bone marrow, testicular, or paranasal sinus involvement; or those with at least two extranodal disease sites.

**Management**

- **CNS prophylaxis:** Can be considered for aggressive lymphomas warranting LP or MRI as outlined above, as CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisone) therapy has poor CSF penetration. Prophylactic modalities include intrathecal and/or IV cytarabine or methotrexate, cranial radiation, and/or IV rituximab.
- NHL can be roughly divided into three subtypes based on natural history:
  - **Low grade:** Indolent; demonstrates high response rates to chemotherapy, but **generally not curable**. Treatment is based on reducing symptoms. Median survival is 6 to 10 years.
  - **Intermediate grade:** Curable. The standard chemotherapy, CHOP, cures approximately half of all patients and is given in six to eight cycles of therapy. Evidence indicates that adding **rituximab**, an **anti-CD20 antibody** that targets B-cell lymphoma cells, **improves survival**.
  - **High grade:** Highly aggressive and rapidly growing cancers, but potentially **curable with chemotherapy**. Lymphoblastic lymphomas are treated like ALL. Burkitt lymphoma is associated with EBV in Africa. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive high-grade lymphoma in adults. There is a risk of tumor lysis syndrome with high-grade lymphomas, so initiate hydration, urinary alkalinization, and administration of a xanthine oxidase inhibitor before chemotherapy by way of prevention.
- **Important subtypes** are as follows:
  - **MALT lymphoma:** See the section under gastric cancer.
  - **Mantle cell lymphoma:** Acts like an intermediate-grade lymphoma in aggressiveness but is not curable with conventional chemotherapy (as with low-grade lymphoma). Median survival is 8-10 years.

**Important Translocations**

- **Burkitt lymphoma:** t(8;14).
- **Follicular lymphoma:** t(14;18).
- **Philadelphia chromosome:** t(9;22), CML and a subset of ALL.
- **Good-prognosis AML (M4-Eo):** inv16, and t8:21.
- **Acute promyelocytic leukemia:** t(15;17) retinoic acid receptor and promyelocytic leukemia gene.

**HIV and Cancer**

HIV is associated with an  $\uparrow$  incidence of NHL, anal cancer, cervical cancer, Kaposi sarcoma, and Hodgkin disease.

**Management:**

- **Kaposi sarcoma** is associated with **HHV-8** and is treated with HAART,  $\alpha$ -interferon, topical retinoids, localized radiation, or liposomal doxorubicin.
- The treatment of NHL in HIV is the same as that for non-HIV NHL, but need to be mindful of drug-drug interactions. NHL accounts for 15% of AIDS-related deaths.
- **Complications:**
  - CNS NHL risk is also  $\uparrow$  in HIV.
  - The risk of cervical cancer and anal cancer is  $\uparrow$  by HPV and impaired cellular immunity.

## Plasma Cell Dyscrasias

Plasma cell dyscrasias represent a group of disorders characterized by abnormal production of paraproteins, often due to a *monoclonal* proliferation of plasma cells.

### MULTIPLE MYELOMA

Symptoms are due to two aspects of myeloma:

- **Plasma cell infiltration:** Lytic bone lesions, hypercalcemia, anemia, plasmacytomas.
- **Paraprotein:** Depression of normal immunoglobulins leads to infections; excess protein may cause renal tubular disease, amyloidosis, or a narrowed anion gap (due to positively charged paraproteins).

### Diagnosis

The updated diagnostic criteria for multiple myeloma are summarized in Table 9.19.

- **SPEP with immunofixation electrophoresis (IFE)** to detect and quantify the M spike. Up to 20% of myeloma patients will have normal SPEP and IFE.
- **Serum free light chains** with abnormal kappa to lambda ratio: can identify the monoclonal disorder if the SPEP and IFE are normal. Serum free light chains may also be used to monitor response to therapy.
- Bone marrow aspirate and biopsy (Figure 9.17).
- **Skeletal bone plain film survey:** Lytic lesions are identified in 60% to 90% of patients and may be seen on plain radiographs, CT (Figure 9.18), or MRI.

### Management

Myeloma is rarely curable. The exception is a patient who can receive allogeneic stem cell transplantation. See Table 9.20 for treatment options.

**TABLE 9.19. Diagnostic Criteria for Multiple Myeloma**

≥10% monoclonal plasma cells on bone marrow biopsy without CRAB criteria is diagnostic of smoldering multiple myeloma

>10% monoclonal plasma cells on bone marrow biopsy or extramedullary plasmacytoma PLUS one or more of the following CRAB features and myeloma-defining events (MDEs):

- Calcium ↑ (hypercalcemia)
- Renal impairment
- Anemia
- Bone lesions (ie, lytic lesion on radiographs)

Evidence of one or more of the following biomarkers of malignancy (MDEs) associated with near-inevitable progression to end-organ damage:

- ≥60% plasma cells on bone marrow biopsy
- Serum free light chain ratio ≥100
- **MRI with >1 lesion in bone or bone marrow**

(Data from the International Myeloma Working Group [IMWG] Criteria for the Diagnosis of Multiple Myeloma.)

### KEY FACT

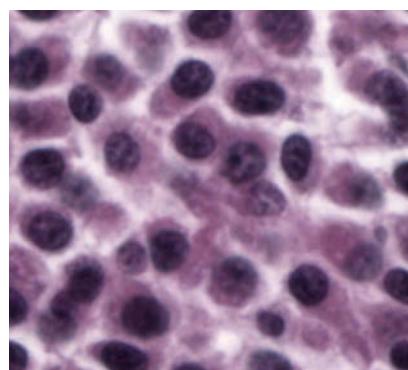
The classic features of multiple myeloma are bone pain, anemia, hypercalcemia, and renal failure. However, don't forget subtle clues such as a narrowed anion gap and proteinuria that is not detected on dipstick (which only tests for albumin) and is present on 24-hour urine (which measures all proteins).

### KEY FACT

Bone lesions in myeloma are purely osteolytic, so bone scans will be  $\ominus$  and alkaline phosphatase will be normal. Order a plain film skeletal survey—not a bone scan—to evaluate for bone disease in myeloma.

### KEY FACT

The only potentially curative treatment for multiple myeloma is allogeneic stem cell transplantation, but this is feasible only in younger patients with good functional status.



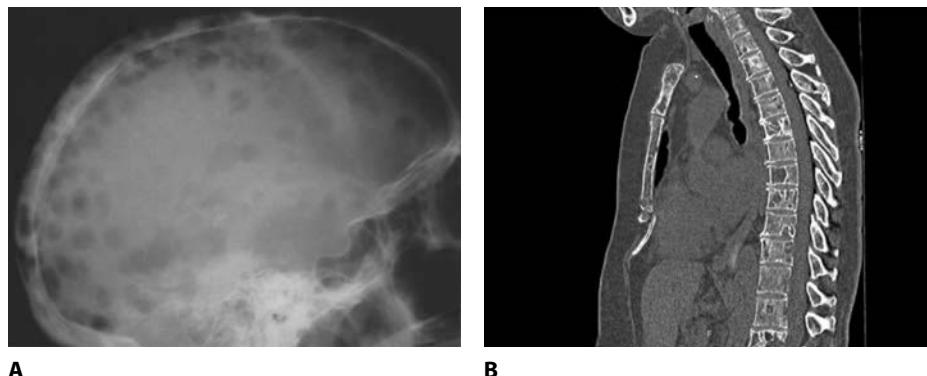
**FIGURE 9.17. Multiple myeloma on bone marrow biopsy.** Sheets of plasma cells with eccentric nuclei with clock-face chromatin infiltrating bone marrow of 60-year-old woman with multiple myeloma, detected by M-spike on serum protein electrophoresis. (Reproduced with permission from USMLE-Rx.com.)

**KEY FACT**

Don't be tricked: Don't treat MGUS, and do not use melphalan induction for HSCT candidates.

**KEY FACT**

Thalidomide, lenalidomide, and pomalidomide ↑ the risk of VTE. Bortezomib and thalidomide ↑ risk of peripheral neuropathy.



**FIGURE 9.18. Lytic lesions of multiple myeloma.** Multiple lytic lesions can be seen in a plain film of the skull (A) and in a CT scan of the osseous structures of the spine (B). (Reproduced with permission from USMLE-Rx.com.)

**AMYLOIDOSIS**

Amyloidosis is a rare disorder characterized by the deposition of amyloid material throughout the body. The most common are AA and AL amyloid (Table 9.21).

**Symptoms/Exam**

The characteristics of amyloidosis are somewhat dependent on the type of protein deposited and organs involved (Figure 9.19):

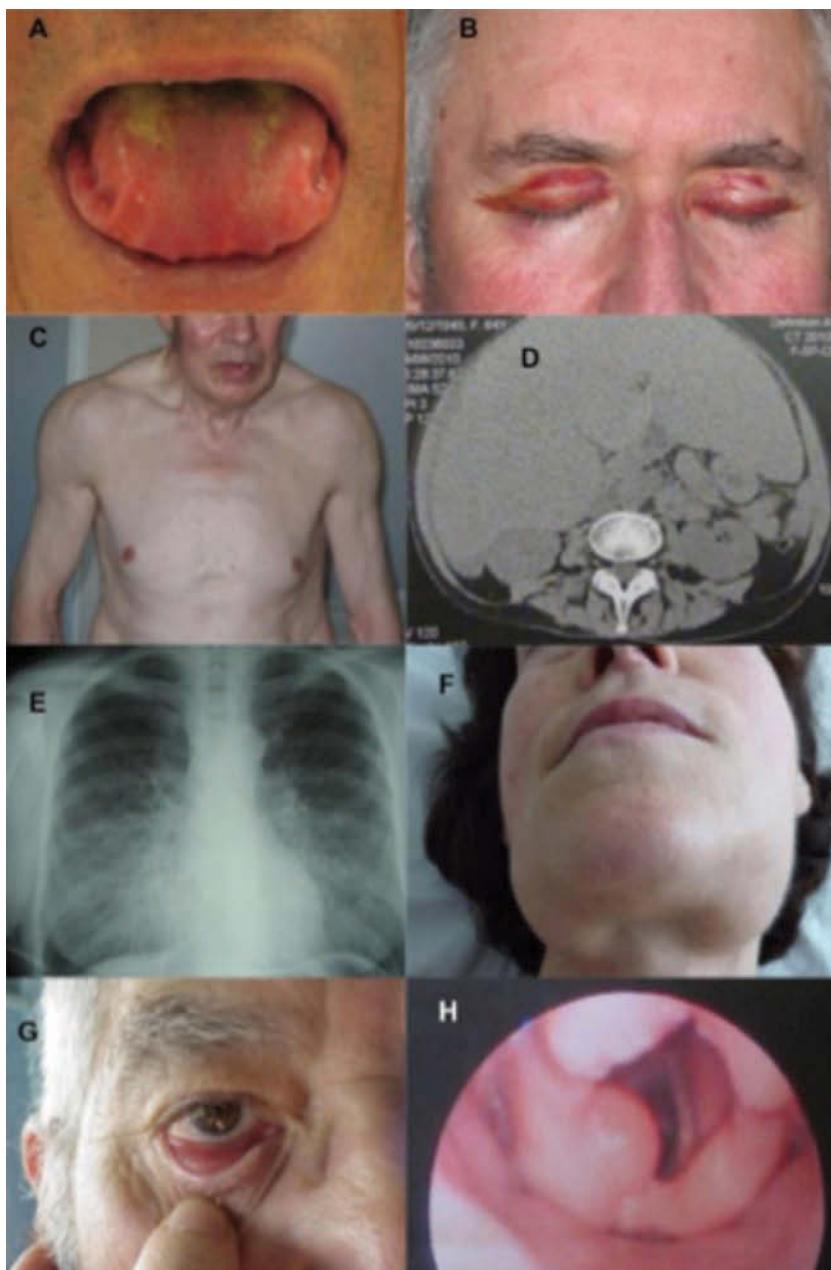
- **Renal:** Proteinuria, nephrotic syndrome, renal failure.
- **Cardiac:** Infiltrative cardiomyopathy, conduction block, arrhythmia, low-voltage ECG, ↑ LV thickness on echocardiogram, and a “speckled” pattern on echocardiography (only on older Echo machines).
- **GI tract:** Dysmotility, obstruction, malabsorption.
- **Soft tissues:** Macroglossia, carpal tunnel syndrome, “shoulder pad” sign, “raccoon eyes.”
- **Other:** Peripheral neuropathy, bleeding, factor X deficiency, lung nodules.

**TABLE 9.20. Treatment of Multiple Myeloma**

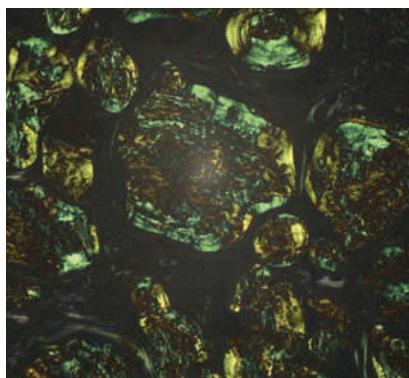
GOAL	TREATMENT
Reduce paraprotein and overall disease burden (eg, cytopenias due to marrow involvement)	Standard of care is induction with doublet or triplet, which includes a steroid plus alkylating agent (eg, cyclophosphamide), an immunomodulatory agent (eg, lenalidomide or thalidomide), and/or a proteasome inhibitor (eg, bortezomib). Following induction consider consolidation with autologous HSCT. Maintenance therapy is often a corticosteroid plus one of the above drugs.
Prevent skeletal complications	<b>IV bisphosphonate</b> if there is any evidence of skeletal compromise (bony lesions, osteopenia, hypercalcemia). No data exist for oral bisphosphonates. Radiation therapy and/or orthopedic surgery for impending pathologic fractures in weight-bearing bones.
Prevent infections	Pneumococcal and <i>Haemophilus</i> vaccines if not already immune.
Alleviate anemia	Reduce paraprotein. Consider erythropoietin or transfusion if severely symptomatic.
Prevent renal failure	Reduce paraprotein. Prevent hypercalcemia, dehydration.

**TABLE 9.21. Amyloid Types and Fibrillar Components**

TYPE	FIBRILLAR COMPONENT	ASSOCIATION
AA	Acute-phase apolipoproteins	Chronic inflammation (TB, osteomyelitis, leprosy, familial Mediterranean fever)
AL	Immunoglobulin light chain	Plasma cell dyscrasia (eg, multiple myeloma)
ATTR	Transthyretin	Familial
AM	$\beta_2$ -microglobulin	Hemodialysis



**FIGURE 9.19. Clinical features of amyloidosis.** (A) Macroglossia, (B) periorbital “pinch” purpura, (C) shoulder pad sign, (D) hepatomegaly, (E) diffuse bilateral interstitial lung disease, (F) submandibular gland enlargement. Both (G) nodular conjunctival amyloidosis and (H) laryngeal supraglottic amyloid lump are signs of localized AL amyloidosis. (Reproduced from Desport E, et al. AL amyloidosis. *Orphanet Journal of Rare Diseases*. 2012;7:54.)



**FIGURE 9.20. Amyloidosis.** Lymph node biopsy in a patient with amyloidosis demonstrating characteristic apple green birefringence under polarizers. (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Ed Uthman.)

### KEY FACT

In chronic hemodialysis patients with carpal tunnel syndrome, consider AM amyloid from  $\beta_2$ -microglobulin accumulation in the wrists. This form of amyloid generally does not cause systemic disease.

### Diagnosis

- **Tissue biopsy** in amyloid yields the characteristic **apple-green birefringence** with Congo red stain (Figure 9.20). The choice of biopsy site depends on the clinical situation:
  - Biopsy of involved tissue has the highest yield.
  - Fat pad aspirate or rectal biopsies are generally lower yield but less invasive.
- Also consider SPEP, serum free light chain, and bone marrow biopsy to evaluate for plasma cell dyscrasias that cause AL amyloidosis. Once amyloid identified, investigate whether major organs are involved by ordering an ECG, echocardiography, and 24-hour urinary protein.

### Management

Chemotherapy to  $\downarrow$  the production of light chains is often recommended but is not very effective in AL amyloidosis.

### OTHER DISEASES ASSOCIATED WITH A PARAPROTEIN

- Table 9.22 lists distinguishing features of various monoclonal paraproteinemias.
- **Monoclonal gammopathy of undetermined significance (MGUS):**
  - Monoclonal paraprotein  $<3 \text{ g/dL}$ ,  $<10\%$  plasma cells on bone marrow biopsy, and **no evidence of organ involvement** due to plasma cell disorder (ie, no CRAB criteria).
  - $\uparrow$  incidence in older population and approximately 1% per year convert to myeloma, so monitor regularly for the development of myeloma.
- **Smoldering multiple myeloma:**
  - Monoclonal paraprotein  $\geq 3 \text{ g/dL}$  and/or 10% to 60% monoclonal plasma cells on bone marrow biopsy *and no evidence of organ involvement* due to plasma cell disorder (ie, no CRAB criteria).
  - Most patients will progress to multiple myeloma or AL amyloidosis thus monitor closely, but generally do not treat unless develops into MM or amyloidosis.

**TABLE 9.22. Distinguishing Features of Various Monoclonal Paraproteinemias**

	MYELOMA	SMOLDERING MYELOMA	MGUS	WALDENSTRÖM MACROGLOBULINEMIA	AMYLOIDOSIS
Abnormal cell	Plasma cell	Plasma cell	Plasma cell	Lymphoplasmacytes	Plasma cell
Lytic bone lesions	<b>Present</b>	Absent	Absent	Absent	Absent
Paraprotein	$>3.5 \text{ g IgG}$ or $>2 \text{ g IgA}$	$>3 \text{ g/dL}$	$<3 \text{ g/dL}$	<b>Any IgM</b>	Any
Bone marrow	<b>&gt;10% plasma cells with CRAB criteria or &gt;60% without CRAB criteria</b>	10%-60% plasma cells and no CRAB criteria	<b>&lt;10% plasma cells</b>	Lymphoplasmacytes	Amyloid deposition
Tissue involvement	Plasmacytomas	None	None	None	Amyloid deposition
Splenomegaly or adenopathy	Absent	Absent	Absent	Present	Absent

■ **Waldenström macroglobulinemia:**

- A low-grade indolent B-cell neoplasm characterized by IgM paraprotein.
- Exam findings include lymphadenopathy, splenomegaly, hepatomegaly, and dilated, tortuous veins (“sausage link” veins) on retinal exam.
- Treatment is the same as that for low-grade non-Hodgkin lymphoma.
- Beware of **hyperviscosity syndrome:** ↑ serum viscosity from IgM, causing blurry vision, headaches, bleeding, and strokes. Emergent plasmapheresis ↓ serum viscosity by removing the IgM paraprotein.

 **KEY FACT**

When you see splenomegaly and an IgM spike, think Waldenström's. Headache and visual changes are common symptoms of hyperviscosity, which is treated with emergent plasmapheresis.

## Growth Factors

### MYELOID GROWTH FACTORS

Myeloid growth factors (G-CSF, GM-CSF) are used for the prophylaxis of febrile neutropenia, but *only in selected patients* (see section on Febrile Neutropenia). Other uses for myeloid CSFs include mobilization of stem cells for transplant; neutropenia after bone marrow transplantation; congenital, cyclic, or idiopathic neutropenia; neutropenia after leukemia treatment or in MDS; and chemotherapy-induced neutropenic fever, uncontrolled cancer, or severe sepsis.

■ **Administration:**

- Dosing begins at least 24 to 48 hours after chemotherapy administration and should always stop at least 24 hours before subsequent chemotherapy.
- **Pegfilgrastim** is a long-acting, pegylated version of G-CSF.

■ **Side effects:** The most common G-CSF side effect is bone pain.

 **KEY FACT**

MGUS is distinguished from smoldering myeloma by a smaller quantity of M-protein and less involvement of bone marrow by plasma cells.

### ERYTHROPOIETIN

Anemia in cancer and/or chemotherapy impairs quality of life. Erythroid growth factors are approved for use in chemotherapy-associated anemia and has been shown to improve anemia and ↓ transfusion requirements in some patients with transfusion-dependent MDS.

■ **Administration:**

- Patients often need supplemental iron to respond to erythropoietin.
- Darbepoetin alfa is a new agent with a long half-life; less frequent dosing may be used (q 2-3 weeks).

■ **Complications:** Erythropoietin failure in patients receiving dialysis can be caused by iron deficiency, folate deficiency, ongoing blood loss, or iron overload. Vitamin C can improve the response to erythropoietin in patients receiving dialysis by mobilizing iron stores.

 **KEY FACT**

The 1° side effect of G-CSF is bone pain, most often in the sternum and long bones.

## Bleeding Disorders

### APPROACH TO ABNORMAL BLEEDING

Excessive bleeding occurs due to a defect in one of three variables: **blood vessels, coagulation factors, or platelets.**

#### Blood Vessel Disorders

- A rare cause of petechiae or purpura.
- Weakness of the vessel wall may be **hereditary** (eg, Ehlers-Danlos, Marfan syndromes) or **acquired** (eg, vitamin C deficiency [scurvy], trauma, vasculitis).

 **KEY FACT**

In a malnourished patient with gum bleeding and purple lesions located around the hair follicles of the legs, think scurvy and replace vitamin C.

 **QUESTION**

A 54-year-old woman is evaluated for fatigue, weight loss, and dyspnea of 2 weeks' duration. Exam reveals a BP of 120/70 mm Hg reclining and 80/60 mm Hg while standing. She has bilateral lower extremity pitting edema and mild hepatomegaly. Laboratory results: Hb, 12.8 g/dL; leukocyte count, 8000/ $\mu$ L; platelet count, 230,000/ $\mu$ L; INR, 2.0; alkaline phosphatase, 640 IU/L; and 4 g of protein in a 24-hour urine collection. ECG shows low voltage in all leads. What is the most likely diagnosis?

**KEY FACT**

A classic patient with acquired Factor VIII inhibitor is a postpartum woman with bruising and bleeding who has an isolated prolonged PTT. A 1:1 mixing study will fail to correct the PTT. Factor VIII inhibitor levels can be checked to confirm the diagnosis.

**Coagulation Factor Disorders**

- Pose significant bleeding risk only when clotting factor activity falls below 10%.
- Present with **hemarthroses** or deep tissue bleeds typically.
- Clotting factor disorders are either inherited or acquired (see also Tables 9.23 and 9.24).
- **Inherited disorders** include hemophilia (A and B) and vWD, discussed in the following sections.
- **Acquired disorders** include:
  - Factor inhibitors: Elderly patients or patients with autoimmune diseases may acquire inhibitor, usually against factor VIII (most common) or factor VII.
  - Anticoagulants: Warfarin (see Table 9.25 for management of supratherapeutic INR), heparin.
  - Amyloid: Associated with absorption of factor X in amyloid protein.
  - Dysfibrinogenemia: Seen in liver disease, HIV, lymphoma, and DIC.
  - Vitamin K deficiency.
  - Liver disease.
  - DIC.

**Platelet Disorders**

- Cause **petechiae** (Figure 9.21), mucosal bleeding, and menorrhagia; **exacerbated by ASA** and other antiplatelet agents.
- A prolonged bleeding time is seen but is not necessary for diagnosis and not often tested.
- Defects may be **quantitative** (see the Thrombocytopenia section) or **qualitative**.
- **Qualitative platelet disorders:**
  - The most common inherited defect is **vWF deficiency**.
  - **Others:** Medications (ASA, NSAIDs, IIB/IIIA inhibitors), uremia, and rare inherited defects (Glanzmann thrombasthenia, Bernard-Soulier syndrome).

**HEMOPHILIA**

Hemophilia is an **X-linked recessive** deficiency in clotting factors, so almost all patients are **male**. There are two types:

- **Hemophilia A:** Factor VIII deficiency (“**A eight**”).
- **Hemophilia B:** Factor IX deficiency (“**B nine**”).

**T A B L E 9 . 2 3 . Diagnosis of Clotting Factor Disorders**

CONDITION	PT	PTT	MIXING STUDY
Factor VII deficiency, warfarin use, vitamin K deficiency	Elevated	Normal	Corrects
Hemophilia	Normal	Elevated	Corrects
Heparin	Normal	Elevated	No correction unless heparin adsorbed
Factor VIII inhibitor	Normal	Elevated	No correction
Lupus anticoagulant	Normal	Elevated	No correction (test with Russell viper venom)
DIC	Elevated	Elevated	Minimal correction
Liver disease	Elevated	Elevated	Corrects
Dysfibrinogenemia	Elevated	Elevated	Variable correction (test with reptilase time)

**ANSWER**

Amyloidosis should be suspected in patients with multiorgan dysfunction and wasting. Common symptoms include weight loss, postural hypotension, hepatomegaly with ↑ alkaline phosphatase, a low-voltage ECG, and proteinuria. Macroglossia and cardiac involvement point to AL (light chain production) as the cause.

**TABLE 9.24. Comparison of Special Coagulation Tests**

TEST	OBJECTIVE
Mixing study	First test to order when a patient has a prolonged PTT—distinguishes factor <b>deficiency</b> from factor <b>inhibitor</b>
Reptilase time	To test for dysfibrinogenemia—used to evaluate for fibrinogen abnormalities or the presence of heparin
Dilute Russell viper venom test (dRVVT)	To test for lupus anticoagulant
Ristocetin cofactor assay	Used in evaluation of vWD

**Symptoms/Exam**

- Characterized by spontaneous bleeding in deep tissues, GI tract, and joints (**hemarthroses**).
- Variable in severity due to baseline percent factor activity.

**Diagnosis**

- Labs reveal a normal PT and a prolonged PTT; a **mixing study corrects the defect**. **Exception:** A hemophiliac who has been treated with factor replacement may develop antibodies to the synthetic factor, resulting in a prolonged PTT that does not correct after mixing.
- Factor VIII or factor IX activity is low (0%-10%).

**Management**

- There are two options for factor replacement:
  - Recombinant factor:** Associated with less danger of HIV and HCV transmission than purified factor, but expensive.
  - Purified factor concentrates:** Derived from donor plasma. Currently much safer than previous concentrates.
- Patients should be taught to self-administer factor in the event of spontaneous bleeding.
- Prophylaxis before procedures:
  - Minor procedures:** For hemophilia A, DDAVP can be used if baseline factor VIII is 5% to 10%. Otherwise, replace with factor concentrates.
  - Major procedures:** Replace with factor concentrate during and in the days following procedure.

**TABLE 9.25. Warfarin Management of Elevated INRs**

INR	BLEEDING	MANAGEMENT
Normal to <5	No	Lower dose or skip next warfarin dose.
>5 to 9	No	Skip next one to two doses and resume warfarin at lower dose once INR is in the therapeutic range or skip a dose and give 1-2.5 mg of oral vitamin K.
>9	No	Hold warfarin and give 2.5-5 mg oral vitamin K. Resume warfarin at lower dose once INR is in the therapeutic range.
Any	Yes	Hold warfarin and give 10 mg IV vitamin K. If significant bleeding, give four-factor prothrombin complex concentrate or FFP.

**FIGURE 9.21. Petechia and purpura from low platelet count.** (Reproduced from Wikipedia; courtesy of Dr. James Heilman.)

■ Acute bleeding:

- **Minor bleeding:** Replace with factor concentrate to 25% to 50% activity.
- **Major bleeding** (hemarthroses, deep tissue bleeding): Replace to 50% activity for 2 to 3 days.

### VON WILLEBRAND DISEASE

#### KEY FACT

Consider vWD in a patient with a normal platelet count in one of the following common clinical scenarios:

- Heavy menses.
- Bleeding after a minor dental procedure or arthroscopic surgery.
- A history of frequent epistaxis or epistaxis after starting ASA.
- A bleeding history that improves during pregnancy or on OCPs (estrogen ↑ vWF levels, so vWD often improves with the presence of additional hormones).

von Willebrand disease is the **most common inherited bleeding disorder**. vWF complexes with factor VIII to induce platelet aggregation, and if there is dysfunction or deficiency of vWF, adequate platelet aggregation does not occur.

■ **Symptoms/Exam:**

- Bleeding pattern similar to that of platelet disorders (**petechiae, mucosal bleeding/epistaxis, heavy menses, exacerbated by ASA**).
- Bleeding generally provoked, not spontaneous (eg, by ASA, trauma, surgery, circumcision, or dental work).

■ **Diagnosis:**

- There are three basic types; type I ( $\downarrow$  vWF) is the most common (Table 9.26).
- Labs reveal a normal PT and a normal or prolonged PTT.
- If vWD is suspected, check ristocetin cofactor assay, von Willebrand antigen, and factor VIII activity level.

■ **Management:**

- Avoid NSAIDs.
- DDAVP is helpful in type I vWD but is not generally useful in the other types.
- Synthetic vWF preparation (eg, Humate P) may be used for prophylaxis or for severe bleeding.

### DISSEMINATED INTRAVASCULAR COAGULATION

DIC is a consumptive coagulopathy characterized by **thrombocytopenia, ↑ PT and PTT, and schistocytes** on peripheral smear in association with serious illness.

■ **Symptoms/Exam:** Acute DIC is often a catastrophic event and manifests as bleeding (eg, oozing from venipuncture sites) and/or clotting. In contrast, chronic DIC shows milder features and is associated with chronic illness (disseminated malignancy, intravascular thrombus).

■ **Diagnosis:** Look for  $\downarrow$  fibrinogen,  $\downarrow$  platelets, prolonged PT/PTT,  $\uparrow$  d-dimer, and **schistocytes** (present in only ~50% of cases).

■ **Management:** Treat the underlying cause:

- **Bleeding:** Cryoprecipitate can be given to achieve a fibrinogen level of  $>100$  mg/dL, and platelet transfusions can be administered to achieve a platelet count of  $>50 \times 10^9/L$ .

**TABLE 9.26. Diagnosis of von Willebrand Disease**

TYPE	FACTOR VIII	VWF ANTIGEN	VWF ACTIVITY (RISTOCETIN COFACTOR)	NOTES
I	Low/Normal	Low	Low	<b>The most common form</b>
IIA	Low/Normal	Low/Normal	Absent	Abnormal vWF multimers
IIB	Low/Normal	Low/Normal	Low/Normal	Abnormal vWF multimers
III	Low	Low	Absent	<b>Cannot use DDAVP</b>

- Clotting:** Low-dose IV heparin can be used to treat thrombotic complications. Given the risk of bleeding in a patient with DIC, a hematologist should be involved if a heparin drip is being used.

### IDIOPATHIC THROMBOCYTOPENIC PURPURA

Idiopathic thrombocytopenic purpura, also known as immune thrombocytopenic purpura or immune thrombocytopenia, is a disorder of reduced platelet survival, typically by immune destruction in the spleen. ITP commonly occurs in childhood with viral illnesses but may also affect young adults. Subtypes and their associated causes are:

- 1°: No identifiable cause.
- 2°: Medications (gold, quinine,  $\beta$ -lactam antibiotics), CLL, SLE, HIV, HCV.
- Symptoms/Exam:**
  - Typically presents with **petechiae, purpura, mucosal bleeding, and menorrhagia.**
  - Spleen size is normal.**
- Diagnosis:**
  - Made by excluding other causes of thrombocytopenia. Peripheral smear shows reduced number but giant platelets.
  - Antiplatelet antibodies, platelet survival times, degree of ↑ in platelet count after platelet transfusion, and bone marrow biopsy are **not** needed for diagnosis. However, if the patient is >60 years of age, a bone marrow biopsy is recommended to evaluate for myelodysplasia as the cause of thrombocytopenia.
- Management:** Treatment goal is to prevent significant bleeding, **not** normalizing platelet count. Highest bleeding risk is when platelet count is <10,000/ $\mu$ L.
- No bleeding:
  - Platelets >30,000/ $\mu$ L, generally no treatment indicated.
  - Platelets <30,000/ $\mu$ L, first-line therapies are corticosteroids or IVIG. Second-line treatments are rituximab and TPO-mimetic drugs (romiplostim or eltrombopag).
- Bleeding: Give platelets, corticosteroids, and IVIG. Table 9.27 lists further treatment guidelines.

TABLE 9.27. Treatment of ITP

TREATMENT	EFFICACY	NOTES
Corticosteroids	60% response rate	Time to remission is 1-3 weeks <b>First-line treatment, but 90% of adults will relapse</b>
IVIG	80%-90% response rate	Rapid remission but short-lived; used for acute bleeding risk
Splenectomy	70% remission rate	May require looking for accessory spleen
Danazol	10%-80% response rate	Infrequently used in the modern era
Anti-RhD	80%-90% response rate	Induces hemolytic anemia; works only with Rh-positive patients
Rituximab	30% response rate in chronic refractory ITP	Can cause allergic reactions
Romiplostim Eltrombopag	80% ↑ for both agents	Thrombopoietin mimetics are generally second line because of cost and because platelets will drop again as soon as these meds are stopped

### KEY FACT

For ITP patients without life-threatening bleeding, initial treatment is prednisone. Prednisone failures may be treated with IVIG, anti-D immunoglobulin in RhD-positive patients, rituximab, thrombopoietin mimetics (romiplostim and eltrombopag), or splenectomy. For life-threatening bleeding due to ITP, therapy should include platelet transfusion, IV corticosteroids, IVIG, or splenectomy.

### KEY FACT

Isolated thrombocytopenia in an otherwise healthy young adult is most likely ITP. ITP is a clinical diagnosis of exclusion, and bone marrow examination is not required. Bone marrow aspirate and biopsy are reserved for those who do not respond to prednisone therapy or who are >60 years. 2° ITP may occur in SLE, HIV, CLL, HCV, pregnancy, and post-transfusion.

### KEY FACT

In ITP, avoid transfusing platelets unless the patient is actively bleeding.

### KEY FACT

If a patient has ITP with a platelet count of >30,000-50,000/ $\mu$ L and no bleeding, consideration should be given to surveillance with no active treatment.

### KEY FACT

In an adult with ITP that is refractory to corticosteroids, splenectomy is the most effective way to induce remission.

### QUESTION

A 30-year-old woman presents with a 15-year history of heavy menses lasting 10 days and once-monthly episodes of epistaxis that frequently require packing. Her mother and two sisters also have heavy menses. Gynecologic evaluation is unremarkable. Exam is normal. Lab results: PT, 11 sec; activated PTT, 40 sec; Hb, 9.6 g/dL; MCV, 75 fL; platelet count, 400,000/ $\mu$ L; and normal leukocyte count. What is the most likely cause of her menorrhagia?

**KEY FACT**

Looking for very rare genetic conditions to explain a common problem is not cost-effective. Evaluation for rare causes of thrombophilia should be done only after common causes have been eliminated and in consultation with a hematologist since it will unlikely change management.

**KEY FACT**

In a patient with active cancer who develops a DVT or PE, treatment with LMWH or fondaparinux is preferred for both initial and long-term anticoagulation.

**KEY FACT**

In a patient with new DVT or PE, LMWH or fondaparinux is superior to UFH for initial anticoagulation. UFH should be used only in the setting of renal failure, extreme obesity, or bleeding concerns.

**KEY FACT**

If you see a patient with mesenteric vein thrombosis, pancytopenia, and dark urine (hemoglobinuria), think PNH and order flow cytometry to confirm.

**KEY FACT**

In a patient with unprovoked DVT whose baseline PTT is prolonged, consider antiphospholipid antibody syndrome.

**ANSWER**

vWD. Hemophilia is generally associated with marked prolongation of activated PTT rather than with mild prolongation, and bleeding in patients with hemophilia most commonly occurs in the joints, not in the mucosa.

## Clotting Disorders

**APPROACH TO THROMBOPHILIA**

Major risk factors for venous thromboembolism (VTE) include prior VTE, pregnancy, surgery, smoking, prolonged immobilization, hospitalization for any cause, and active malignancy. Consider **inherited thrombophilia** in the following conditions:

- Unprovoked clots occurring in young persons (<50 years of age).
- Clots in unusual locations (eg, mesenteric vein, sagittal sinus).
- Unusually extensive clots.
- Both arterial and venous clots.
- Strong family history.

**Differential**

If arterial clots are present, the list of possible disorders shortens (Table 9.28).

**Diagnosis**

Diagnostic testing at time of diagnosis of VTE includes history and physical, CBC, PTT, ultrasonography (Figure 9.22), and age-appropriate screening (see Table 9.28). **Additional testing for hereditary thrombophilia is rarely indicated** as it does not affect management.

**Management**

Anticoagulant medications are listed in Table 9.29. Treatment duration depends on type of VTE:

- **Provoked VTE** (eg, postop): 3 months.
- **Unprovoked VTE:** Treat for minimum of 3 to 6 months, and consider indefinite anticoagulation with ongoing discussions weighing bleeding risk vs recurrent VTE risk.
- **Antiphospholipid antibody syndrome:** Indefinite duration to ↓ the rate of recurrent VTE.
- After acute treatment (first 5-7 days), remainder of treatment can be with novel oral anticoagulant or warfarin. **Exceptions are active cancer and APLS:** Treat cancer-related VTE with LMWH or fondaparinux, and APLS-associated VTE with LMWH or warfarin.

**SPECIFIC THROMBOPHILIC DISORDERS**

### Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APLA) is a syndrome of **vascular thrombi** or **recurrent spontaneous abortions** associated with laboratory evidence of autoantibody against phospholipids. **Catastrophic APLA** is a rare severe form that is associated with multiorgan failure and high mortality.

- **Diagnosis:** Requires a clinical event **and** antiphospholipid antibody. Clinical characteristics are:
  - Venous and/or arterial thrombi.
  - Thrombocytopenia.
  - Livedo reticularis.
  - Recurrent spontaneous abortions.
- **Antiphospholipid antibody testing:** Can include a variety of autoantibodies, but only one need be present. However, the autoantibody needs to be present on repeated testing separated by 12 weeks to exclude false-positive results.

**TABLE 9.28.** Differential Diagnosis of Clotting Disorders

DIFFERENTIAL DIAGNOSIS	MODE OF EVALUATION
<b>Arterial and venous:</b>	
Malignancy	Age-appropriate cancer screening
HIT syndrome	HIT antibody (antiplatelet factor 4, functional testing); pretest probability based on 4T score
Hyperhomocysteinemia <sup>a</sup>	Homocysteine level, but generally not indicated as treatment does not affect risk of subsequent VTE
PNH	<b>Flow cytometry</b> (to detect abnormal RBCs lacking CD55 and CD59)
Myeloproliferative disorders <sup>b</sup>	CBC, blood smear, JAK2, BCR/ABL, CALR, and MPL testing
Antiphospholipid antibody syndrome	Lupus anticoagulant, anticardiolipin antibody, anti-β <sub>2</sub> glycoprotein
Nephrotic syndrome	Urine protein measurement
<b>Venous only:</b>	
Factor V Leiden <sup>c</sup>	Factor V Leiden mutation, but generally not indicated as does not change recommended treatment
Prothrombin 20210 mutation <sup>d</sup>	Prothrombin 20210 mutation, but generally not indicated
Protein C or S deficiency <sup>e</sup>	Protein C and S levels, but generally not indicated as very rare
Antithrombin III deficiency <sup>e</sup>	Antithrombin III level, but generally not indicated as very rare
Oral estrogens	N/A
Postsurgical, pregnancy, immobilization	N/A
Behçet disease	N/A
Thromboangiitis obliterans	N/A
<b>Arterial only:</b>	
Atherosclerosis	N/A
Vasculitis	N/A

<sup>a</sup>Genetic or acquired ( $B_6$ ,  $B_{12}$ , folate deficiencies, smoking, older age, renal insufficiency).

<sup>b</sup>Essential thrombocythemia, polycythemia vera.

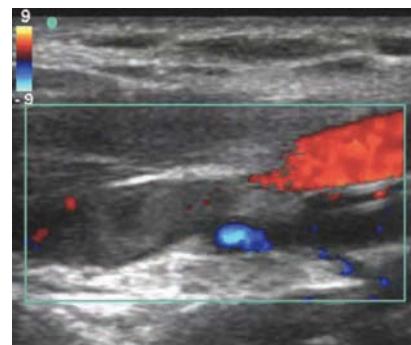
<sup>c</sup>Five percent of Caucasians carry gene. Heterozygotes → 3-8× risk VTE, homozygotes → 50-80× risk VTE.

<sup>d</sup>Primarily seen in Caucasians.

<sup>e</sup>Higher risk of VTE than factor V Leiden and 20210.

■ Additional studies include:

- **Lupus anticoagulant:** A clue to this may be prolonged PTT; confirm with a mixing study and a **Russell viper venom test**.
- **Anticardiolipin antibody:** Associated with **false-positive VDRL or RPR**.
- **Anti-β<sub>2</sub> glycoprotein I.**



**FIGURE 9.22. Axillary and subclavian vein thrombosis.** Long-axis view of emergency department color Doppler ultrasonography shows DVT. (Reproduced from Rosen T, et al. Emergency department diagnosis of upper extremity deep venous thrombosis using bedside ultrasonography. *Crit Ultrasound J*. 2012;4(1):4.)

**KEY FACT**

Suspect antiphospholipid antibody syndrome in a young woman with recurrent spontaneous abortions and a prolonged PTT.

**KEY FACT**

Don't be tricked: Do not select thrombolytic therapy for most patients with DVT or PE. Do not use new oral anticoagulants in renal insufficiency (estimated GFR rate <30) or obesity (BMI >40).

TABLE 9.29. Guide to Anticoagulant Medications

MEDICATIONS	PROS	CONS	TESTS USED TO MONITOR	NOTES
UFH	Short half-life; can turn off quickly if the patient bleeds  Although falling out of favor, this is still appropriate for acute coronary syndromes, cardiopulmonary bypass, acute thrombotic events, mechanical heart valves, and anticoagulation in renal failure	Requires continuous IV infusion and laboratory monitoring  Long-term use is associated with osteoporosis  May cause HIT	Need to monitor PTT and platelet count at least daily (for HIT)  Reversible with <b>protamine</b>	
LMWH	No need to monitor PTT, as dosing is weight based	Requires injection  Not reversible with protamine  Contraindicated in renal failure	Cannot rely on PTT for monitoring; if monitoring is required, measure anti-factor Xa activity	First-line for malignancy-associated VTE  Preferred agent for pregnancy VTE
Warfarin	Oral	Slow to reach therapeutic effect; requires the addition of UFH or LMWH when starting for an acute clot  <b>Teratogenic</b> ; many drug interactions  Warfarin skin necrosis (rare)	Monitor with INR; the usual goal range is an INR of 2-3  Duration varies with the clinical situation  Reversible with FFP or vitamin K	
Parenteral factor Xa inhibitors (fondaparinux)	No need for monitoring, as dosing is weight based  Once-daily dosing	Requires injection  Contraindicated in renal failure  No reversing agent if the patient bleeds	Cannot rely on PTT for monitoring	First-line for malignancy-associated VTE
Parenteral direct thrombin inhibitors (lepirudin, argatroban)	Used for anticoagulation in patients with HIT	Irreversible thrombin inhibitors; require continuous IV infusion	Monitor with PTT	
Novel oral anticoagulants  Xa inhibitors (apixaban, edoxaban, rivaroxaban)  Direct thrombin inhibitors (dabigatran)	No monitoring required, no injections required, no dietary restrictions, more time in therapeutic range compared to warfarin, lower bleeding risk than warfarin	More expensive than warfarin  Reversal agent only currently available for dabigatran (idarucizumab)	Not typically monitored	Now first choice for long-term oral anticoagulation for VTE in most patients

## Heparin-Induced Thrombocytopenia

The two types of HIT are outlined in Table 9.30. Type I is characterized by a mild fall in platelet count that occurs in the first two days after heparin is initiated and usually returns to normal with continued heparin use. It has no clinical consequences. Type II is the more serious type and is an immune-mediated disorder in which antibodies form against the heparin–platelet factor 4 (PF4) complex. Risk of type II HIT approximately 10-fold higher for UFH versus LMWH.

### KEY FACT

In a patient with a high suspicion of HIT II, stop heparin and LMWH and initiate treatment with the direct thrombin inhibitor argatroban while awaiting results of HIT testing.

### Symptoms/Exam

- Type II HIT presents as:
  - ↓ in platelet count after 5–10 days of exposure to heparin.
  - **Arterial or venous clots.**
- Can follow *any* heparin exposures—heparin flushes, heparin-coated catheters, mini-dose SQ heparin.

### Diagnosis

- Type II HIT requires a high degree of clinical suspicion. Based on platelet drop of >50% or thrombosis 5 to 10 days after heparin start with appearance of antiplatelet antibodies. **4T score** can help estimate the pretest probability of HIT (Table 9.31).
- Lab testing includes the following:
  - **Antibody against PF4 (excellent sensitivity).**
  - **Functional assays (excellent specificity):** Detects abnormal platelet activation in response to heparin (heparin-induced platelet activation, serotonin release assay).

### Management

- If high suspicion, **immediately stop heparin**, start anticoagulation with argatroban. Do **not** delay treatment while awaiting results of anti-PF4 testing and C-serotonin release assay.
- **Warfarin monotherapy is contraindicated in acute HIT** because of risk for limb gangrene or limb loss due to ↓ protein C. Warfarin started once platelets >150K for at least 2 days and continued for 3 to 6 months. Argatroban therapy should overlap with warfarin for a minimum of 5 days.

## Pregnancy-Related Hematology

- Starting at approximately 4 weeks' gestation, both RBC and plasma volume start increasing. Plasma volume increases to a greater extent (30%–50%) than RBC count (20%–30%) leading to relative hemodilution. Benefits of this relative anemia include:
  - ↓ blood viscosity → less cardiac work and ↑ placental perfusion.
  - ↑ reserve for blood loss during delivery.

**TABLE 9.30. Types of Heparin-Induced Thrombocytopenia**

TYPE	DOSE DEPENDENT	SEVERITY OF THROMBOCYTOPENIA	TIMING OF THROMBOCYTOPENIA	CLINICALLY SIGNIFICANT	ETIOLOGY
I	Yes	Mild	Immediate	No	Heparin-induced platelet clumping
II	No	Moderate/ severe	4–7 days after exposure	Yes	Antibody against heparin-platelet complex



### QUESTION 1

A 70-year-old man is admitted to the ICU with severe sepsis from pneumonia. To facilitate resuscitation, a central venous catheter is inserted in his right internal jugular vein. Four days later, he develops right upper extremity swelling; ultrasound reveals right axillary vein thrombosis. He has a normal creatinine level and weighs 187 lb. LMWH and warfarin are started. Does his catheter need to be removed?



### QUESTION 2

Several days later the patient is transferred from the ICU to the ward, and you begin discharge planning. Assuming the patient has no contraindications, what is the optimal duration of anticoagulation for upper extremity DVT, and does his catheter need to be removed?

TABLE 9.31. 4T Score for Heparin-Induced Thrombocytopenia<sup>a</sup>

THROMBOCYTOPENIA		TIMING OF PLATELET COUNT FALL	THROMBOSIS	OTHER CAUSES OF THROMBOCYTOPENIA
2 points	Platelet count fall >50% and nadir ≥20K	Clear onset 5-10 days after heparin exposure or ≤1 day if heparin exposure in past 30 days	Confirmed new thrombosis, skin necrosis, or systemic reaction following IV UFH bolus	None apparent
1 point	Platelet count fall 30%-50% or nadir 10-19K	Consistent with fall at 5-10 days but unclear or onset after day 10 or ≤1 day and heparin exposure within 30-100 days	Recurrent or progressive thrombosis, non-necrotizing skin lesions, or suspected (unproven) thrombosis	Possible
0 points	Platelet count fall <30% or nadir <10K	Platelet count fall <4 days and no recent heparin exposure	None	Definite

<sup>a</sup>Total score is sum of 4 subcategories: 0-3 points = low probability; 4-5 points = intermediate probability; 6-8 = high probability.

**A****ANSWER 1**

No, catheter-associated upper extremity DVTs do not require catheter removal. Remove the catheter as soon as it is no longer needed or it is not functioning properly.

- Because of changes in clotting factors, pregnancy is a relatively hypercoagulable state. Thrombotic risk is highest in the postpartum period, 3 to 4× risk compared to during pregnancy. Plasma volume and RBC count return to normal approximately 8 weeks after delivery.

**Transfusion Medicine****PRETRANSFUSION TESTING**

Pretransfusion tests include:

- Type and cross:** Use when transfusion is **probable** (eg, in an acutely bleeding patient). Test recipient plasma for **reactivity against RBC from the donor**—ie, perform an indirect Coombs test on **donor RBCs**.
- Type and screen** (aka “type and hold”): Use when transfusion is **possible** (eg, in preoperative evaluation). **Screen recipient plasma for antibodies**—ie, perform an indirect Coombs test on **recipient RBCs**.

**MANAGEMENT OF TRANSFUSION REACTIONS**

Consider the risks of transfusions (Table 9.32).

- Stop the transfusion immediately.**
- Contact the blood bank immediately to initiate double-checking of paperwork.
- In acute hemolytic reactions, anticipate labs consistent with intravascular hemolysis: decreases in hemoglobin and haptoglobin and increases of LDH, indirect bilirubin, and free hemoglobin.
- Repeat type and screen in case of prior lab or blood bank error. Send all untransfused blood back to the blood bank with attached tubing.

**TRANSFUSION PRODUCTS**

Table 9.33 lists common types of transfusion products and their applications.

TABLE 9.32. Risks of Transfusion Therapy

	RISK	CLINICAL FEATURES	TREATMENT	CAUSE	COMMENTS
Febrile nonhemolytic reactions	1-4 in 1000	Chills, rigors within 12 hours of transfusion	Acetaminophen, diphenhydramine	WBC or bacterial contaminant, cytokines	<b>Most common reaction</b>
Allergic reaction	1-4 in 1000	<b>Urticaria or bronchospasm</b>	As usual for urticaria or bronchospasm	Allergic reaction to plasma contaminant	<b>Seen in IgA deficiency;</b> prevented through use of washed RBCs
Delayed hemolysis	1 in 1000	Extravascular <b>hemolysis 5-10 days after transfusion:</b> jaundice, ↓ in hematocrit, + Coombs test, microspherocytes in peripheral smear	Supportive care; send sample to blood bank to work up new alloantibody	Low-titer antibodies against minor blood antigens	Multiparous women or multiply transfused patients may be at ↑ risk
Transfusion-related acute lung injury (TRALI)	1 in 5000	Noncardiogenic pulmonary edema, usually within 6 hours of transfusion	Supportive care	<b>Donor antibodies to recipient leukocytes</b> in pulmonary capillaries	Most cases resolve after 96 hours
Transfusion-associated circulatory overload (TACO)	1 in 1500 (plasma) 1 in 70 (RBCs)	Dyspnea, orthopnea, tachycardia, hypertension, hypoxemia	Diuresis and oxygen supplementation	Volume overload	↓ risk by avoiding rapid transfusion rates
Acute hemolytic transfusion reaction	1 in 12,000	Chills, fever, backache, headache, hypotension, tachypnea, tachycardia. DIC may occur in severe cases	Vigorous hydration to prevent acute tubular necrosis; if hemolysis is severe, consider forced diuresis with mannitol and urinary alkalinization	Severe intravascular hemolysis due to antibody against donor RBCs ( <b>typically ABO incompatibility</b> )	Usually due to a clerical error
HBV	1 in 66,000				
HCV	1 in 103,000				
HIV	1 in 676,000				

### PLATELET TRANSFUSION THRESHOLD

The criteria for determining the platelet transfusion threshold are controversial but are as follows:

- A bleeding patient with a platelet count <50,000/µL.
- CNS bleeding with a platelet count <100,000/µL.
- Major surgery with a platelet count <50,000/µL.
- Asymptomatic with a platelet count <10,000/µL.

TABLE 9.33. Types of Transfusion Products

PRODUCT	DISTINGUISHING FEATURES	USE
Whole blood	Contains RBC and plasma	Massive blood loss, as from trauma; graft-versus-host disease
Packed RBCs	Each unit of packed RBCs raises hemoglobin 1 g/dL	Most patients who require RBC transfusion
Washed RBCs	RBCs with plasma removed	Prior allergic reactions, as seen in <b>IgA deficiency</b>
Irradiated RBCs	Irradiation	<b>Allogeneic stem cell transplant to prevent graft-versus-host disease</b>
Leukocyte-depleted (leukoreduced) RBCs	Deplete donor leukocytes with WBC filter; costly	Patients awaiting transplant; CMV-seronegative patients to prevent CMV transmission; patients with a prior transfusion reaction
Random donor platelets	Pooled platelets from six donors; each "6 pack" should raise platelet count by 30,000-50,000/ $\mu$ L	Most patients who need platelet transfusion
Single-donor platelets	Platelets are extracted from a single donor by apheresis Each unit should bump platelets by 30,000-50,000/ $\mu$ L	Patients who are alloimmunized
FFP	All clotting factors, but high fluid volume	To correct coagulopathy of liver disease or excess warfarin
Four-factor prothrombin complex concentrate	Factors II, VII, IX, and X	Rapid reversal of anticoagulation in warfarin-associated bleeding (especially intracranial hemorrhage)
Cryoprecipitate	Factor VIII, fibrinogen, and vWF	<b>Use in DIC if fibrinogen is &lt;100 mg/dL</b> Associated with a <b>high risk of transmitting infection</b> because it is not heat inactivated

## Miscellaneous Hematology

### LYMPHADENOPATHY

#### KEY FACT

A firm, nontender left supraclavicular lymph node is Virchow node and is a clue to GI or intrathoracic malignancy.

#### KEY FACT

Common causes of generalized lymphadenopathy include lymphoma, HIV, EBV, mycobacterial infection, SLE, and drug reactions (eg, phenytoin).

TABLE 9.34. Malignant Versus Reactive Adenopathy

	FAVORS MALIGNANT	FAVORS REACTIVE
Patient characteristics	Smoker; older age	Age <40
Size	Larger	Lesions <1 cm are almost always benign
Consistency	<b>Hard</b> , matted, nontender, <b>fixed</b>	Rubbery, mobile, tender
Location	Supraclavicular (Virchow node); periumbilical (Sister Mary Joseph nodule)	Inguinal nodes up to 2 cm are normal

## PORPHYRIAS

Porphyrias and genetic disorders are characterized by defects in heme synthesis. The following two disorders may present in adults.

- **Acute intermittent porphyria:**
  - Caused by a defect in **porphobilinogen deaminase**. **Autosomal dominant**; most common in women in their 20s.
  - Look for attacks of **abdominal pain, psychosis, and possibly SIADH**.
  - **Look for classic triggers:** menses, alcohol, caffeine, or medications (barbiturates, phenytoin, sulfonamides, estrogens).
  - **Diagnosis made by finding excess aminolevulinic acid or porphobilinogen in the urine.**
  - Treatment includes **avoidance of triggers**. IV heme used to abort severe acute attacks.
- **Porphyria cutanea tarda** (Figure 9.23):
  - Classic patient has chronic liver disease, most commonly hepatitis C.
  - Unlike acute intermittent porphyria, porphyria cutanea tarda is limited to the skin.
  - Diagnosis confirmed with measurement serum total and fractionated porphyrins
  - Treatment is phlebotomy and hydroxychloroquine. UV light should be avoided until plasma porphyrin levels normalize.
  - Patients with porphyria cutanea tarda should avoid smoking, alcohol, excess iron, and exogenous estrogen to ↓ risk of recurrence.



### KEY FACT

In a patient with cirrhosis and new blistering skin lesions over sun-exposed hands and facial hypertrichosis, consider porphyria cutanea tarda.



**FIGURE 9.23. Porphyria cutanea tarda.** (Reproduced with permission from USMLE-Rx.com.)

## VITAMIN DEFICIENCIES

Table 9.35 outlines common vitamin deficiencies and their associated disorders.

## METHEMOGLOBINEMIA

Methemoglobin is an abnormal state of heme where the iron is oxidized from the ferrous ( $\text{Fe } 2+$ ) to the ferric ( $\text{Fe } 3+$ ) state. Ferric heme in methemoglobin is unable to bind oxygen. The remaining ferrous heme groups in a molecule of hemoglobin have ↑ oxygen affinity, thus causing a “left-shift” in the oxygen dissociation curve.

**TABLE 9.35. Common Vitamin Deficiencies**

VITAMIN	DEFICIENCY	CLINICAL SYMPTOMS
A (retinol)		Night blindness, conjunctival xerosis, Bitot spots (white spots on conjunctiva), keratomalacia
B <sub>1</sub> (thiamine)	Dry beriberi, wet beriberi	Peripheral neuropathy, Wernicke-Korsakoff syndrome, high-output CHF, vascular leak
B <sub>2</sub> (riboflavin)		Cheilosis, angular stomatitis, glossitis, weakness, corneal vascularization, anemia
Niacin	Pellagra	<b>Dermatitis, Diarrhea, Dementia (then Death)—the 3 (or 4) D's</b>
B <sub>6</sub> (pyridoxine)		Peripheral neuropathy, seizures, anemia (may be precipitated by INH)
C (ascorbic acid)	Scurvy	Perifollicular hemorrhage, petechiae, bleeding gums, hemarthrosis, poor wound healing
D		Osteomalacia in adults; rickets in children
E ( $\alpha$ -tocopherol)		Areflexia, ophthalmoplegia, ↓ proprioception

- **Differential:** Methemoglobinemia occurs congenitally or can be acquired from drugs. Associated drugs include:
  - Benzocaine and other topical anesthetics.
  - Dapsone.
  - Nitrites (ie, amyl nitrite).
  - Sulfonamides.
- **Diagnosis:** Clues to the presence of methemoglobinemia include:
  - History of exposure to agent known to cause methemoglobinemia.
  - Hypoxemia that does not improve with supplemental O<sub>2</sub>, with O<sub>2</sub> saturation plateauing at 85% on pulse oximetry.
  - Abnormally colored blood on phlebotomy (often described as “chocolate brown”).
- **Management:** Treat those who are symptomatic or have methemoglobin levels >20%. Commonly used agents for treatment are methylene blue and vitamin C (ascorbic acid).

## CHAPTER 10

# Hospital Medicine

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## Venous Thromboembolic Disease

### KEY FACT

In a patient with PE, syncope and hypotension are ominous findings, as they may represent a hemodynamically massive PE with impending cardiogenic shock.

### KEY FACT

d-dimer testing is only useful in patients with low likelihood of having a PE, in whom a ↓ d-dimer level essentially rules out PE. In all other patients, you should not obtain a d-dimer.

### KEY FACT

PE is ruled out when the Wells score is ≤4, d-dimer is normal, and clinical suspicion is low. If modified Wells score >4, further testing for PE is indicated.

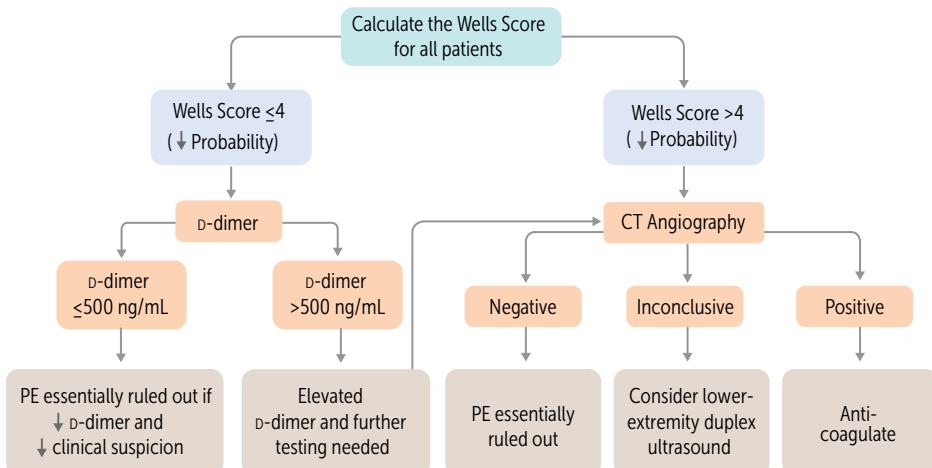
### PULMONARY EMBOLISM

#### Symptoms/Exam

- There are no specific signs or symptoms for pulmonary embolism (PE).
- **Dyspnea and pleuritic pain** are each seen in >50% of cases. Less common are hemoptysis, fever, and cough.
- Tachypnea, tachycardia, and a **loud P2** may be seen.

#### Diagnosis

- Validated diagnostic algorithms (Figure 10.1) combine clinical probability, d-dimer, and imaging tests (Figures 10.2 and 10.3) to establish the diagnosis.
- Key points:
  - **Before ordering tests**, clinicians should first determine the likelihood of PE using a validated prediction rule—either the **Modified Wells criteria** (Table 10.1) or the revised Geneva Score.
  - **d-dimer** is very sensitive but not very specific for PE. d-dimer should **not** be obtained in patients with intermediate to high pretest probability of PE (ie, those with modified Wells score >4).
- Ancillary lab tests:
  - **Troponin**: If ↑, implies right heart injury and more severe PE.
  - **BNP**: If ↑, implies right heart strain and more severe PE.
  - **ABG**: May demonstrate nonspecific respiratory alkalosis with an ↑ A-a gradient, but not that useful in differentiating PE from other causes of hypoxic respiratory distress.
- **ECG**: Usually abnormal, but may not be very specific for PE:
  - **Common findings, but do not imply right heart strain**: Sinus tachycardia (most common finding), anterior T-wave inversion.
  - **Uncommon findings, but indicate possible right heart strain**: Right axis deviation, RBBB, S1Q3T3 (S wave in lead I and a Q wave with an inverted T wave in lead III; Figure 10.4).



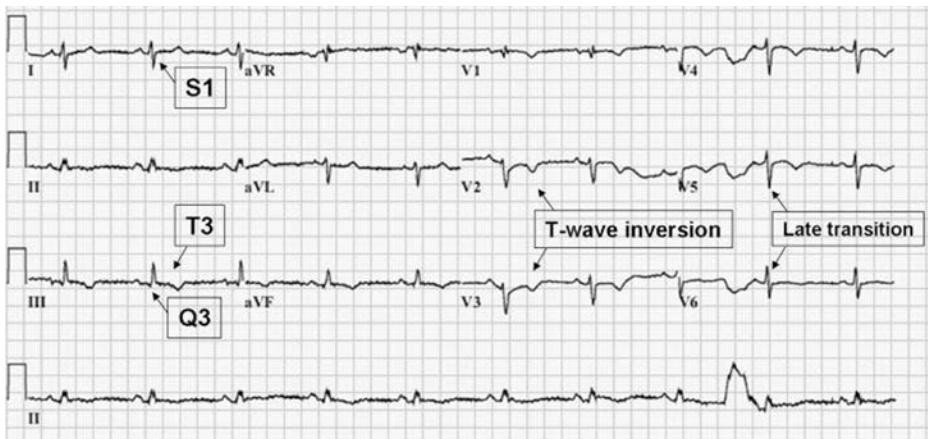
**FIGURE 10.1. Diagnostic algorithm for PE using the modified Wells criteria.** (Reproduced with permission from USMLE-Rx.com.)

**TABLE 10.1. Modified Wells Criteria for Pulmonary Embolism<sup>a</sup>**

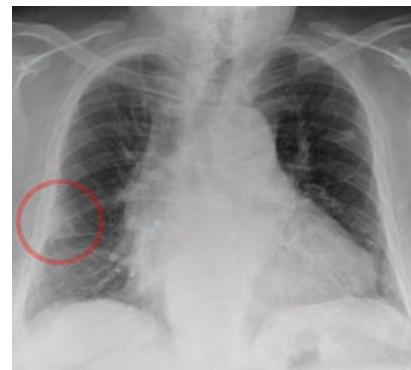
CLINICAL FINDINGS THAT INCREASE RISK	POINTS
Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than PE	3.0
Heart rate >100 bpm	1.5
Immobilization ( $\geq 3$ days) or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0

<sup>a</sup>Scores >4: PE is likely; scores  $\leq 4$ : PE is unlikely.

- Imaging:
  - **CXR:** Often shows nonspecific pleural effusion, atelectasis, or is normal. Two rare findings suggest PE:
    - **Hampton hump:** A pleural-based density representing pulmonary infarction (see Figure 10.2).
    - **Westermark sign:** Radiolucency distal to a pulmonary embolus due to oligemia.
  - **CT angiography and ventilation-perfusion (V/Q) scans:** CT angiography (see Figure 10.3) is generally preferred over V/Q in patients with suspected PE. See Table 10.2 for the pros and cons of CT angiography versus V/Q scanning.
  - **Echocardiography:** Two-dimensional transthoracic echocardiography (TTE) is useful for identifying right ventricular strain, which may lead to a change in management (ie, consider thrombolysis).
  - **Lower-extremity venous Doppler ultrasound:** A thrombus is present in approximately 30% of PE cases. Not necessary to obtain when a diagnosis of PE is already established by CT angiography or V/Q.
  - **Pulmonary angiography:** Gold standard, but rarely done since it is invasive and other modalities can detect PE reliably.



**FIGURE 10.4. ECG changes in PE.** S1Q3T3 is rarely seen, but indicates right heart strain. (Reproduced from Todd K, et al. ECG for the diagnosis of pulmonary embolism when conventional imaging cannot be utilized: a case report and review of the literature. *Indian Pacing Electrophysiol J.* 2009;9(5):268-275.)



**FIGURE 10.2. Hampton hump in pulmonary embolism.** (Reproduced from Wikimedia Commons/Hellerhoff.)



**FIGURE 10.3. CT angiogram demonstrating pulmonary emboli and saddle embolus.** (Reproduced from Wikimedia Commons/Hellerhoff.)



## QUESTION

A 56-year-old woman with metastatic breast cancer has had mild dyspnea, pleuritic chest pain, and left leg edema for 3 days. HR is 110 beats per minute, RR is 20 breaths per minute; exam is otherwise normal. Contrast-enhanced helical CT of the chest shows several segmental pulmonary emboli. Her Cr level is 0.7 mg/dL. What is the most appropriate treatment?

TABLE 10.2. Pros and Cons of Diagnostic Tests in Pulmonary Embolism

MODALITY	PROS	CONS	COMMENTS
V/Q scan	Noninvasive; results are well characterized; used in patient with CKD	Often not available after normal business hours; frequently nondiagnostic	Performs best when baseline CXR is normal
CT angiography	Specific; may reveal alternative diagnosis; better availability than V/Q in most hospitals	Risk of contrast dye nephropathy; uncertain sensitivity, especially for smaller thrombi	Sensitivity is >95%; a $\ominus$ CT angiogram does not rule out PE
Pulmonary angiography	The gold standard	Most invasive; requires local expertise	Perform only when other tests fail to establish the diagnosis

### Management

- **Acute treatment:** First objective is to determine severity of PE—massive, submassive, or lower-risk (Table 10.3).
- **“Massive” hemodynamically unstable PE:**
  - First-line treatment is systemic thrombolytic (tPA).
  - Second-line treatment (expert consultation required): Catheter-directed thrombolysis or surgical thrombectomy—last-ditch option for patients who are not candidates for thrombolysis or for those in whom thrombolysis fails.
- **Submassive PE** (hemodynamically stable patients with right heart strain): Controversial, but current guidelines recommend treat as for lower-risk PE, but have a low threshold to administer a thrombolytic if the patient begins to deteriorate.
- **Lower-risk PE** (hemodynamically stable PE with no RV dysfunction): Select one of three first-line anticoagulants for initial treatment based on contraindications (Table 10.4):
  - **Low-molecular-weight heparin (LMWH):** Caution in CKD and obese patients.
  - **Fondaparinux:** Factor Xa inhibitor. Easy daily dosing. Caution in CKD. Used in patients with history of HIT.
  - **IV unfractionated heparin (UFH):** Inferior to LMWH or fondaparinux, higher risk of HIT, but safe option for CKD patients.
  - **Other options for initial treatment:** Direct Xa inhibitor (rivaroxaban, apixaban, or edoxaban—caution in obesity [BMI >40] and CKD [GFR <30 mL/min] as all three are not dialyzable) and direct thrombin inhibitor (dabigatran, which is renally excreted, dialyzable agent; reverse with idarucizumab).
- **Long-term treatment options:**
  - **Warfarin:** Parenteral anticoagulation must overlap with warfarin for 5 days until INR >2 for over 24 hours.
  - **Dabigatran and edoxaban:** Use parenteral anticoagulation for 5 days, then transition to either agent. No overlapping needed.
  - **Rivaroxaban and apixaban:** Can start immediately without initial parenteral anticoagulation.

### KEY FACT

In hemodynamically stable PE, LMWH is more efficacious than UFH. Use LMWH as first-line therapy if the patient has no renal impairment.

### KEY FACT

LMWH and fondaparinux are superior to warfarin for the treatment of DVT or PE in patients with **active cancer**, but CKD and obesity are relative contraindications.

### KEY FACT

The two main indications for IVC filters in patients with PE are failed anticoagulation or a contraindication to anticoagulation.

### A

### ANSWER

SQ injections of low-molecular-weight heparin (LMWH). Patients with PE are typically treated acutely with LMWH in the short term and started on long-term warfarin. In patients with underlying malignancy, long-term use of LMWH instead of warfarin has been associated with improved mortality.

TABLE 10.3. Spectrum of PE Severity

	MASSIVE PE	SUBMASSIVE PE	LOWER-RISK PE
Hypotension present? (SBP <90 mm Hg after fluid bolus)	Yes	No	No
RV dysfunction/strain (imaging, ECG, labs)	Yes	Yes	No

**TABLE 10.4.** Contraindications to All Anticoagulation

ABSOLUTE	RELATIVE
Hemorrhagic stroke	Recent internal bleeding (within 6 months)
Active internal bleeding	Prior hemorrhagic stroke
Suspected aortic dissection	Thrombocytopenia
	CNS mass lesion (especially RCC and melanoma)

■ **Duration of anticoagulation:** Depends on nature of the clot (provoked vs unprovoked), presence of ongoing high-risk factor for recurrence (specifically active malignancy or antiphospholipid antibody syndrome), and bleeding risk. See Table 10.5. Special circumstances include the following:

- **Active cancer:** Indefinite anticoagulation with either LMWH or fondaparinux shown to be superior to warfarin. Extensive work-up to identify malignancy not indicated in patients with idiopathic PE or DVT. Rather, make sure age-appropriate cancer screening is up to date in these patients.
- Extensive evaluation for hypercoagulable states **not indicated**. Testing for **antiphospholipid antibodies** should be done in patients who have a clinical suspicion of this condition, since detecting these would be an indication to extend anticoagulation indefinitely.
- Initial **outpatient treatment** of PE has been shown to be safe but only in selected patients who can demonstrate understanding of anticoagulants and/or injection techniques and who are low-risk as defined by the Simplified PE Severity Index (**PESI**).
- Incidental small subsegmental PE may not require treatment.

#### KEY FACT

**Simplified PESI:** Consider hospitalization for a patient with PE who meets any of the following criteria:

- History of **Cancer**
  - History of chronic **Cardiopulmonary disease**
  - Age **>80** years
  - O<sub>2</sub> saturation **<90%**
  - SBP **<100** mm Hg
  - Heart rate **≥110** bpm
- (To remember this, think **C & C** and the **"80, 90, 100, 110" Rule**)

#### KEY FACT

All patients with PE or proximal DVT should be treated for a minimum of 3 months. Anticoagulation should be extended indefinitely if patient has active cancer or antiphospholipid antibody syndrome.

### DEEP VENOUS THROMBOSIS

The mortality rate for untreated venous thromboembolic disease exceeds 15%. Risk factors include **prior thromboembolic disease, malignancy, recent surgery, immobility, inherited thrombophilia, certain medications (eg, OCPs, HRT), tobacco use, stroke, and obesity**.

Risk factors for DVT are the same as those for PE. DVT of the lower extremities are more common than that of the upper extremities, which is often associated with central venous catheters and repetitive activity (Paget-Schroetter syndrome).

**TABLE 10.5.** Duration of Anticoagulation in Patients With DVT or PE

THROMBOTIC EVENT	DURATION OF ANTICOAGULATION
<b>Proximal leg DVT or PE</b>	
Provoked	3 months
Unprovoked	3 months
Recurrent unprovoked	Indefinitely if low to moderate risk of bleeding or 3 months if high risk bleeding
<b>Distal leg DVT (provoked or unprovoked)</b>	
Without severe symptoms	No anticoagulation needed; serial duplex ultrasound every 2 weeks. If extension to proximal vein, then treat for 3 months.
With severe symptoms	3 months

**KEY FACT**

Average-risk surgical patients (those without additional major risk factors) and medical inpatients should receive DVT prophylaxis with UFH, LMWH (eg, enoxaparin, dalteparin), or fondaparinux. Use nonpharmacologic therapy (eg, TEDS, SCDs) if anticoagulation is contraindicated.



**FIGURE 10.5. Deep vein thrombosis of right leg showing swelling and redness.** (Reproduced from Wikipedia/Dr. James Heilman.)



**FIGURE 10.6. Phlegmasia cerulea dolens, a complication of DVT.** (Source: Demircan A, et al. Pulmonary embolism presenting as syncope: a case report. *J Med Case Reports*. 2009;3:7440.)

**Symptoms/Exam**

- Pain, swelling, or erythema of the affected extremity (Figure 10.5) is most common.
- A palpable cord and low-grade fever are less commonly seen.
- Rarely, **phlegmasia cerulea dolens** (Figure 10.6)—complete venous obstruction resulting in a painful, swollen, and bluish extremity—may be seen.

**Diagnosis**

- **Compression/duplex ultrasonography:** Diagnostic test of choice for high-risk patients with DVT Wells Score >1 (Table 10.6).
- **D-dimer:** Highly sensitive for ruling out DVT in low-risk patients with DVT Wells score <1.

**Management**

Treatment is as outlined above for PE. Note: **Outpatient therapy** may be an option for patients who meet the following criteria:

- Clinical stability with normal vital signs.
- Low risk of bleeding.
- Normal or near-normal renal function.
- Adequate outpatient follow-up to ensure compliance **and** to monitor for complications.
- **Thrombolytic/thrombectomy therapy:** Rarely indicated for DVT; however, consider in patients (especially younger patients) with massive DVT (including phlegmasia cerulea dolens) or patients with no response to medical therapy.

**Prevention**

Prophylaxis should be considered in all hospitalized patients (see Table 10.7).

**TABLE 10.6. Wells Criteria for DVT**

CLINICAL FINDINGS THAT INCREASE RISK	POINTS <sup>a</sup>
Active cancer	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days, major surgery in last 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the deep venous system	1
Entire leg swollen	1
Calf swelling >3 cm compared to asymptomatic leg	1
Pitting edema confined to symptomatic leg	1
Non-varicose collateral superficial veins	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

<sup>a</sup>Scores: <0 = low pretest probability; 1-2 = moderate pretest probability; ≥3 = high pretest probability.

**TABLE 10.7. Strategies for Venous Thromboembolism Prophylaxis**

MEDICAL INPATIENTS <sup>a</sup>	PATIENTS UNDERGOING SURGERY
Low-dose UFH, LMWH, or fondaparinux Nonpharmacologic therapy with elastic stockings (ES) or intermittent pneumatic compression (IPC), if anticoagulation is contraindicated	<b>Low risk</b> (minor procedures, age <40, no clinical risk factors): ■ Early ambulation <b>Moderate risk</b> (minor procedures + thrombosis risk factors, age 40-60, no other clinical risk factors): ■ ES, low-dose UFH, LMWH, IPC + early ambulation if possible <b>High risk</b> (major operation <sup>b</sup> ; age >40, or with additional risk factors): ■ First line—LMWH, fondaparinux, or direct oral anticoagulant in combination with IPC or ES ■ Second line—warfarin or adjusted-dose IV UFH + IPC or ES

<sup>a</sup>Most medical patients with expected length of stay >3 days, especially patients with cancer, CHF, or severe pulmonary disease.

<sup>b</sup>Including orthopedic surgery, such as elective total hip or knee replacement surgery or hip fracture surgery.

## Acute Pain Management

Several basic principles guide the management of acute pain in the hospitalized patient:

- The patient's description of symptoms is the most reliable indicator of pain.
- **Mild to moderate pain:** Try nonopioid treatments first (acetaminophen, NSAIDs, lidocaine patch, heated pads).
- **Severe pain:** First select an **appropriate parenteral loading dose** with repeat doses every 10 to 15 minutes until pain relief has been achieved. Patients with active pain should not be treated with PRN medications alone.
- **Adjunctive measures:**
  - Neuropathic pain: Capsaicin cream and lidocaine patch are effective for localized neuropathic pain. TCAs, SSRIs, pregabalin, and gabapentin are systemic options.
  - Postoperative pain: Combination of NSAIDs and opioids.

## Delirium

Up to 30% of hospitalized elderly patients have delirium. Delirium (including postoperative delirium) in hospitalized patients may be caused by the following:

- **Underlying medical conditions:** Infection (eg, pneumonia), fever, depression, dementia, substance abuse, pain, metabolic derangement, unstable coronary syndrome.
- **CNS-altering medications:** Opioids, anticholinergics, benzodiazepines.
- **Other:** Advanced age, male gender, alterations in the sleep-wake cycle.

### Symptoms/Exam

- Characterized by an alteration in consciousness and cognition with rapid onset over hours to days.
- Symptoms wax and wane.
- **Cognitive dysfunction:** Disorganized thinking, hallucination, delusion, and inattention.

### Diagnosis

- Administer the **Confusion Assessment Method (CAM)** screening tool to enhance detection of delirium.

### KEY FACT

The lack of an adequate loading dose may result in frustrating efforts to "catch up" with the pain.

### KEY FACT

Avoid fentanyl in a patient who is opioid naïve since it can cause rapid respiratory suppression.

### KEY FACT

**Rule of 10s** for opioids: IV-equivalent doses can be remembered as differing by roughly a factor of 10: fentanyl is 10 times as strong as hydromorphone, which is 10 times as strong as morphine.

### KEY FACT

Although "hyperactive" delirium is easier to recognize, "hypoactive" delirium in the elderly is also common and has similar consequences.



### QUESTION

A 30-year-old woman develops a lower-extremity DVT 1 month following a cesarean section. She has had no previous venous thromboembolic events. She returns to the clinic after 6 months of anticoagulation with warfarin. Should warfarin be continued?

**MNEMONIC****Criteria for CAM Delirium Screen:****DIWA**Disorganized thinking or **Delirium****I**nattention**W**axing and waning**A**ltered level of consciousness**KEY FACT**

Avoid benzodiazepines for delirium unless in management of alcohol withdrawal as they can worsen symptoms.

**KEY FACT**

Beware of QT prolongation in patients being treated with typical or atypical antipsychotics.

**KEY FACT**

Mechanical ventilation for  $\geq 48$  hours and coagulopathy are the two most important risk factors for stress ulcer formation.

- To investigate the cause of delirium, high-yield steps include: detailed physical exam, review of the medication list, and limited lab studies (eg, electrolytes, serum calcium, UA, and CXR in the setting of new pulmonary findings).
- **CT of the head** is rarely useful, but consider in patients who are anticoagulated or have a history of trauma.
- **LP** is rarely useful, but consider in patient with clinical suspicion for meningitis.

**Management****First-line treatment:**

- Treat underlying cause.
- **Behavioral and environmental interventions** (eg, a quiet, supportive environment with orientation cues, nutrition, adequate sleep, hydration, regular mobility, and hearing aids/eyeglasses) can prevent up to one-third of delirium cases.

**Pharmacologic treatment:**

- There are no FDA-approved therapies for delirium.
- When given in low doses, **haloperidol** can be effective as a second-line therapy.
- Second-generation antipsychotic agents (**risperidone**, **olanzapine**, **quetiapine**) may also be effective.

**GI Prophylaxis in the Hospitalized Patient**

**Coagulopathy** (platelet count  $<50,000/\text{mL}$ ; INR  $>1.5$ ) and **respiratory failure necessitating mechanical ventilation for at least 48 hours** are the most powerful risk factors for stress-related hemorrhage. Other indications for prophylaxis are as follows:

- A history of ulceration or bleeding in the past year.
- Two or more of the following: Sepsis, an ICU stay of  $>1$  week, glucocorticoid therapy ( $>250$  mg of hydrocortisone daily), or an occult GI bleed for  $>6$  days.
- Table 10.8 lists the pros and cons of GI prophylaxis.

TABLE 10.8. **Prophylaxis for GI Bleeding**

TREATMENT	PROS	CONS
Sucralfate	Effective; reduces bleeding by 50%	Interferes with the absorption of multiple medications; requires frequent dosing Must be administered PO or through a feeding tube
H <sub>2</sub> receptor blockers	As effective as sucralfate and easier to use; can be given IV or PO	May be associated with an $\uparrow$ risk of nosocomial pneumonia, thrombocytopenia
PPIs	Likely as effective and easy to use as H <sub>2</sub> blockers	Not as well studied for this purpose as the others; may $\uparrow$ the risk of nosocomial pneumonia and <i>Clostridium difficile</i> infection
Enteral feeding	May $\downarrow$ bleeding risk	Not as well studied for this purpose

**ANSWER**

No. The patient had her first thrombotic event with transient risk factors (postpartum, following surgery). Therefore, it is appropriate to discontinue anticoagulation therapy after 3 to 6 months at a therapeutic INR.

## Perioperative Management

### PREOPERATIVE CARDIAC EVALUATION

- Assessment of cardiac risk:
  - Can be accomplished through use of a validated **risk prediction score** (Table 10.9).
  - Involves evaluation of three elements: **Patient-specific variables, exercise capacity, and surgery-specific risk** (Figure 10.7).
- Patients who do not need further cardiac evaluation include:
  - Asymptomatic patients with no history of CAD.
  - Patients with a cardiac history undergoing low-risk surgeries (cataract, inguinal hernia, and breast surgery).
- Further cardiac evaluation may be warranted in the following situations:
  - Consider obtaining a preoperative ECG within 3 months of surgery in patients with a history of PAD, TIA, CVA, CAD, or arrhythmia.
  - Consider cardiac stress testing prior to surgery in a high-risk cardiac patient only if it would change management (ie, delaying an elective surgery). Preoperative cardiac stress testing is rarely indicated.
  - Elective surgery should be postponed for 6 months after drug-eluting stent placement or 1 month for bare metal stent placement.

### PREOPERATIVE PULMONARY EVALUATION

The major risk factors for perioperative pulmonary complications are as follows:

- **Surgical factors:** Surgery near the diaphragm (chest or abdominal surgery), head and neck surgery, prolonged surgery, and use of general anesthesia (vs spinal/epidural).
- **Patient factors:**
  - American Society of Anesthesiologists (ASA) class  $\geq 2$  (mild systemic disease that does not limit the patient's function).
  - Chronic lung disease, an abnormal chest exam or radiograph, a history of a prior stroke, or functional dependence.
  - Smoking or alcohol: Patients who have smoked within the prior year or have had  $>2$  drinks of alcohol per day in the last 2 weeks.
  - Chronic steroid use.

Preoperative pulmonary risk assessment:

- All patients should be screened for obstructive sleep apnea with a validated screening survey.

**TABLE 10.9. Revised (Simplified) Cardiac Risk Index**

RISK FACTOR	INTERPRETATION
Add one point for each risk factor: <ul style="list-style-type: none"> <li>■ Higher-risk surgery (thoracic, abdominal, or major vascular operation above the inguinal ligament)</li> <li>■ Ischemic heart disease</li> <li>■ CHF</li> <li>■ Diabetes requiring insulin</li> <li>■ Cerebrovascular disease (a history of stroke or TIA)</li> <li>■ Renal insufficiency (<math>\text{Cr} &gt; 2 \text{ mg/dL}</math>)</li> </ul>	The risk of major complications: <ul style="list-style-type: none"> <li>■ Points 0 (Class I): Very low risk (0.4% complications)</li> <li>■ Points 1 (Class II): Low risk (0.9% complications)</li> <li>■ Points 2 (Class III): Moderate risk (6.6% complications)</li> <li>■ Points <math>\geq 3</math> (Class IV): High risk (<math>&gt; 11\%</math> complications)</li> </ul>

### KEY FACT

Exercise treadmill testing, nuclear stress imaging, and dobutamine stress echocardiography, when normal, predict a low risk of perioperative cardiac complications, but are rarely indicated prior to noncardiac surgery.

### MNEMONIC

**To recall the six risk components of the Revised Cardiac Risk Index—**

**4 C's + 2**

**CAD, CHF, CVA, CKD, + high-risk surgery and DM on insulin.**

### KEY FACT

Patients considered for noninvasive ischemia testing should generally undergo such testing only if the test result might lead to coronary revascularization—ie, if they have new symptoms or worsening of symptoms suggestive of active CAD.



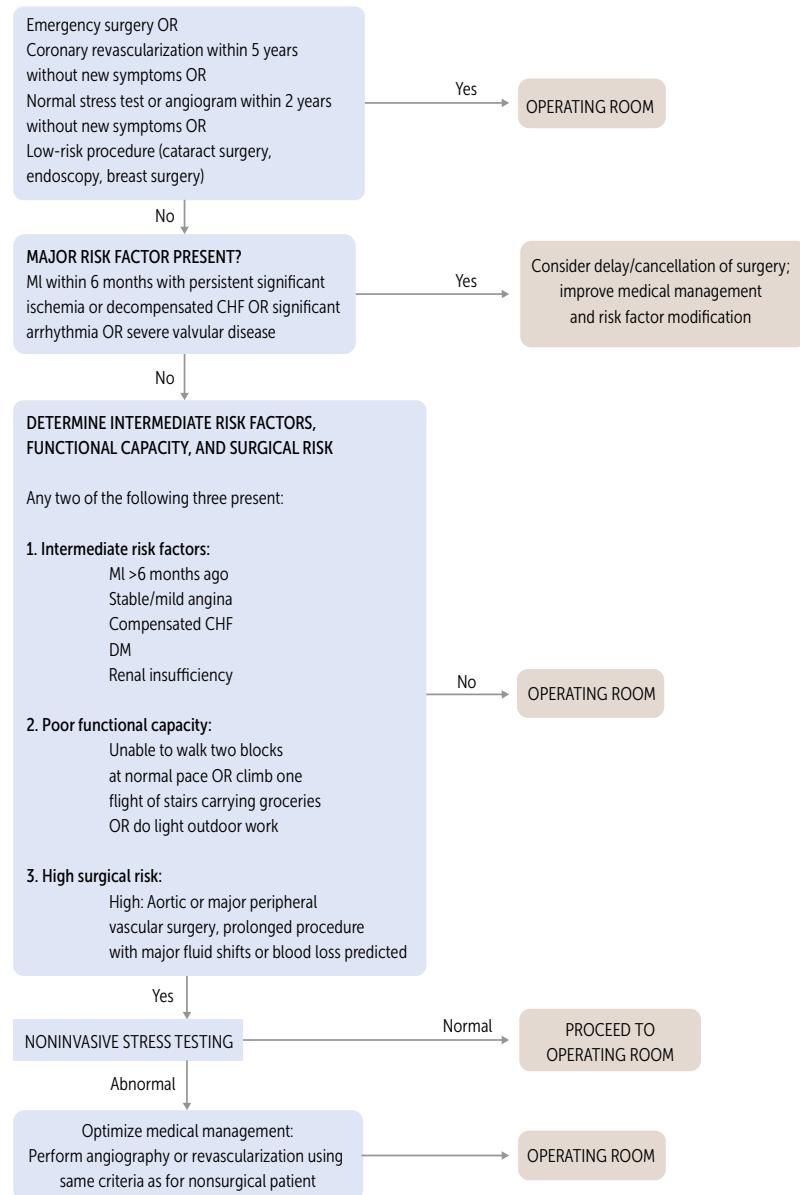
### QUESTION 1

A 70-year-old man with metastatic lung cancer is hospitalized for severe pain of the hip and chest wall from bony metastases. The pain is not controlled with ibuprofen, acetaminophen, or oxycodone-acetaminophen, but it is adequately controlled with a continuous morphine sulfate infusion at a rate of 1 mg/hr, with breakthrough doses of IV morphine sulfate at a rate of 2 mg/hr. What would be an appropriate home regimen for this patient?



### QUESTION 2

An 80-year-old man with a history of hypertension, and atrial fibrillation (on warfarin) is evaluated one week before a Whipple procedure. INR is 2.6. He is otherwise asymptomatic. How would you manage this patient's anticoagulation in the preoperative period?



**FIGURE 10.7. Algorithm for further cardiac evaluation and intervention.** (Reproduced with permission from USMLE-Rx.com.)

- Preoperative testing not routinely necessary includes PFTs in asymptomatic patients, CXR, and ABG analysis.

Preventive measures that ↓ the risk of pulmonary complications include:

- Smoking cessation if done at least 2 months preoperatively.**
- Incentive spirometry, including deep breathing exercises,** should be taught to the patient preoperatively.
- Selective NG decompression** to prevent postoperative pulmonary complications after abdominal surgery in patients with nausea, vomiting, or abdominal distention.
- Optimization of chronic lung disease.**
- Antibiotics** should not be given routinely.

#### PERIOPERATIVE MANAGEMENT OF CHRONIC MEDICAL CONDITIONS

See Table 10.10 for pre- and postoperative management of chronic disorders. Table 10.11 lists guidelines for the perioperative management of chronic conditions.

**TABLE 10.10.** Pre- and Postoperative Management of Chronic Disorders

CONDITION	POTENTIAL COMPLICATIONS	PREOPERATIVE MANAGEMENT	POSTOPERATIVE MANAGEMENT
DM, on insulin as outpatient	Hypo- and hyperglycemia, DKA, infection	Give 50% of usual long-acting insulin on the morning of surgery with a glucose drip (the exception being glargine, which should be given at the usual dose the evening before surgery).	Consider insulin drip titrating to normoglycemia; otherwise restart long-acting insulin with supplemental short-acting insulin (rapid titration of long-acting insulin).
DM, not on insulin	Hypo- and hyperglycemia; nonketotic hyperosmolar state; lactic acidosis (from metformin)	Omit oral hypoglycemic, noninsulin injectable, and metformin the day before surgery.	Consider insulin drip; use regularly scheduled short-acting insulin if needed and restart oral agent once able.
Chronic steroid use (especially > the equivalent of 20 mg prednisone × 3 weeks)	Adrenal crisis (rare)	Continue the usual dose.	Can usually give chronic dose; consider "stress-dose" steroids for longer/major surgeries (hydrocortisone 100 mg q 8 h × 2-3 days).
Liver disease	Mortality, hemorrhage, infection	Optimize treatment of underlying complications; elective surgery not recommended for patients with Model for End-stage Liver Disease (MELD) score ≥15.	Optimize treatment of underlying complications.

**TABLE 10.11.** Guideline for Perioperative Medication Management (except hypoglycemic agents)

PERIOPERATIVE MEDICATIONS	CONTINUE/DISCONTINUE	COMMENTS	
β-blockers	Continue, but do not initiate <2 weeks prior to surgery	Help control arrhythmia and reduce risk of ischemia; may lead to ↑ mortality with acute withdrawal	 <b>KEY FACT</b> Poor perioperative glycemic control is associated with a higher incidence of infection as well as with delayed wound healing.
α <sub>2</sub> -agonists (clonidine, methyldopa)	Continue, but do not initiate	Abrupt withdrawal can precipitate rebound hypertension	 <b>KEY FACT</b> PFTs, CXR, and ABGs are not part of a routine preoperative pulmonary risk assessment. Obtain these only if you would do so even if the patient were not undergoing surgery.
CCBs	Usually continue, but do not initiate	Limited data regarding risks and benefits of CCBs in the perioperative setting; may reduce ischemia and atrial arrhythmia	 <b>KEY FACT</b> Preoperative reduction of pulmonary complications in at-risk patients should focus on three things: <ul style="list-style-type: none"><li>■ Smoking cessation ≥2 months before</li><li>■ Education on incentive spirometry use</li><li>■ Optimization of chronic lung disease</li></ul>
ACEIs	<b>Discontinue the morning of surgery if there is concern for perioperative hypotension</b>	Conflicting data on benefits and risk of perioperative ACEI; may ↑ risk of hypotension	
Diuretics	<b>Discontinue the morning of surgery, especially if taking for BP control</b>	A dose of diuretic can be given if patient appears to be fluid overloaded the morning of surgery	
Nonstatin hypolipidemic agents (niacin, ezetimibe, fibrate)	<b>Discontinue before surgery</b>	Combining these agents can ↑ the risk of rhabdomyolysis in setting of surgery	

(continues)

**TABLE 10.11. Guideline for Perioperative Medication Management (except hypoglycemic agents) (continued)**

PERIOPERATIVE MEDICATIONS	CONTINUE/DISCONTINUE	COMMENTS
Statins	Continue especially in patients with CAD	Reduce postoperative ACS and mortality
Digoxin	Continue during perioperative period	Preoperative digoxin level not required
Inhaled $\beta$ -agonists and anticholinergics	Continue during perioperative period	Reduced postoperative pulmonary complication
Inhaled and systemic steroids	Continue during perioperative period	Risk of adrenal insufficiency with abrupt withdrawal of steroid
Theophylline	<b>Discontinue the evening before surgery</b>	Risk of arrhythmia and neurotoxicity
Leukotriene inhibitors	Continue the morning of surgery	Help control postoperative asthma
Warfarin	<b>Discontinue 5 days prior to surgery</b>	Indications for bridging with heparin or LMWH include procedure with significant bleeding risk, <b>and</b> any of these: <ul style="list-style-type: none"> <li>■ Mechanical heart valve</li> <li>■ VTE within last 3 months</li> <li>■ AF with CHADS2 score &gt;4 or recent CVA or TIA</li> </ul>
Direct oral anticoagulants	<b>Discontinue 1-2 days prior to surgery</b>	No heparin bridging needed

#### KEY FACT

In malnourished hospitalized patients who require supplemental feeding, enteral feeding is preferable to parenteral feeding. Nasojejunal tubes are more challenging to insert and provide minimal advantage over nasogastric tubes.

### Nutrition in the Hospitalized Patient

Nutritional options for hospitalized patients are summarized in Table 10.12. See Table 10.13 for metabolic complications of TPN.

### Overdose/Toxic Ingestion

General guidelines for overdose and toxic ingestion are as follows (see also Tables 10.14 and 10.15):

- **Supportive care**, including volume/electrolyte repletion, is the mainstay of treatment.
- **Airway protection**, including endotracheal intubation if necessary.
- Screen all patients for **co ingestions** for which there is a specific antidote or treatment (eg, acetaminophen, ASA).

**TABLE 10.12. Indications for Enteral Feeding, TPN, and PPN**

	INDICATIONS	PROS	CONS
Enteral feeding	Nutritional needs cannot be met through oral feeding and supplements	Less invasive; lower incidence of infectious complications Preserved mucosal immunity and bowel integrity More rapid transition to regular oral feeding	Requires a functional GI tract; necessitates tube placement Associated with an ↑ incidence of aspiration
TPN	Long-term need (>1-2 weeks) for supplemental or replacement nutrition; inability to use the GI tract	Long-term therapy is possible	The need for maintenance of central venous access can lead to catheter-related complications (2%-3%)—thromboses, infection, metabolic complications (see Table 10.13)
PPN	Short-term need (<1-2 weeks) for supplemental or replacement nutrition; inability to use the GI tract	Does not require central venous access	Effective only as a short-term option (1-2 weeks) Large-volume infusion

### ACUTE COMPLICATIONS OF SUBSTANCE ABUSE

- Symptoms/Exam:** Table 10.16 depicts an overview of the main types of acute toxicoses.
- Management:** Table 10.17 delineates guidelines for treating acute complications associated with the ingestion of controlled substances.



### KEY FACT

The combination of an **elevated** anion gap and an **elevated** osmolar gap suggests the ingestion of ethanol, methanol, or ethylene glycol. The combination of a **normal** anion gap and an **elevated** osmolar gap suggests the ingestion of isopropyl alcohol.

**TABLE 10.13. Metabolic Complications of TPN**

COMPLICATION	TREATMENT
Abnormal LFTs (cholestatic pattern)	↓ carbohydrate load; reconfigure the balance between fats, carbohydrates, and amino acids
Acalculous cholecystitis (4% with long-term TPN)	Surgery
Elevated BUN	Assess volume status; if adequate, ↓ the infusion rate and/or amino acid load
Hyperglycemia	Frequent glucose checks; addition of insulin to TPN
Micronutrient deficiencies (zinc, selenium, vitamin B <sub>12</sub> , copper)	Regular supplementation
Refeeding syndrome (hypophosphatemia, hypokalemia, hypomagnesemia)	Consider ↓ the infusion rate; electrolyte supplementation



### QUESTION

A 70-year-old suicidal man with a history of alcoholism is brought to the ICU following ingestion of an unknown quantity of unspecified OTC pills. He is unresponsive and intubated; has diffuse crackles on lung exam; and is tachypneic, tachycardic, and febrile. Lab results are: Na 147 mEq/L, Cl 108 mEq/L, HCO<sub>3</sub> 14 mEq/L, BUN 29 mg/dL, Cr 1.5 mg/dL, glucose 65 mg/dL, and serum osmolarity 319 mOsm/L. What substance is the likely cause of this overdose, and how would you treat it?

**KEY FACT**

Agents **not** bound by activated charcoal include lithium, ethanol/methanol/ethylene glycol, hydrocarbons, and heavy metals such as iron.

**KEY FACT**

Liver enzymes and INR may be normal when a patient presents within 12 hours of a potentially lethal acetaminophen ingestion. Maintain a low threshold to initiate treatment with *N*-acetylcysteine.

**KEY FACT**

Overdoses of anticholinergics and stimulants cause dilated pupils, tachycardia, hypertension, agitation, and fever. To differentiate the two, look for warm, dry skin due to anticholinergics vs clammy skin from stimulants.

**ANSWER**

Salicylate overdose, which presents with altered mental status, hyperthermia, respiratory alkalosis, anion-gap metabolic acidosis, intravascular volume depletion, hypoglycemia, and noncardiogenic pulmonary edema. Treat with activated charcoal, IV sodium bicarbonate infusion to alkalinize the urine to enhance salicylate excretion, and because this is a severe toxicity (severely altered mental status) hemodialysis.

**TABLE 10.14. Comparison of Methods for Removing Toxins**

METHOD	PROS	CONS
Activated charcoal with cathartics ("gut dialysis")	Binds most medications	Not effective for lithium, iron, alcohols, or hydrocarbons; must be given immediately Contraindications include altered mental status (aspiration risk), nausea, and bowel obstruction
Gastric lavage	Can consider for removal of undigested pill fragments	Has fallen out of favor, ↑ risk of aspiration Intubate prior to lavage if mental status is impaired Useful only within the first 1-4 hours after ingestion
Emetics (eg, ipecac)	Useful only when implemented <1 hour after ingestion (if at all)	↑ risk of aspiration <b>Avoid in most adults</b>
Urine alkalinization to a pH >7 with IV sodium bicarbonate	↑ the excretion of <b>ASA, TCAs, and phenobarbital</b>	Ineffective for all other ingestions
Hemodialysis	Effectively clears salicylates, digoxin, and toxins that are not bound by charcoal (lithium, methanol, ethylene glycol, isopropyl alcohol)	Invasive; not effective for removing benzodiazepines, opiates, or TCAs
Charcoal hemoperfusion	Highly effective for digoxin, theophylline, and salicylates	Invasive

**ETHANOL WITHDRAWAL**

The mortality rate from ethanol withdrawal is approximately 5% and results primarily from the hemodynamic instability seen in delirium tremens (DTs).

- **Symptoms/Exam:** See Table 10.18.

- **Management:**

- **Benzodiazepines** (eg, lorazepam or diazepam) are the cornerstone of treatment for withdrawal symptoms as well as for withdrawal seizures. Use the Clinical Institution Withdrawal Assessment (CIWA) scale to provide as needed benzodiazepines rather than a scheduled dosing to prevent over sedation.
- **Gabapentin and carbamazepine:** May be useful adjuncts, but their use should not supplant the role of benzodiazepines.
- All patients should receive **thiamine** supplementation to prevent Wernicke-Korsakoff syndrome, which can manifest as ophthalmoplegia, confusion, ataxia, and amnesia.
- Symptom-triggered protocols to treat alcohol withdrawal (eg, the CIWA protocol) have been well studied and result in lower doses of benzodiazepines used, but they require frequent reassessment.

TABLE 10.15. Characteristics and Treatment of Common Ingestions

SUBSTANCE	MANIFESTATIONS	LAB TESTS	TREATMENT	COMMENTS
Acetaminophen	Initially presents with nausea and vomiting An asymptomatic interval is followed by recurrent nausea, abdominal pain, and jaundice	Elevated acetaminophen level (level depends on time) LFTs begin to rise within 12 hours (can be markedly elevated in the thousands) PT/INR most indicative of prognosis	Consider treating with <b>activated charcoal</b> if patient presents early <b>N-acetylcysteine</b> is the mainstay of therapy <b>Immediate transfer to a liver transplant center</b> for progressive coagulopathy, acidosis, or liver failure	<i>N</i> -acetylcysteine is most effective within 10 hours but may be effective significantly later
Aspirin	Nausea and vomiting; tinnitus; GI bleeding and volume depletion; mental status changes	<b>Anion-gap metabolic acidosis with concomitant respiratory alkalosis</b>	Activated charcoal	
	Noncardiogenic pulmonary edema	<b>Elevated PT</b>	<b>Sodium bicarbonate</b> to alkalinize serum and urine to promote renal elimination	
	Hyperthermia	Elevated serum salicylate Hepatotoxicity, hypoglycemia	<b>Consider hemodialysis in severe toxicity</b>	
Digoxin	GI symptoms, visual disturbance, confusion, arrhythmias	Hyperkalemia (potassium level correlates with the degree of acute toxicity) Digoxin level	Activated charcoal is effective if given within 6-8 hours of ingestion Digoxin-specific Fab fragments for K >5 mEq/dL, hemodynamic instability, life-threatening arrhythmias, severe bradycardia, or a digoxin level of >10 ng/mL	Verapamil, diltiazem, erythromycin, tetracycline and renal failure can ↑ digoxin levels
Cyanide	Almond odor breath, headache, tachycardia, tachypnea, pulmonary edema Cherry-red cyanosis is a late finding	Bright red venous blood Cyanide levels Severe metabolic acidosis with an elevated anion gap and lactate level ↓ arterial-venous oxygen gradient	Resuscitate, ABCs, decontaminate, activated charcoal (1) Amyl nitrate inhalation; (2) 3% sodium nitrite IV; (3) sodium thiosulfate IV	
Organophosphate	↑ salivation, miosis, nausea, vomiting, diarrhea, abdominal cramps, chest tightness, weakness		Decontaminate; give atropine PRN for moderate to severe symptoms; 2-protopam IV	
Lithium	Altered mental status progressing to encephalopathy/coma, tremor, seizures, hyperreflexia, clonus, parkinsonism	Elevated serum lithium level	Volume repletion; consider alkalinization of urine Consider hemodialysis for severe toxicity	Levels may "rebound" and require repeat dialysis Not bound by activated charcoal

(continues)

TABLE 10.15. Characteristics and Treatment of Common Ingestions (continued)

Substance	Manifestations	Lab Tests	Treatment	Comments
SSRIs	<b>Serotonin syndrome</b> with somnolence or agitation, nausea, vomiting, fever, tachycardia, and clonus	None	Supportive care	Rarely fatal There is an ↑ risk of serotonin syndrome with mixed ingestions
TCAs	" <b>Mad as a hatter, red as a beet, dry as a bone, blind as a bat, hot as a hare</b> "—ie, altered mental status, flushed, dry mouth, dilated pupils	Look for tachycardia with widened QRS (>0.12)	Activated charcoal; IV <b>sodium bicarbonate</b> boluses may ameliorate cardiotoxicity	Serum TCA levels not helpful—do not order
Methanol	Altered mental status, seizures, nausea, vomiting, visual disturbances, blindness	Anion-gap metabolic acidosis with elevated osmolar gap ( $\text{osm}_{\text{measured}} - \text{osm}_{\text{calculated}}$ ) Elevated serum methanol level	<b>Mild cases:</b> Sodium bicarbonate and IV <b>fomepizole</b> <b>Severe cases: hemodialysis</b>	Mortality is >80% with seizures or coma
Ethylene glycol	Same as methanol Oxalate crystals in the urine	Anion-gap metabolic acidosis with elevated osmolar gap ( $\text{osm}_{\text{measured}} - \text{osm}_{\text{calculated}}$ ) Elevated serum ethylene glycol level	Treatment is the same as that for methanol, including consideration of hemodialysis	
Isopropyl alcohol (eg, rubbing alcohol)	Altered mental status progressing to coma; ataxia; hypotension 2° to myocardial depression	Elevated osmolar gap ( $\text{osm}_{\text{measured}} - \text{osm}_{\text{calculated}}$ ) but <b>no anion gap</b> metabolic acidosis	<b>Hemodialysis</b> for coma or for a plasma isopropanol level >400 mg/dL	
Carbon monoxide	Headache, altered mental status, seizures, coma	<b>Elevated carboxyhemoglobin saturation</b> on ABG (values may normally be up to 15% in smokers) Toxicity is seen when level is >15%-30% <b>Pulse oximetry and <math>\text{Po}_2</math> may be normal</b>	<b>High-flow <math>\text{O}_2</math> via an endotracheal tube</b> for severe cases Hyperbaric oxygen if immediately available for severe poisoning	Cherry-red lips are infrequently seen

TABLE 10.16. Toxidrome Patterns

	PUPILS	HEART RATE	CNS	SKIN	BOWEL MOVEMENTS	TEMPERATURE
<b>Anticholinergic</b>	Dilated	Tachycardia	Confused	Dry	↓	↑
<b>Cholinergic</b>	Constricted	Bradycardia/normal	Lethargy	Diaphoretic	↑	Normal
<b>Opioid</b>	Constricted	Bradycardia/normal	Depressed	Normal	↓	↓
<b>Sympathomimetic</b>	Dilated	Tachycardia	Hyperactive	Diaphoretic	↑	↑

**TABLE 10.17.** Acute Complications of Substance Abuse

SUBSTANCE	MANIFESTATIONS	LAB TESTS	TREATMENT	COMMENTS
Gamma-hydroxybutyrate (GHB)	Somnolence and respiratory depression; bradycardia; muscle twitching and seizures	None	Consider activated charcoal if ingestion was very recent Supportive care	Most patients spontaneously recover within 6 hours
Opioids	Somnolence followed by respiratory depression and coma Constricted pupils, hypotension, bradycardia, apnea, hypothermia Pulmonary edema and aspiration are possible Meperidine and tramadol may cause seizures	⊕ urine toxicology screen, though lots of cross-reactivity and false positives (except methadone and tramadol)	Supportive care Naloxone 0.4-1.0 mg PRN (the effect of naloxone lasts only 2 hours, and repeated doses may be necessary)	Fentanyl may require very high doses of naloxone Patients should be observed for at least 24 hours (or longer for methadone coingestion) Screen for coingestion (many opioids, such as Tylox and Percocet, are compounded with acetaminophen)
Cocaine	Agitation, palpitations, chest pain Tachycardia, hypertension Myocardial ischemia/infarction Stroke	Toxicology screen Always obtain an ECG to assess for ischemic changes	Benzodiazepines	Avoid β-blockers with myocardial ischemia (unopposed α constriction)
Amphetamines (including MDMA)	Agitation, tachycardia, hypertension, hyperthermia, seizures, rhabdomyolysis	Elevated CK with rhabdomyolysis Hyponatremia may accompany MDMA ingestion	Benzodiazepines Specific treatment of complications (cooling and neuromuscular paralysis for hyperthermia; hydration and alkalinization for rhabdomyolysis)	Avoid β-blockade
Ethanol	Disinhibition, agitation, slurred speech Somnolence progressing to stupor with respiratory depression and coma	Elevated blood alcohol level	Supportive care Attention to nutritional deficiencies in chronic alcoholics Screen for coingestions	
PCP (phencyclidine)	Agitation, psychosis, and nystagmus that may be in any direction (including rotatory)	May not be detected by a standard urine toxicology screen; request specific test	Supportive care	Patients on PCP are prone to sudden violent outbursts

TABLE 10.18. Symptom Progression of Ethanol Withdrawal

	MINOR WITHDRAWAL	WITHDRAWAL SEIZURES	HALLUCINATION	DELIRIUM TREMENS
Time since last drink	6-36 hours	6-36 hours	12-48 hours	48-96 hours
Symptoms	Anxiety, tremulousness, headaches, diaphoretic, tachycardic, hypertensive	Usually a singular tonic-clonic seizure Third seizure will progress to DTs	Auditory or tactile with otherwise clear sensorium	Hyperthermia, hypertensive, hallucination, agitation
Comments	CIWA protocol and treat with benzodiazepines	Treat with benzodiazepines	Precursor to DTs	5% mortality

## Hypertensive Urgency and Emergency

### KEY FACT

Poorly controlled essential hypertension usually due to medication noncompliance is by far the most common cause of hypertensive urgency/emergency.

Hypertensive **emergency** occurs when an elevated BP leads to **active end-organ damage** that is likely to result in death or serious morbidity in the absence of immediate treatment. Hypertensive emergencies may occur at BPs that are not considered “critically” high. Hypertensive **urgency** occurs with severe hypertension (>220/120 mm Hg) **without end-organ complications**.

### Symptoms/Exam

- Systolic BP is usually >180 mm Hg; diastolic BP is usually >120 mm Hg. The BP level tolerated may depend on the chronic baseline BP.
- Funduscopic exam may reveal papilledema and flame hemorrhages (Figure 10.8).
- **Hypertensive encephalopathy:** Nausea/vomiting, headache, confusion, lethargy, and/or irritability.
- **Intracranial hemorrhage:** Focal neurological deficits, seizures, altered mental status.
- **Cardiovascular injury:** Aortic dissection, myocardial infarction, heart failure.
- **Acute kidney injury:** ↑ creatinine, hematuria and proteinuria.

### KEY FACT

In a young patient with refractory or severe hypertension, palpitations, and headache, consider pheochromocytoma and order 24-hour urine metanephrenes and catecholamines or plasma free metanephrenes.



**FIGURE 10.8. Flame hemorrhages.** Color fundus photograph of the right eye demonstrating cotton wool spots and flame hemorrhages in a 57-year-old woman with hypertension. (Reproduced with permission from USMLE-Rx.com.)

## Differential

Poorly controlled essential hypertension is most common, but consider other 2° causes.

## Diagnosis

Evaluate further if symptoms suggest a complication or an unusual etiology:

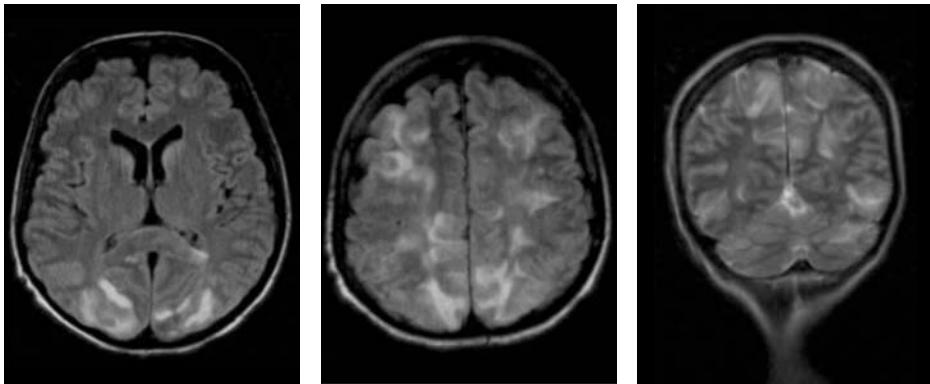
- **CT of the head** in patients with mental status changes or focal neurologic deficits to exclude intracranial hemorrhage.
- **MRI** in hypertensive encephalopathy may demonstrate **posterior reversible leukoencephalopathy syndrome**, white matter edema, particularly in the posterior circulation territories (Figure 10.9).
- **Emergent transesophageal echocardiography or thoracic CT angiography** in suspected aortic dissection.
- **Electrocardiography** in patients with suspected myocardial ischemia.

## Management

- **Pharmacologic** treatment is dictated by the specific end-organ complications (Table 10.19).
- **Hypertensive emergency:** BP should be lowered by 10% to 15% or a ↓ in diastolic BP to <120 mm Hg within 1 hour, then by 25% in next 6 to 12 hours to prevent stroke or MI with parenteral agents.
- **Hypertensive urgency:** Use oral medications (eg, captopril and clonidine) to control BP more gradually.

## Syncope

Defined as a transient loss of consciousness and postural tone; accounts for 3% of all ED visits and up to 6% of all hospital admissions. Table 10.20 lists common etiologies of syncope.



**FIGURE 10.9. Posterior reversible leukoencephalopathy syndrome (PRES).** Axial FLAIR images (A and B) show bilateral cortical and subcortical hyperintense lesions involving occipital lobes and frontal and parietal watershed zones. Coronal T2 image (C) demonstrates predilection of PRES for posterior circulation-bilateral edema in parietal and occipital lobes and cerebellar hemispheres. (Reproduced from Plavetić ND, et al. Fatal outcome of posterior “reversible” encephalopathy syndrome in metastatic colorectal carcinoma after irinotecan and fluoropyrimidine chemotherapy regimen. *World J Surg Oncol.* 2014;12:264.)

## KEY FACT

In hypertensive urgency and emergency, mean arterial pressure should be lowered by no more than 10% to 15% within the first hour. BP should subsequently be lowered by 25% over the ensuing 6 to 12 hours.



## QUESTION 1

A 40-year-old alcoholic man is admitted for pancreatitis. His friends report that he had been drinking liquor all day for several weeks and eating only salty foods. During hospitalization, he aspirated requiring vasopressor support and mechanical ventilation. Eventually, TPN, 2000 calories daily in 2 L, is started. For what condition is the patient at high risk?



## QUESTION 2

A 22-year-old male college student is brought to the ED from a party and is found to be febrile, hypertensive, tachycardic, and combative. While in the ED, he has a witnessed generalized tonic-clonic seizure that lasts approximately 3 minutes. His pupils are dilated. What is the diagnosis, and how should he be treated?



## QUESTION 3

A 68-year-old man with CAD and stent placement one year ago presents with headache, nausea, vomiting, and chest pain radiating to his back. A stress test 2 months ago was normal. BP is 220/120 mm Hg in both arms, an S4 gallop and crackles are heard at both bases, and he is diaphoretic. ECG shows ST depressions in the lateral leads. What are the drugs of choice for treatment?

**KEY FACT**

Rapid-acting oral or sublingual nifedipine should be avoided, as it may lower BP too drastically and precipitate stroke.

**A****ANSWER 1**

Refeeding syndrome with high-carbohydrate loads in severely malnourished patients results in a dramatic ↑ in insulin levels, causing glucose, potassium, phosphate, and magnesium to shift into cells. The severe hypophosphatemia that results can lead to CHF, respiratory failure, rhabdomyolysis, cell dysfunction, seizures, and coma. Thus, phosphate levels should be closely monitored in severely malnourished patients. These patients need aggressive electrolyte supplementation.

**A****ANSWER 2**

Cocaine intoxication (sympathomimetic syndrome). The patient's hypertension, tachycardia, fever, agitation, and seizure should all respond to benzodiazepines.

**A****ANSWER 3**

For aortic dissection, the goal is to ↓ BP to prevent end-organ damage but not to the degree that it might cause cerebral, cardiac, and renal ischemia due to autoregulation. IV labetalol followed by sodium nitroprusside are the drugs of choice.

**TABLE 10.19. Medications for Specific Complications of Hypertensive Emergency**

INDICATION	TREATMENT	CONTRAINDICATED	COMMENTS
Aortic dissection	Nitroprusside and labetalol	Nicardipine, hydralazine	Beware of <b>thiocyanate toxicity</b> from nitroprusside, especially in patients with renal or hepatic insufficiency
Pulmonary edema	Nitroprusside, nitroglycerin		
Myocardial ischemia/ infarction	Nitroglycerin, labetalol	Nicardipine, hydralazine	
Hypertensive encephalopathy	Labetalol, nicardipine	Nitroprusside	
Eclampsia	Labetalol, hydralazine	Enalapril, nitroprusside	
Acute renal failure	Labetalol		
Scleroderma hypertensive crisis	<b>ACEIs</b>		<b>Even if scleroderma crisis is associated with AKI, ACEIs should be used as first-line!</b>
Sympathomimetics (eg, cocaine)	Nicardipine, nitroprusside, benzodiazepine	β-blocker	
Pheochromocytoma	Phentolamine, nitroprusside	Avoid starting β-blocker until after phentolamine	Use of β-blocker first can cause <b>unopposed α-adrenergic receptor agonism</b> , leading to vasoconstriction and worsening of HTN
Renal artery stenosis	Revascularization may be useful in select circumstances ACEIs for unilateral renal artery stenosis	ACEIs contraindicated in bilateral renal artery stenosis	Careful monitoring with ACEIs required; do not use if bilateral renal artery stenosis is suspected
Hyperthyroidism	β-blocker		See the Endocrinology chapter
Hyperaldosteronism	Nifedipine, ACEI, ARBs		

**TABLE 10.20. Differential Diagnosis of Syncope**

MECHANISM	SUGGESTIVE FEATURES	COMMENTS
Orthostatic hypotension (volume depletion, autonomic insufficiency, medication related)	History of presyncope upon standing; advanced age; drop in BP (systolic BP by $\geq 20$ mm Hg or diastolic BP by $\geq 10$ mm Hg) upon standing	Orthostasis plus Parkinsonian features suggest Parkinson disease or multiple system atrophy Medications to consider include diuretics, antihypertensives
Neurally mediated ( <b>vasovagal</b> , vasomotor, neurocardiogenic, situational, carotid sinus hypersensitivity)	Preceded by nausea, flushing, diaphoresis, and tachycardia Look for occurrence during emotional stress or pain or in specific situations (eg, while coughing, micturating, or defecating)	Carotid hypersensitivity typically seen in older patients, classically provoked by neck stretching (eg, while shaving or reversing a car)
Cardiac (arrhythmia, structural, MI, PE, aortic dissection)	Arrhythmia: No premonitory symptoms or residual symptoms upon awakening Look for characteristic murmurs on exam to suggest aortic stenosis or hypertrophic obstructive cardiomyopathy	Syncope due to PE suggests large PE In a patient with syncope, the first priority is to search for a cardiac cause, as patients with cardiogenic syncope are at $\uparrow$ risk for sudden death
Miscellaneous causes and mimickers	Migraine: Subsequent headache Vertebrobasilar insufficiency: Tinnitus, dysarthria, diplopia; focal neurologic findings Seizure: Postictal state, incontinence, slow recovery (>5 minutes), prodromal aura Psychiatric: Diagnosis of exclusion	

### Symptoms/Exam

- The history and physical exam establish a diagnosis in almost 50% of patients with syncope. However, specific findings are dependent on the underlying etiology, and knowledge of the differential diagnosis is critical (see Table 10.20).
- Situational syncope includes syncope associated with vagal stimulation—eg, straining, micturition, defecation, cough, and occasionally swallowing (cold liquids).

### Diagnosis

After history and physical, orthostatic BP measurements and ECG are the next highest-yield tests to perform in patients with syncope:

- Orthostatic vital signs:** When moving the patient from a supine to an upright position results in a  $\downarrow$  in systolic BP of  $\geq 20$  mm Hg, an  $\uparrow$  of  $\geq 20$  beats in HR, or the reproduction of symptoms, consider orthostatic hypotension.
- ECG:** Look for evidence of ischemia, arrhythmia, nodal or bundle branch blocks, or a prolonged QT interval.
- Patients <45 years of age with a normal ECG and no history of structural heart disease are at low risk for an adverse outcome in syncope.
- Older patients—especially those with risk factors for or a history suggestive of cardiac disease or arrhythmia—should undergo more detailed testing, including echocardiography and noninvasive testing for CAD.

Other testing is only useful in selected individuals:

- Echocardiogram:** Consider in patient with heart disease, abnormal cardiac exam, or suspicious ECG findings.
- Outpatient cardiac rhythm monitoring:** Generally low yield, obtain only when symptoms suggest arrhythmia and ECG/telemetry monitoring failed to detect arrhythmia. Two options:
  - Holter monitoring for 24 to 96 hours:** Consider when the patient has frequent symptoms that suggest arrhythmia.



### QUESTION

A 75-year-old man with a history of CAD, DM, hypertension, and hyperlipidemia is brought to the ED after experiencing a one-minute episode of syncope while getting out of his car. He reports diaphoresis and palpitations before the episode but denies incontinence; records show no new medications in the past few months and no diuretics. On admission, exam is normal, ECG shows an old bifascicular block. An exercise stress test, an echocardiogram, and 24-hour Holter monitoring are all normal. What is the next step in the evaluation?

**KEY FACT**

Low-yield testing to be avoided in majority of patients with syncope include: cardiac enzymes, extended cardiac rhythm monitoring, cardiac stress test, tilt-table test, and testing for neurologic disease with carotid ultrasound, CT, MRI, or EEG.

- **30-day loop recorders and event monitors:** ↑ the yield in patient with less frequent symptoms.
- **Cardiac enzymes** (eg, troponin): Should not be routinely obtained in the evaluation of syncope; order only when other findings suggest cardiac ischemic event.
- **Tilt-table testing:** Rarely indicated; consider in patients with recurrent unexplained syncope or in high-risk occupations (surgeons, construction worker, pilots, bus driver).
- **Carotid ultrasound:** Not routinely recommended in the evaluation of syncope.
- **CT and MRI:** Not recommended unless there is head trauma or neurological deficits.
- **EEG:** Useful only when seizures are suspected.

**Management**

Treatment is directed at the underlying condition. Use the **San Francisco Syncope Rule**, “CHESS,” to help determine when hospital admission may be safely avoided. Guidelines for hospital admission are as follows:

- **Definite admission:** History or exam suggestive of arrhythmia, ACS, heart failure, or patients with significant comorbidities (eg, anemia).
- **Possible admission:** Patients >70 years of age; those with exertional or frequent syncope, orthostasis, or injury due to a syncopal episode.

**MNEMONIC****San Francisco Syncope Rule—CHESS**

**CHF**  
Hematocrit <30%

ECG abnormalities that are new  
Systolic BP <90 mm Hg  
Shortness of breath

**Patients with none of the CHESS features may avoid hospital admission.**

**Community-Acquired Pneumonia****Symptoms/Exam**

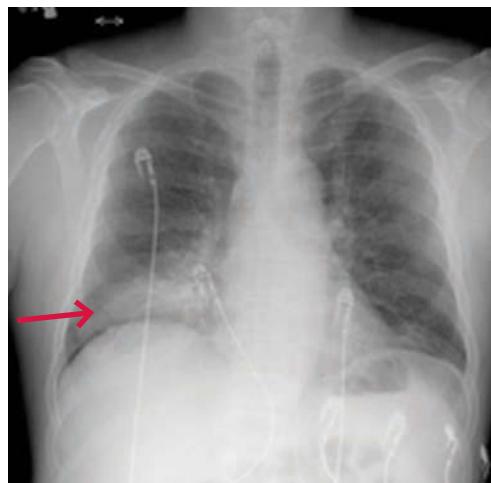
- Fever, dyspnea, and cough productive of purulent sputum are most commonly seen in community-acquired pneumonia (CAP).
- **Pleuritic chest pain and chills/rigors** are also possible.

**Diagnosis**

- **CXR:** Shows an infiltrate (Figure 10.10), but radiographic findings cannot predict the microbiologic cause. False-negative CXR results have been reported in patients who are dehydrated on admission.

**A****ANSWER**

A continuous loop recorder. Long-term ( $\geq 30$ -day) event monitoring is warranted if the suspicion of an arrhythmia is still high after inpatient telemetry and outpatient Holter monitoring are found to be normal. With CAD and a bifascicular block, strongly suspect arrhythmia. The 1-year cardiac mortality and sudden death rates are higher in cardiac than in noncardiac or idiopathic syncope.

**A****B**

**FIGURE 10.10. Community-acquired pneumonia.** Frontal (A) and lateral (B) radiographs show airspace consolidation in the right middle lobe (red arrows) in a patient with community-acquired pneumonia. (Reproduced with permission from USMLE-Rx.com.)

- Sputum Gram stain and culture:** Variable utility and generally indicated for patients who are hospitalized in the ICU, have complications (pleural effusions or cavitation, immunocompromised), or have not responded to outpatient treatments.
- Blood cultures:** Same indications as sputum cultures.  $\oplus$  in approximately 10% of cases.
- Other:** Tests for specific and rare etiologies (Table 10.21), including serologies for Q fever and psittacosis, culture and urine antigen testing for *Legionella* and pneumococcus, and IgM titers for *Mycoplasma*, should be obtained only when there is high clinical suspicion or severe CAP.
- Certain historical features may suggest a specific microbiologic etiology for CAP, but none is adequately specific to establish a diagnosis.

## Management

Use the CURB-65 tool to triage patients.

- Outpatient treatment:** For healthy individuals, prescribe a macrolide (eg, azithromycin) or doxycycline; for individuals with comorbidities (eg, cardiopulmonary disease), prescribe respiratory fluoroquinolones (eg, moxifloxacin, levofloxacin).
- Inpatient treatment:** Two first-line options are broad  $\beta$ -lactam (eg, ceftriaxone) plus a macrolide or doxycycline, **or** monotherapy with a respiratory fluoroquinolone.

TABLE 10.21. Causative Organisms and Historical Features of Community-Acquired Pneumonia

ORGANISM	CAUSE (%)	SUGGESTIVE HISTORICAL FEATURES
<i>Streptococcus pneumoniae</i>	20-60	Acute onset; often follows a URTI; underlying COPD Drug resistance is more likely in patients >65 years; in those who have had $\beta$ -lactam therapy in the last 3 months; and in the setting of EtOH abuse, immunosuppression, multiple comorbidities, and/or exposure to a sick child in day care
<i>Haemophilus influenzae</i>	3-10	Often follows a URTI; COPD
<i>Staphylococcus aureus</i>	3-5	May follow influenza infection; cavitary disease
<i>Legionella</i> spp	2-8	Associated with exposure to humidifiers, hot tubs, or air-conditioning cooling towers Pleuritic chest pain and pleural effusion are common; diarrhea, hyponatremia
<i>Klebsiella</i> , other gram-negative rods	3-10	Associated with ethanol abuse, DM, residence in a nursing home, recent antibiotic use, and multiple comorbidities
<i>Mycoplasma pneumoniae</i>	1-6	Commonly affects young adults in summer and fall; associated rash and bullous myringitis CXR appears worse than symptoms suggest
<i>Chlamydia pneumoniae</i>	4-10	Commonly affects young adults; pneumonia often occurs 2-3 weeks after a prolonged sore throat (biphasic pattern)
Q fever ( <i>Coxiella burnetii</i> )	Rare	Exposure to livestock (cattle, goats, sheep); elevated LFTs
<i>Chlamydia psittaci</i>	Rare	Exposure to birds, including parrots, pigeons, and chickens; headache; temperature-pulse dissociation

## KEY FACT

Blood cultures are the most definitive way to establish a causative organism in CAP but are  $\oplus$  in only 10% of cases.

## MNEMONIC

**Criteria to determine CAP severity and type of treatment—**

### CURB-65

Confusion

Urea nitrogen >20 mg/dL (7.14 mmol/L)

Respiratory rate  $\geq$ 30 breaths/min

BP (systolic <90 mm Hg, diastolic  $\leq$ 60 mm Hg)

65 years or older

Add 1 point per criterion:

■ **Outpatient therapy:** CURB-65 score of 0-1

■ **Inpatient admission:** CURB-65 score of 2

■ **ICU admission:** CURB-65 score of  $\geq$ 3



## QUESTION

A 65-year-old nonsmoking man with a chronic productive cough and a history of severe pneumonia 20 years ago presents with a cough, fever, and yellow-green sputum production. He reports that he usually requires antibiotics once or twice yearly, when his sputum production  $\uparrow$  or gets darker and his cough becomes worse than his baseline. On exam, he is febrile with coarse breath sounds at the right lung base, a CXR shows a patchy right lower lobe infiltrate where 4 years ago there were nonspecific  $\uparrow$  markings on CXR. The patient also has leukocytosis and bandemia. What organism should be covered in the selection of an empiric regimen for this patient?

**KEY FACT**

There is no benefit to observing patients in the hospital after conversion to oral therapy once they have met the criteria for clinical stability.

- **ICU treatment:** A  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination plus a macrolide or fluoroquinolone. Consider coverage for MRSA (eg, vancomycin, linezolid) and anti-pseudomonal coverage (eg, meropenem, piperacillin-tazobactam).
- **Early conversion from parenteral to oral therapy** should be considered in patients with  $\downarrow$  leukocytosis, improvement in cough/dyspnea, and no fever for at least 8 hours. This can usually be done within 3 days of starting treatment.
- Patients may be **discharged** without delay at the time of conversion to oral therapy as long as they meet discharge criteria (Table 10.22).
- **Duration of treatment** is usually 1 week.
- **Repeat CXR** is not indicated during hospitalization except when complications (eg, pleural effusion) are suspected. A follow-up CXR in 4 to 6 weeks to ensure clearing and to assess for underlying processes can be considered in smokers and patients  $>50$  years.
- **Pneumococcal vaccine:** Given to all patients with CAP prior to discharge unless already vaccinated.

**Hospital-Acquired Pneumonia**

Defined as pneumonia that develops in a patient who was hospitalized for  $>48$  hours and who had no pneumonia or signs of developing pneumonia at the time of admission. Previously, the entity “health care–associated pneumonia” was developed for nonhospitalized patients thought to be at risk for multidrug resistant (MDR) infections due to health care exposures. However, further research has demonstrated that this risk is not as high as previously thought.

**KEY FACT**

Risk factors for multidrug resistant infections include a triad of *host, agent, and environment*:

**Host:** Patient is immunosuppressed or received antibiotics within the last 90 days

**Agent:** Nosocomial exposure to many agents if hospitalization  $\geq 5$  days

**Environment:** High prevalence of antibiotic resistance in the community

**A****ANSWER**

*Pseudomonas aeruginosa* is more likely in patients with bronchiectasis (chronic productive cough after a severe pneumonia; chronic CXR changes), especially in those who have received multiple antibiotic regimens.

**Management:** Empiric therapy is guided by local antibiotic resistance data and risk factors for MRSA or *Pseudomonas*:

- Risk factors for MRSA: IV antibiotics within 90 days or treatment in a unit with  $>20\%$  MRSA prevalence.
- Risk factors for MDR *Pseudomonas*: IV antibiotics within 90 days or structural lung disease.

**Empiric regimens:**

- No risk factors for MRSA or MDR *Pseudomonas*: Antipseudomonal (cephalosporin, carbapenem, piperacillin-tazobactam, aztreonam).
- Risk factors for MRSA: Antipseudomonal + vancomycin or linezolid.
- Risk factors for MDR *Pseudomonas*: Antipseudomonal + consider second antipseudomonal (fluoroquinolone, aminoglycoside, aztreonam).
- Risk factors for MDR *Pseudomonas* and MRSA: Antipseudomonal + vancomycin or linezolid + consider second antipseudomonal.

**TABLE 10.22. Criteria for Discharge in Community-Acquired Pneumonia**

CRITERION	COMPONENTS
Clinical stability	<ul style="list-style-type: none"> <li>■ Improvement in cough/dyspnea</li> <li>■ <math>O_2</math> saturation <math>&gt;90\%</math></li> <li>■ Temperature <math>&lt;37.8^\circ C</math> (<math>100^\circ F</math>)</li> <li>■ Resolution of tachycardia</li> <li>■ Resolution of tachypnea</li> <li>■ Resolution of hypotension</li> </ul>
No evidence of complicated infection	For example, no extrapulmonary or pleural involvement
Ability to tolerate oral medications	

## Environmental (Accidental) Hypothermia

Risk factors for environmental hypothermia include advanced age, trauma, alcohol or drug use, cognitive impairment, and psychiatric disease. **Cold water exposure is common.**

### Symptoms/Exam

Symptoms based on severity are as follows:

- **Mild hypothermia:** Temperatures 32 to 35°C (82-90°F). Tachycardia, tachypnea, and shivering are seen.
- **Moderate and severe hypothermia:** Temperatures <28 to 32°C (<82°F). Lethargy, irritability, and confusion are common. **Loss of shivering, bradycardia, hypotension, respiratory depression, and coma** may develop.

### Diagnosis

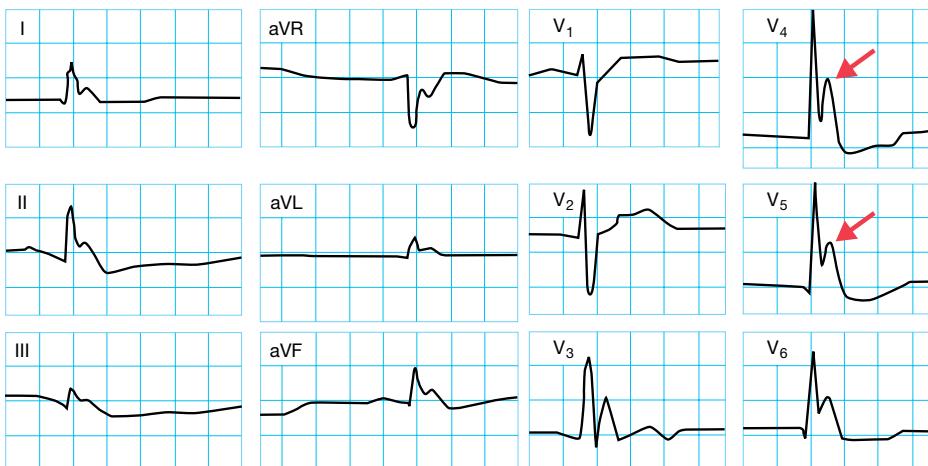
- **Laboratory abnormalities:** Metabolic acidosis, hypo- and hyperglycemia, DIC, hyperkalemia, and hyperamylasemia.
- Look for Osborn waves on ECG (Figure 10.11). ECG may also show **J waves** (notching of the terminal aspect of the QRS complex, best seen in lead V<sub>4</sub>), **slow atrial fibrillation**, and **prolonged cardiac intervals**.

### Management

- **Limit movement and manipulation of the patient;** unnecessary stimulation (eg, central lines, NG tubes, pacemakers) can result in ventricular dysrhythmias. The treatment of accidental hypothermia is summarized in Table 10.23.
- If cardiac arrest occurs, resuscitation should not cease until the core temperature reaches at least 32°C (89.6°F). **“A patient with hypothermia is not dead until he/she is warm and dead.”**

### Complications

Potential complications of all types of rewarming that should be anticipated are compartment syndromes, rhabdomyolysis, DIC, pulmonary edema, acute tubular necrosis, and hypoglycemia.



**FIGURE 10.11. Osborn wave in hypothermia (arrows).**



### MNEMONIC

#### Causes of hypothermia—

How did Old MacDonald get hypothermia when working on the farm?

Answer: **EIEIO**

**E**nvironmental exposure

**I**nfections

**E**ndocrine (hypothyroidism, DKA, and adrenal insufficiency)

**I**ngestions (barbiturates, phenothiazine, alcohol)

**O**thers: Liver failure, spinal cord injury



### MNEMONIC

#### ECG findings in hypothermia—

##### COLD

**C**ardiac arrest (VT, VF, asystole)

**O**sborn waves

**L**ong PR, QRS, QT

**D**ecreased heart rate

TABLE 10.23. Rewarming Techniques in Accidental Hypothermia

METHOD	DESCRIPTION	INDICATIONS	COMMENTS
Passive external rewarming	Removal of wet clothes; coverage with blankets	Mild hypothermia	Limited efficacy
Active external rewarming	Warmed blankets (including hot air blankets over the torso only); warmed baths	Mild hypothermia	Rewarming the extremities can cause <b>paradoxical lowering of core temperature</b> because of the return of chilled blood from the extremities
Active internal or core rewarming <sup>a</sup>	Warmed IV fluids; warmed humidified air	Moderate and severe hypothermia; can prevent hypotension due to peripheral vasodilation	Widely available; limited efficacy
	Extracorporeal blood rewarming via cardiopulmonary, arteriovenous, or venovenous bypass	Moderate and severe hypothermia; cardiac arrest	The most effective technique, but invasive. Also requires the application of specialized knowledge and equipment
	Peritoneal/pleural lavage with warmed fluids	Moderate and severe hypothermia	Useful when extracorporeal techniques are not available

<sup>a</sup>The decision to proceed with invasive active internal rewarming is individualized to the patient and dependent on both temperature and clinical manifestations. Noninvasive measures may suffice for most patients with moderate hypothermia.

### KEY FACT

Remember that **“all that wheezes is not asthma.”** Consider common diagnoses such as CHF, PE, upper airway obstruction, vocal cord dysfunction, bronchiolitis, bronchiectasis, COPD, postnasal drip.

## Acute Exacerbations of Asthma

**Viral infection** is the most common cause. Bacterial infections, environmental exposure to smoke or allergens, GERD, medical noncompliance, and use of certain medications (NSAIDs,  $\beta$ -blockers) are also potential factors (for more on asthma, see the Pulmonary and Critical Care chapter).

### Symptoms/Exam

- Presents with **dyspnea, wheezing, coughing, and chest tightness**.
- Fever and purulent sputum usually represent a complicating process such as pneumonia.
- Severe asthma exacerbation: Tachycardia, tachypnea, pulsus paradoxus, poor air movement, accessory muscle movement, and altered mental status.

### Diagnosis

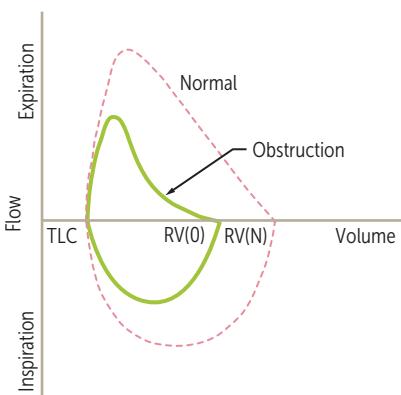
- **Peak expiratory flow rate (PEF):** Obtain in all patients as most predictive of the severity of the exacerbation (Figure 10.12). Patient-effort dependent.
- **ABG analysis:** Typically shows a  $\downarrow$   $\text{PCO}_2$  unless the patient is developing ventilatory failure at which point  $\text{PCO}_2$  begins to rise.
- **CXR:** Usually normal, but helpful to evaluate for possible 2° processes.
- **Pulse oximetry:** Normal  $\text{O}_2$  saturation is falsely reassuring as hypoxia is a late sign of respiratory failure.

### Management

Treatment should proceed as outlined below (see also Table 10.24):

- **Systemic corticosteroids:** Oral and IV steroids are equally effective.
- **Inhaled corticosteroids (ICS):** Currently the mainstay for chronic maintenance therapy.

FIGURE 10.12. Flow volume loop showing obstruction from asthma.



**TABLE 10.24.** Treatment of Acute Asthma Exacerbations

ALL PATIENTS	SELECTED PATIENTS	NOT USEFUL OR HARMFUL
Oral or IV corticosteroids	Antibiotics	Theophylline
Inhaled bronchodilators	O <sub>2</sub> Mechanical ventilation Noninvasive mechanical ventilation	Injected bronchodilators Chest physiotherapy Mucolytic agents Magnesium

**KEY FACT**

A normal or ↑ P<sub>CO<sub>2</sub></sub> indicates severe airway obstruction and that the patient may be starting to fatigue. Mild/early asthma exacerbations usually cause tachypnea and resultant ↓ P<sub>CO<sub>2</sub></sub>.

**KEY FACT**

A PEF <50% of predicted indicates severe airflow obstruction.

- **Inhaled bronchodilator therapy:** With either β<sub>2</sub>-agonist or ipratropium should be given to all patients; consider combination bronchodilator therapy in patients who do not respond to monotherapy or who have severe asthma.
  - **Levalbuterol:** Not recommended in adults, is more costly and no more effective than other β<sub>2</sub>-agonists, and has similar rates of tachycardia.
  - **Drug delivery:** Metered-dose inhalers (MDIs) and nebulizer therapy are equally effective. Early conversion to MDI is cost saving and allows patients to be educated on inhaler technique while in the hospital.
- **Methylxanthines** (eg, theophylline): Not recommended, as they add no benefit to the above therapy.
- **Antibiotics:** Generally **unnecessary**; reserve for patients with evidence of an underlying bacterial infection.
- **O<sub>2</sub> therapy:** Should be provided to keep O<sub>2</sub> saturations above 90%.
- **Noninvasive positive pressure ventilation:** Therapies such as bilevel positive airway pressure (BiPAP) can be attempted in patients with persistent respiratory acidosis who do not respond to medical therapies. In some cases, this may bridge the patient until medical therapies work and prevent intubation.
- **Endotracheal intubation and mechanical ventilation indications:**
  - Persistent hypercapnia.
  - Altered mental status.
  - Progressive and persistent acidemia (pH <7.30).
  - Respiratory fatigue.

## NOTES

# CHAPTER 11

## Infectious Diseases

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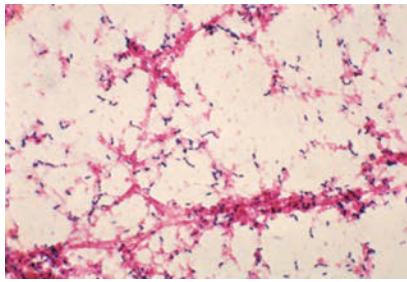
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**MNEMONIC****Gram-positive cocci—****The Grapes of Staph (like The Grapes of Wrath):**

Staphylococci are frequently seen in grapelike clusters.

**Strep = strip:**

Streptococci are often seen in long strips or chains.

**FIGURE 11.1. *Streptococcus***

***pneumoniae*.** Lancet-shaped diplococcus shown on a blood culture. (Source: Centers for Disease Control and Prevention/Dr. Mike Miller.)

**KEY FACT**

Remember that enterococcus and listeria are intrinsically resistant to cephalosporins!

**MNEMONIC****Gram-positive rods—****Bad ChORal ACTs Need CLOSe and PROPer LISTening**

**Bacillus**

**CORynebacterium**

**ACTinomycetes**

**Nocardia**

**CLOStridium**

**PROPionibacterium**

**LISTERIA**

**MNEMONIC****To remember lactose-fermenting gram-negative rods—****SEEK Carbs**

**Serratia**

**E. coli**

**Enterobacter**

**Klebsiella**

**Citrobacter**

**Microbiology Principles****GRAM-POSITIVE COCCI**

- In clusters: *Staphylococcus*.
  - Coagulase  $\oplus$ : *Staphylococcus aureus*.
  - Coagulase  $\ominus$ : *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, etc.
- In chains or pairs: *Streptococcus*.
  - Lancelet-shaped pairs: *Streptococcus pneumoniae* (Figure 11.1).
- In pairs or short chains: *Enterococcus*.

**GRAM-POSITIVE RODS**

- Large with spores: *Bacillus*, *Clostridium*.
- Small, pleomorphic (diphtheroids): *Corynebacterium*, *Propionibacterium*.
- Filamentous, branching, beaded:
  - Aerobic: *Nocardia*.
  - Anaerobic: *Actinomyces*.
  - Other: *Listeria*, *Lactobacillus*.

**GRAM-NEGATIVE COCCI**

In pairs (diplococci): *Neisseria gonorrhoeae*, *N meningitidis*, *Moraxella catarrhalis*.

**GRAM-NEGATIVE RODS**

- Enterobacteriaceae (lactose-fermenters): *Serratia*, *E. coli*, *Enterobacter*, *Klebsiella*, *Citrobacter*.
- Nonfermenters: *Proteus*, *Salmonella*, *Shigella*, *Yersinia*, *Acinetobacter*, *Stenotrophomonas*, *Pseudomonas*.
- Anaerobes: *Bacteroides*, *Fusobacterium*.
- Fusiform (long, pointed): *Fusobacterium*.
- Other: *Bartonella*, *Haemophilus*, *Legionella*.

**ACID-FAST BACTERIA**

- Mycobacteria, including *Mycobacterium tuberculosis* and *Mycobacterium leprae*, are also gram-positive on a standard Gram stain.
- *Nocardia* (weakly or partially acid-fast).

**Specific Microbes****ACTINOMYCES VERSUS NOCARDIA**

Table 11.1 contrasts the clinical presentation, diagnosis, and treatment of *Actinomyces* infections with that of *Nocardia* infections.

**BARTONELLA**

A gram-negative rod, *Bartonella henselae* is transmitted by kittens or feral cats; *Bartonella quintana* by body lice. Clinical manifestations vary depending on the transmitted

**TABLE 11.1. Diagnosis and Treatment of *Actinomyces* and *Nocardia* Infections**

	<i>ACTINOMYCES</i>	<i>NOCARDIA</i>
Gram stain	Gram-positive, branching rod	Gram-positive, branching rod
Acid-fast stain	⊖	Weakly AFB ⊕
Pathology	Sulfur granules and draining sinuses	Abscess
Infected host	Immunocompetent; poor dentition	Often immunocompromised
Sites of infection	Mandible, lung, abdomen/pelvis	Lung, CNS, skin
Treatment	Penicillin × 6–12 months	TMP-SMX × 3–6 months

species and the immune status of the host. *B henselae* can cause cat-scratch disease and bacillary angiomatosis. *B quintana* infection may result in trench fever, bacteremia, endocarditis, and bacillary angiomatosis.

### Symptoms/Exam

- Cat-scratch disease (*B henselae*; immunocompetent patients): Presents with fever, malaise, a papule or pustule at the site of the cat scratch or bite, and regional adenopathy (usually in the head, neck, or axillae).
- Bacillary angiomatosis (*B henselae*, *B quintana*; AIDS patients): The skin nodules of bacillary angiomatosis are friable, red-to-purplish lesions that may ulcerate. Often confused with Kaposi sarcoma.
- Trench fever (*B quintana*; immunocompetent patients): Relapsing febrile paroxysms last up to 5 days each and are sometimes accompanied by headache, myalgias, hepatosplenomegaly, and leukocytosis. Seen in the homeless and in those from war-torn regions.

### Diagnosis

- Serologic tests are not highly sensitive but more so than blood cultures.
- Lymph node aspirate in cat-scratch disease may show sterile pus.
- Lymph node biopsy shows granulomas that may coalesce to form stellate necrosis. Warthin-Starry silver stain demonstrates bacilli.

### Management

- Macrolides (erythromycin or azithromycin) or doxycycline.
- Cat-scratch disease usually resolves in several months and may not require treatment other than needle aspiration for symptom relief.

## CNS Infection

### MENINGITIS

#### Symptoms/Exam

Meningitis presents with fever, headache, neck stiffness, altered mental status (ranging from mild lethargy to confusion, stupor, and coma), and disturbances in speech and behavior.

- Aseptic:** Defined as clinical and CSF findings of meningitis but without a bacterial etiology. Viral etiology most common—enteroviruses and arboviruses in the late summer and early fall and HSV-2 (typically more benign course than HSV encephalitis).
- Bacterial:** Common microorganisms in Table 11.2.

### KEY FACT

Actinomycosis can spread without regard to tissue planes. It commonly presents with a “lumpy jaw” or draining fistula and is diagnosed by sulfur granules in a pathology specimen.

### MNEMONIC

**To remember treatment of Nocardia and Actinomycosis—oh SNAP!**

Sulfamethoxazole—*Nocardia*  
*Actinomycetes*—Penicillin

### KEY FACT

In a patient with AIDS who has FUO, purple skin lesions that resemble Kaposi sarcoma, and cystic lesions in the liver and spleen, suspect bacillary angiomatosis. Treat with macrolides.



### QUESTION

A 34-year-old man from the Philippines who immigrated to the United States 6 months ago presents with confusion. MRI shows enhancement of the basal cisterns. LP shows ↑ protein, lymphocytic predominance, and ↓ glucose. How should this patient be managed while cultures are pending?

**KEY FACT**

Give steroids along with or prior to antibiotics if you suspect bacterial meningitis.

**KEY FACT**

Neutrophils in cell count of CSF often indicates bacterial meningitis.

**KEY FACT**

Indications for CT prior to LP include **focal neurologic findings, papilledema or seizures, and compromised immunity** (eg, age >60 years).

**KEY FACT**

If high suspicion for meningitis, do not delay antibiotics to await diagnostic studies!

**KEY FACT**

Remember that in bacterial meningitis Gram stain sensitivity is only 60% to 90%!

**A****ANSWER**

Treatment should consist of rifampin, INH, pyrazinamide, and ethambutol  $\pm$  steroids. Basilar meningitis is commonly seen with TB meningitis. A lymphocytic-predominant CSF in the setting of TB risk factors makes TB meningitis the most likely diagnosis.

**TABLE 11.2. Empiric Antibiotic Therapy for Bacterial Meningitis**

AFFECTED PATIENTS	COMMON MICROORGANISMS	EMPIRIC ANTIBIOTICS—FIRST CHOICE
Adults 18-50 years	<i>Streptococcus pneumoniae, Neisseria meningitidis</i>	High-dose ceftriaxone + vancomycin
Adults >50 years	<i>S pneumoniae, Listeria monocytogenes</i> , gram-negative bacilli	High-dose ceftriaxone + ampicillin + vancomycin
Impaired cellular immunity	<i>S pneumoniae, L monocytogenes</i> , gram-negative bacilli (including <i>Pseudomonas</i> )	Ceftazidime or ceftepime + ampicillin + vancomycin
Post-neurosurgery or post-head trauma	<i>S pneumoniae, S aureus</i> , gram-negative bacilli (including <i>Pseudomonas</i> )	Ceftazidime or ceftepime + vancomycin

**Diagnosis**

- Obtain a head CT/MRI before LP if a mass lesion is suspected (eg, in the setting of **focal neurologic findings** such as papilledema, coma, seizures, or in the setting of **compromised immunity**, including age >60 years).
- LP needed. Interpretation is outlined in Table 11.3.

**Management**

Fulminant presentation (<24 hours) or ill-appearing patients with acute bacterial meningitis:

**TABLE 11.3. Lumbar Puncture Interpretation**

DIAGNOSIS	RBC (PER $\mu$ L)	WBC (PER $\mu$ L)	GLUCOSE (MG/DL)	PROTEIN (MG/DL)	OPENING PRESSURE (CM H <sub>2</sub> O)
Normal	<10	<5	~ 2/3 of serum	15-45	10-20
Bacterial meningitis	Normal	↑ (PMNs)	↓	↑	Normal or ↑
Aseptic/viral meningitis, encephalitis	Normal <sup>a</sup>	↑ (lymphs) <sup>b</sup>	Normal	Normal or ↑	Normal or ↑
Chronic meningitis (TB, fungal)	Normal	↑ (lymphs) <sup>b</sup>	↓	↑	Normal or ↑
Spirochetal meningitis (syphilis, Lyme disease)	Normal	↑ (lymphs) <sup>b</sup>	Normal	↑	Normal or ↑
SAH, cerebral contusion	↑↑	↑	Normal	↑↑	Normal or ↑

<sup>a</sup>Note: HSV infection can be associated with ↑ RBCs.

<sup>b</sup>May have PMN predominance in early stages.

- Give antibiotics early (see Table 11.2).
- Give steroids (**dexamethasone**) along with or prior to antibiotics. A 4-day course of steroids reduces mortality and improves neurologic outcomes in patients with pneumococcal meningitis.

### Prevention

- ***N meningitidis* vaccine (serotypes A, C, Y, and W-135, not B):** Appropriate for epidemics as well as for military recruits, international travel to Africa, Southeast Asia. May also be given to college freshmen living in dormitories, asplenic patients, those with terminal complement (C5-C9) deficiency, and men who have sex with men.
- ***H influenzae type b vaccine:*** Routine childhood immunization; consider in adult patients with asplenia.

## ENCEPHALITIS

HSV and arboviruses (eg, **West Nile virus**, eastern and western equine virus, St Louis virus) are the most common causes of encephalitis in the United States. Patients may report travel (Japanese B virus), a tick bite (Rocky Mountain spotted fever, Lyme disease, ehrlichiosis), or an animal bite (rabies). Postinfectious cases are seen 1 to 3 weeks after URI, measles infection, or smallpox vaccination.

### Symptoms/Exam

- **Global confusion or altered mental status** are usually the most prominent finding.
- Fever, headache, focal deficits.
- Exam may also reveal focal neurologic signs, including motor weakness, accentuated DTRs, hemiparesis, cranial nerve palsies (especially CN III and CN VI), and seizures.
- A rash may be seen with Lyme disease, Rocky Mountain spotted fever, and VZV infection; weakness and flaccid paralysis may be seen with West Nile virus infection.

### Diagnosis

- LP (see Table 11.3).
  - RBCs if HSV.
  - PCR for HSV; sensitive and specific. No utility in CSF HSV culture or serum HSV PCR.
  - PCR or serology for other etiologies based on season, geography, and clinical findings.
- EEG shows diffuse slowing of brain waves. **HSV encephalitis may localize to the temporal lobes** with highly characteristic slow-wave (2- to 3-Hz) complexes.
- MRI with gadolinium shows multifocal lesions. Temporal lobe involvement can be seen with HSV.

### Management

- Supportive care (antipyretics, antiseizure medications, lowering of ICP, mechanical ventilation).
- **High-dose IV acyclovir** for HSV and VZV (oral does not penetrate CSF); the other viral causes require only supportive care.

## BRAIN ABSCESS

- A brain abscess is most commonly caused by local spread from head and neck infection (sinusitis, otitis media) but may also be due to hematogenous seeding.
- **Symptoms/Exam:** Fever, seizure, headache, focal neurologic deficits.

### KEY FACT

A low glucose concentration in the CSF is commonly seen in bacterial and mycobacterial (eg, TB) etiologies of meningitis. A high protein reflects inflammation, is less specific and may not be helpful diagnostically.

### KEY FACT

#### ***N meningitidis* chemoprophylaxis:**

Rifampin 600 mg PO BID × 4 doses, ciprofloxacin 500 mg PO × 1 dose, or ceftriaxone 250 mg IM × 1 dose. Give to household contacts, salivary contacts, healthcare contacts if direct oral/respiratory secretion contact (not masked).

### KEY FACT

If recurrent meningococcal infections, consider testing for terminal complement deficiency.

### KEY FACT

Encephalitis that develops in the summer or fall is often due to arboviruses. In late spring or early summer, think of tick-borne infections. In the winter or spring, think of measles, mumps, and HSV.

### KEY FACT

Encephalitis preceded by flaccid paralysis is a clue to West Nile virus, which affects anterior horn cells.

### KEY FACT

One of the most dangerous encephalitis etiologies is HSV. Send the PCR on CSF and empirically treat with high-dose IV acyclovir.



### QUESTION

A 45-year-old man presents with confusion of 5 days' duration. He has a low-grade fever. MRI shows enhancement around the temporal lobes. What is the appropriate test to make the diagnosis?

**KEY FACT**

Treatment of brain abscess is typically a 6- to 8-week course of IV antibiotics, guided by aspiration results and follow-up imaging findings.

- **Diagnosis:** Best diagnostic initial test is brain MRI > head CT with contrast; aspiration is necessary to guide therapy and provide source control for larger abscesses.
- **Management:** Empiric therapy will treat anaerobes, strep, and gram-negative bacilli (ceftriaxone + metronidazole), as these are the most common culprits and many brain abscesses are polymicrobial. Add *S aureus* coverage (vancomycin) for patients with neurosurgical history, bacteremia/endocarditis or penetrating head trauma. Replace ceftriaxone with *Pseudomonas* coverage (cefepime or ceftazidime) for neurosurgical patients. IV therapy for 6 to 8 weeks is typical, although follow-up imaging is usually used to help delineate final course.

**SPINAL EPIDURAL ABSCESS**

- Most commonly seeded by either hematogenous spread or local spread from osteomyelitis. **Symptoms/Exam:** Fever, back pain, and neurologic deficit.
- **Diagnosis:** MRI.
- **Management:** Like brain abscess, aspiration for antimicrobial guidance and decompression is vital. Empiric antibiotics should cover *S aureus*, including MRSA. Consider addition of ceftriaxone if gram negative coverage is thought needed based on history/exposures.

**PRION DISEASE**

- Creutzfeldt-Jakob is the most common form of prion disease.
- **Symptoms/Exam:** Rapidly progressive dementia, myoclonus, ataxia, spasticity.
- **Diagnosis:** ↑ CSF levels of 14-3-3 protein. Brain biopsy is definitive.
- **Management:** Supportive care.

**Endocarditis**

Infection of the heart valves. Classified as **native valve endocarditis (NVE)** or **prosthetic valve endocarditis (PVE)**. Patients with a history of injection drug use are especially at risk, particularly for tricuspid valve endocarditis (Table 11.4).

**Symptoms/Exam**

- **Acute bacterial endocarditis:** High fever (80%), chills, embolic phenomena, potentially right or left heart failure symptoms if valves damaged.
- **Subacute endocarditis:** Has an **indolent course**; presents with **nonspecific symptoms** such as low-grade fever, night sweats, malaise, anorexia, weight loss, and more immunologic manifestations.

**TABLE 11.4. Etiologies of Endocarditis**

TYPE	ETIOLOGY
NVE	Viridans streptococci and other streptococci, <i>S aureus</i> (more common in injection drug use), enterococci, HACEK organisms
PVE	<i>Staphylococcus epidermidis</i> , <i>S aureus</i>
"Culture-negative" endocarditis	<b>HACEK organisms:</b> <i>Haemophilus</i> , <i>Actinobacillus</i> , <i>Cardiobacterium</i> , <i>Eikenella</i> , <i>Kingella</i> <b>Candida and Aspergillus:</b> Patients who inject drugs, long-term indwelling catheters, immunosuppressed <b>Rare causes:</b> <i>Chlamydia psittaci</i> , the "ellas" ( <i>Bartonella</i> , <i>Legionella</i> , <i>Brucella</i> , <i>Coxiella</i> ), Whipple disease

**A****ANSWER**

CSF HSV PCR. The symptoms of encephalitis and temporal lobe involvement are classically seen in HSV infection. The next diagnostic step would be to perform LP, which may show a high RBC count from brain necrosis and a  $\oplus$  HSV PCR.

## Exam

Fever and a regurgitant heart murmur are most common. Less commonly seen but highly suggestive of endocarditis are Osler nodes (painful lesions on palms/sole), Janeway lesions (nontender nodules on palms/soles), splinter hemorrhages (reddish-brown streaks in the proximal nail beds), petechiae, and Roth spots (retinal hemorrhages).

## Diagnosis

- **Labs:** Nonspecific inflammatory markers (leukocytosis with left shift, mild anemia, ↑ ESR, + RF). UA may show proteinuria, microscopic hematuria, and RBC casts.
- **Blood cultures** are critical in establishing a diagnosis and are + in 85% to 95% of cases. It is recommended that three sets of blood cultures be taken at least 1 hour apart (before antibiotics).
- **Echocardiography:** Transthoracic echocardiography (TTE) has 60% to 75% sensitivity; transesophageal echocardiography (TEE) has 95% sensitivity. Both are 95% specific.
- **Duke criteria (Table 11.5):** A definitive diagnosis can be made with the following:
  - Pathologic criteria: + culture or histology from removed valve.
  - Clinical criteria: Two major, one major plus three minor, or five minor criteria.

## Management

- **Empiric treatment:** Base choice of therapy on historical and epidemiological risk factors, published guidelines, and ID consultation.
  - In general coverage of gram-positive organisms including MRSA should be included. **Vancomycin at minimum.**
  - Consider additional agents based on the patient and clinical stability (ie, if prosthetic valve, consider gentamicin; if concern for HACEK organisms, consider ceftriaxone).
- **Persistent fever after 1 week of appropriate antibiotic therapy** raises concern for a perivalvular or myocardial abscess or a septic embolic focus.
- **Reappearance of fever** after initial defervescence suggests infectious complication (ie, abscess development), septic emboli, drug fever, or—less commonly—the emergence of resistant organisms.

**TABLE 11.5. Duke Criteria for Endocarditis Diagnosis**

MAJOR CRITERIA
<ul style="list-style-type: none"> <li>■ + blood cultures with typical pathogen (two or more sets drawn at separate sites/times)</li> <li>■ Oscillating vegetation on echocardiogram (TTE/TEE)</li> <li>■ New regurgitant murmur</li> </ul>
MINOR CRITERIA
<ul style="list-style-type: none"> <li>■ Predisposing conditions (valvular heart disease or IV drug use)</li> <li>■ Fever &gt;38°C (100.4°F)</li> <li>■ Embolic disease (pulmonary or intracranial infarcts, mycotic aneurysm, conjunctival hemorrhages, Janeway lesions)</li> <li>■ Immunologic phenomena (glomerulonephritis, Osler nodes, Roth spots, + RF)</li> <li>■ + blood culture not meeting the major criteria</li> </ul>

## KEY FACT

*Streptococcus bovis* and *Clostridium septicum* endocarditis/bacteremia are seen in patients with bowel pathology and should prompt upper and lower GI endoscopies.

## KEY FACT

PR prolongation in a patient with endocarditis may suggest conduction abnormalities due to an aortic valve ring abscess, which is an indication for cardiac surgery.

## KEY FACT

Indications for surgery during active infection include refractory **CHF**, **perivalvular extension** (new conduction abnormalities, myocardial abscess, persistent bacteremia despite antibiotics), **fungal endocarditis**, and **PVE**. Surgery is often also necessary for **vegetation complications** (size >10 mm or recurrent embolic events despite antibiotics).



## QUESTION

A 65-year-old man with a congenital bicuspid aortic valve is found to have aortic valve endocarditis. He is started on antibiotics. On hospital day five, he has weakness. ECG reveals AV dissociation. What is the most appropriate next step in endocarditis management?

### Prevention

**Antibiotic prophylaxis**, consisting of PO amoxicillin, IV ampicillin, or IV/PO clindamycin (penicillin allergy), is recommended in the following situations:

- Immunocompromised patients with prosthetic heart valves.
- Patients with a history of infective endocarditis.
- Cyanotic heart disease (unrepaired or within 6 months after repair).
- Heart transplant with valvulopathy.

Give antibiotics **30 to 60 minutes before certain procedures**, such as dental work involving disruption of the gingival crevice (not cleanings), surgery inside the oral cavity (or when a bacterial infection is present at the surgical site), and GU surgery in the presence of documented infection.

### Complications

- CHF 2/2 valvular destruction: **Most common cause of death due to endocarditis.**
- **Embolic phenomena:** Second most common cause of death—mycotic aneurysms, infarcts, or abscesses in the CNS, kidney, or spleen.
- **Arrhythmias and heart block.**
- **Myocardial or perivalvular abscess** (especially with *S aureus*); may extend to cause pericarditis and tamponade.

## Infectious GI Disease

Acute infectious GI disease in developed countries is often self-limited and associated with either viral or food-borne etiology. Stool cultures are generally low yield, although they may be considered in patients with persistent diarrhea (>72 hour) and fever or bloody/mucoid stools, in severely ill patients, and in patients with inflammatory bowel disease or immune compromise.

- **Upper GI symptoms (nausea, vomiting):** Bacterial etiologies include *S aureus* toxin (dairy, eggs, mayonnaise, meat products), *Bacillus cereus* (rice products). Viral etiology includes norovirus. Incubation period <2 to 14 hours after food exposure (can be slightly longer with *B cereus*), as is toxin-mediated. Treatment is supportive.
- **Lower GI symptoms (fever, diarrhea):** Bacterial etiologies include *Campylobacter* (most common), *Salmonella*, *Shigella*, *E coli* (enterohemorrhagic, enterotoxigenic, enteroinvasive), *yersinia*. Viral etiology includes norovirus. Incubation period 24 to 72 hours. Treatment is supportive; occasionally in patients with severe illness, fluoroquinolones may be used.

## Infectious GU Disease

### URINARY TRACT INFECTION

Infection of the urothelium of urinary tract is more common in women than in men and most frequently occurs in early adult life (age 16–35 years). Majority caused by *E coli* with a smaller percentage caused by other gram-negative bacilli or *S saprophyticus*.

- **Symptoms:** Dysuria, ↑ urinary frequency, suprapubic pain. Change in urine color, odor, hematuria. Elderly may present atypically with altered mental status or incontinence.
- **Diagnosis:** Clinical diagnosis based on symptoms. Other supportive data are UA with pyuria, leukocyte esterase, nitrite (produced by bacteria in urine). Urine culture with  $>10 \times 5$  colony-forming units.
  - **Note:** In men, **acute prostatitis** can mimic UTI; digital rectal examination



### KEY FACT

Patients are usually afebrile in toxin-mediated food-borne illness.



### KEY FACT

Presence of bacteria in urine specimen in absence of symptoms is known as

**asymptomatic bacteriuria.** Screen for and treat only in pregnant women or men undergoing invasive urologic procedure. It should not be treated in other populations.



### ANSWER

Surgical valve repair. This patient has third-degree heart block, which can be a complication of aortic valve endocarditis with perivalvular extension. It is an indication for surgical management of the infected valve.

helps distinguish the conditions and reveals edematous, tender prostate in prostatitis. **Epididymitis** (tender and inflamed epididymis and testes) also may be confused with UTI.

- **Management:** TMP-SMX and nitrofurantoin are first line with fluoroquinolones or macrolides as a second-line option. Duration of treatment depends on antibiotic used and also stratified by uncomplicated or complicated (pregnant women, men, elderly, abnormal immune system, structural urologic abnormality). Frequently extend duration to 7 days if complicated.
  - **Acute prostatitis:** TMP-SMX or a fluoroquinolone is the treatment of choice; duration is 4 to 6 weeks.
  - **Epididymitis:** Often due to gonorrhea/chlamydia in younger sexually active men; treat with ceftriaxone + doxycycline/azithromycin. In older men or men who are not sexually active, more likely to be 2/2 *E coli*; treat with fluoroquinolone.

## PYELONEPHRITIS

Caused by the same bacteria as those responsible for uncomplicated UTI (eg, *E coli*).

### Symptoms/Exam

- Presents with flank pain and fever. Patients often have lower urinary tract symptoms that sometimes occur 1 to 2 days before upper urinary tract symptoms. They may also have nausea, vomiting, diarrhea, or be systemically ill.
- Exam reveals fever, CVA tenderness, and mild abdominal tenderness.

### Diagnosis

UA shows pyuria and bacteriuria and may also exhibit hematuria. CBC reveals leukocytosis with left shift. Urine culture is usually  $\oplus$ , and blood culture may be  $\oplus$  as well.

**Imaging is not required to make a diagnosis of pyelonephritis**, but it may be useful in certain patients at high risk for complications (Figure 11.2).

### Management

Similar antibiotics to cystitis treatment but course is longer. Empiric treatment utilizes either IV cephalosporin (third or fourth generation) or PO/IV fluoroquinolone. Do not use nitrofurantoin, as this antibiotic cannot penetrate the upper urinary tract.

### Complications

- Renal struvite stones (staghorn calculi) are frequently associated with recurrent UTI due to urease-producing bacteria (*Proteus*).
- Perinephric abscess (Figure 11.3) should be considered in patients who remain febrile 2 to 3 days after appropriate antibiotics; UA may be normal and cultures  $\ominus$ . Patients are treated by percutaneous or surgical drainage + antibiotics (guided by aspiration results).
- Intrarenal abscesses (eg, infection of a renal cyst); if  $<5$  cm in size, the abscess usually responds to antibiotics alone.

## Sexually Transmitted Infection

### GENERAL CHARACTERISTICS

Table 11.6 outlines sexually transmitted infections (STIs) that result in genital ulcers as well as urethritis or cervicitis. Please see the Women's Health chapter for discussion of vaginitis.

### KEY FACT

Radiologic evaluation for complications of pyelonephritis may be useful in patients who are severely ill or immunocompromised, those who are not responding to treatment, or those in whom complications are likely (eg, those with nephrolithiasis, transplant or other GU surgery).



**FIGURE 11.2. Pyelonephritis.** CT scan shows enlarged right kidney with striated parenchymal enhancement in a 24-year-old woman with dysuria and right flank pain. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 11.3. Perinephric abscess.** Acute right pyelonephritis complicated by a right perinephric abscess (arrow). (Reproduced with permission from Tanagho EA, McAninch JW. *Smith's General Urology*, 17th ed. New York: McGraw-Hill, 2008, Fig. 13-4.)

### KEY FACT

Do not use Tzanck test for HSV lesions; perform viral PCR of lesion instead.

TABLE 11.6. Diagnosis and Treatment of Selected STIs

DISEASE	PATHOGEN	CLINICAL PRESENTATION	DIAGNOSIS	TREATMENT OPTIONS
<b>GENITAL ULCERS/LESIONS (PAINFUL VERSUS PAINLESS)</b>				
Chancroid	<i>Haemophilus ducreyi</i>	A <b>painful</b> erythematous papule evolving into a pustule that erodes into an <b>ulcer with purulence</b> <b>Marked lymphadenitis</b>	Gram stain shows small gram-negative rods in parallel alignment ("school of fish"); culture	<b>Drain buboes</b> <b>Azithromycin 1 g PO × 1 or ceftriaxone IM × 1</b>
HSV <b>Primary versus Reactivation</b>	Human herpes simplex virus 1 or 2	<b>Painful</b> multiple vesicular or ulcerative lesions Reactive lymphadenopathy	Viral PCR of lesion	<b>Acyclovir</b> or valacyclovir Consider suppressive or episodic treatment for recurrent infection
Granuloma inguinale	<i>Klebsiella granulomatis</i>	<b>Painless, progressive ulcerative lesions</b> <b>Often without regional lymphadenopathy</b> Endemic in tropical regions	Biopsy shows dark-staining Donovan bodies	<b>Doxycycline</b>
Lymphogranuloma venereum	<i>Chlamydia trachomatis</i> (serovar L1, L2, or L3)	A <b>painless</b> , small ulcer at the site of inoculation <b>Large, tender, fluctuant inguinal lymphadenopathy (buboes)</b>	Serology, aspiration of lymph node	<b>Drain buboes</b> <b>Doxycycline</b>
Syphilis	<i>Treponema pallidum</i>	A <b>painless</b> solitary ulcer (rarely multiple) May have painless, rubbery lymphadenopathy	Darkfield microscopy; RPR/VDRL confirmed by FTA-ABS	<b>Penicillin</b> For penicillin-allergic patients, give doxycycline
Condyloma acuminata (genital warts)	HPV	Warty "cauliflower" growths	Clinical if wartlike; 4% acetic acid applied to the lesion turns tissue white with papillae	Trichloroacetic acid; podophyllin (contraindicated in pregnancy); imiquimod
<b>URETHRITIS AND UNCOMPLICATED CERVICITIS</b>				
Gonococcal (GC)	<i>Neisseria gonorrhoeae</i>	Purulent discharge; may present with dysuria. May have pharyngitis, proctitis, and PID. Disseminated GC infection is associated with two syndromes: (1) fever, tenosynovitis, and painful vesiculopustular skin lesions or (2) purulent arthritis without skin lesions	Gram stain of urethral or cervical swab shows intracellular gram-negative diplococci (Figure 11.4) Nucleic acid amplification test (NAAT) of pharynx, urethra, urine, cervix, vagina and/or rectum	Ceftriaxone 250 mg IM × 1 or cefixime PO × 1 <b>plus azithromycin to improve treatment efficacy, slow spread of cephalosporin resistance and to treat possible chlamydia co-infection<sup>a</sup></b>

(continues)

**TABLE 11.6.** Diagnosis and Treatment of Selected STIs (*continued*)

DISEASE	PATHOGEN	CLINICAL PRESENTATION	DIAGNOSIS	TREATMENT OPTIONS
<b>URETHRITIS AND UNCOMPLICATED CERVICITIS (continued)</b>				
Nongonococcal (NG)	<i>C trachomatis</i>	<b>Mucoid or watery discharge; dysuria</b> Other syndromes include proctitis, epididymitis, and PID Has a known association with post-infectious reactive arthritis; consider chlamydia testing in this setting	Gram stain of urethral secretions shows >5 WBCs/hpf plus leukocyte esterase on first-void urine <b><i>C trachomatis:</i></b> NAAT on the urethra, urine, cervix, vagina and/or rectum	Azithromycin 1 g PO × 1 or doxycycline 100 mg PO BID × 7 days

<sup>a</sup>Quinolones are no longer recommended by the CDC for treatment of GC infections in the United States owing to high rates of resistance.

### PELVIC INFLAMMATORY DISEASE

Symptoms include fever, abdominal discomfort, vaginal/cervical discharge, dyspareunia, intramenstrual bleeding. Occasionally with hepatic capsule inflammation, Fitz-Hugh-Curtis syndrome. On exam, patient may have cervical motion, uterine or adnexal tenderness and mucopurulent cervical discharge.

Outpatient treatment includes ceftriaxone 250 mg IM and doxycycline (14-day course). If nausea/vomiting, pregnancy, systemic toxicity, or suspected tubo-ovarian abscess, patient should be hospitalized. Inpatient treatment is typically IV cefotetan or cefoxitin and doxycycline (or alternative of azithromycin in pregnant patients).

### SYPHILIS

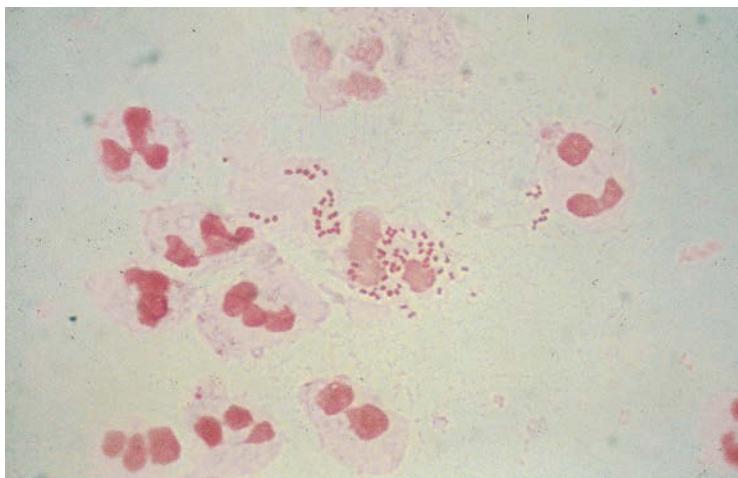
Syphilis is caused by the spirochete *Treponema pallidum*. For the stages, signs and symptoms, and treatment of syphilis, see Table 11.7. Figure 11.5 shows chancres

### KEY FACT

Gonorrhea and chlamydia can also cause proctitis in patients who have receptive anal intercourse. Symptoms may include rectal pain, tenesmus, or rectal discharge.

### KEY FACT

Test of cure 3-4 weeks after treatment for chlamydia and gonorrhea is only recommended for pregnant women.



**FIGURE 11.4.** **Gonococcal urethritis: Gram stain of *Neisseria gonorrhoeae*.** Multiple gram-negative diplococci are seen within PMNs as well as in the extracellular areas of a smear from a urethral discharge. (Reproduced with permission from Wolff K, et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 906.)

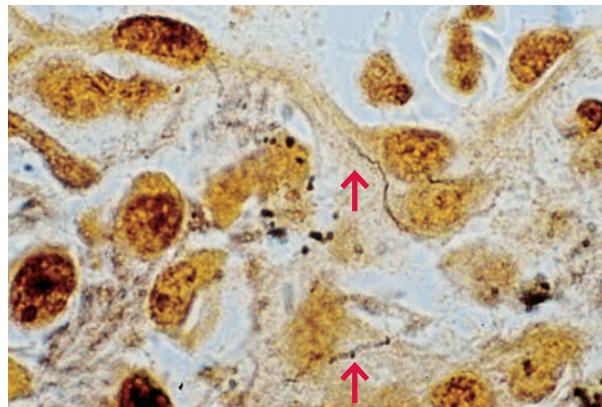
TABLE 11.7. Syphilis Stage, Clinical Features, and Treatment

STAGE	TIME COURSE	CLINICAL FEATURES	TREATMENT
1°	Incubation 3 days to 3 months; chancre resolves in 3-6 weeks	Usually presents with a chancre (Figure 11.5)—a single painless papule that erodes to form a clean-based ulcer with raised/indurated edges—and regional nontender lymphadenopathy	
2°	2-8 weeks after the 1° chancre	Spirochetemia causing disseminated infection leading to a <b>maculopapular rash</b> that may include the palms and soles (Figure 11.6); <b>condylomata lata</b> in intertriginous areas (painless, broad, grayish-white to erythematous plaques that are highly infectious); <b>mucous patch</b> (condylomata lata on the mucosa) May also have nonspecific systemic symptoms	Benzathine penicillin G 2.4 million units IM single dose
Latent	Early latent <1 year	⊕ serology without symptoms	
	Late latent >1 year or unknown	⊕ serology without symptoms	Benzathine penicillin G 2.4 million units IM once weekly × 3
3°	1-20 years after initial infection	May include <b>aortitis</b> , destructive <b>gummas</b> (bone, skin, mucocutaneous areas), <b>neurologic or ocular sequelae</b> with symptoms of tabes dorsalis or Argyll Robertson pupil	Aqueous crystalline penicillin G 3-4 million units IV every 4 hours × 10-14 days

commonly found in 1° syphilis. Figure 11.6 shows the characteristic palmar and plantar lesions of 2° syphilis. Table 11.8 outlines the differential diagnosis of lesions on the palms and soles.

### Diagnosis

- Direct visualization of motile spirochetes by darkfield microscopy (Figure 11.7) from condylomata lata or mucous patches.
- **VDRL and RPR:** Nontreponemal, nonspecific antibody tests are useful for *screening, testing for repeat infection, and monitoring treatment response* as titers wane and revert to ⊖ with time and adequate antibiotic treatment.
- **FTA-ABS and MHA-TP:** Specific treponemal antibody tests that are used to *confirm* VDRL and RPR. Antibodies remain ⊕ for life so are not useful in testing for repeat infection.

**A****B****C**

**FIGURE 11.5. 1° syphilis.** (A) Male and (B) female genital chancres. (C) Silver stain of sample from a chancre showing spiral-shaped spirochetes (arrows). (Reproduced with permission from Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill, 2008, Figs. 200-2, 200-5, and 200-1.)

**A****B**

**FIGURE 11.6. 2° syphilis.** Characteristic lesions can be seen on the palms (A) and soles (B). (Source: Centers for Disease Control/Public Health Image Library.)

- LP: Indicated for patients with neurologic/ophthalmic symptoms and previous treatment failure raising concern for CNS reservoir. CSF findings include a WBC count of  $>5$ , ↑ protein, and a  $\oplus$  CSF-VDRL (although sensitivity of CSF-VDRL is low, 50%).

### Management

- See Table 11.7.
- Repeat RPR or VDRL at 3, 6, 12, and 24 months; titer should  $\downarrow$  at least fourfold 6 to 9 months after the treatment of 1° or 2° syphilis. If the titer does not fall after this period, it suggests treatment failure, reinfection, or HIV (in which titers fall more slowly).
- Treat again if clinical signs persist or recur or if the VDRL/RPR titer does not  $\downarrow$  fourfold.

### KEY FACT

Pregnant women and those with neurosyphilis who are allergic to penicillin should be desensitized and treated with penicillin. Other penicillin allergic patients can be treated with doxycycline.

### KEY FACT

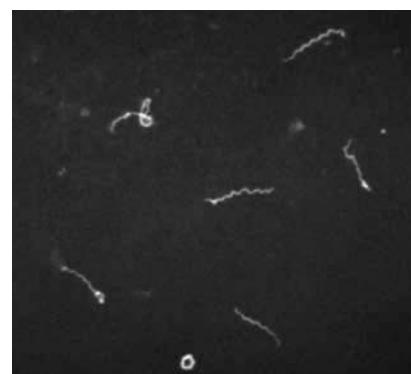
Neurosyphilis (ocular, otic, meningitis, tabes dorsalis) can occur at any stage of syphilis and is treated the same as 3° syphilis with 10 to 14 days of penicillin therapy.

**TABLE 11.8. Differential Diagnosis of Lesions on the Palms and Soles**

DISEASE	LESION FEATURES	DISTRIBUTION/CLUES
Rocky Mountain spotted fever	Macules, then petechiae	Begins on the wrists and ankles; then <b>spreads centrally</b> ; then affects the palms and soles late in the disease course
2° syphilis	Reddish-brown, copper-colored papules; never vesicular (see Figure 11.6)	Condylomata lata or mucous patches on mucosa Diffuse, symmetric involving entire trunk and extremities
Erythema multiforme	Targetoid lesions	Symmetric over the elbows, knees, palms, and soles; may become diffuse and involve the mucosa
Acute meningococcemia	Blanching macules; then gun-metal-gray petechiae and purpura	Begins on the distal extremities; then spreads to the trunk and “pressure spots” <b>over hours</b>
Endocarditis	Janeway lesions are painless, hemorrhagic macules Osler nodes are subcutaneous, tender, pink or purplish nodules	Janeway lesions appear on the palms and soles Osler nodes are found on the pads of digits
Hand-foot-and-mouth disease	Tender vesicles	Peripheral and in the mouth Outbreaks occur within families

### QUESTION

A 33-year-old HIV-positive man presents with new visual complaints. He is referred to an ophthalmologist who notes bilateral choriorretinitis and an RPR of 1:64 (previous RPR 18 months ago, nonreactive). How should this patient be treated?



**FIGURE 11.7. Spirochetes on darkfield microscopy.** (Source: Centers for Disease Control and Prevention/WF Schwartz.)

**KEY FACT**

**Jarisch-Herxheimer reactions** are commonly seen in the first 24 hours of syphilis treatment and are characterized by low-grade fever, headache, myalgias, malaise, and new skin lesions. They are thought to be due to cytokine release and may be seen following the treatment of other spirochetal illnesses (eg, Lyme disease, relapsing fever). Treat with antipyretics.

**KEY FACT**

Bone scan is not the first-line for imaging for osteomyelitis unless there is contraindication to MRI.

**KEY FACT**

Don't be tempted to use sinus tract culture to guide therapy in osteomyelitis; bone biopsy is needed.

**A****ANSWER**

A 14-day course of IV penicillin for neurosyphilis. Having a  $\oplus$  RPR with the most recent  $\ominus$  RPR taken >1 year ago would place this patient in the category of late latent syphilis, but the finding of ocular involvement qualifies this as neurosyphilis.

**Osteomyelitis**

Spread of osteomyelitis may be contiguous or hematogenous. **Local spread** occurs in diabetics and in patients with prosthetic joints, decubitus ulcers, and recent neurosurgery where area is initially seeded by silent transient bacteremia. **Hematogenous spread** affects patients with injection drug use, those with sickle cell disease, and elderly patients.

Common pathogens include *S aureus* and, to a lesser extent, streptococci, coagulase-negative staphylococci (prosthetic joints or postoperative infections), anaerobes (bites, diabetic foot infections, decubitus ulcers), *Pseudomonas* (nail punctures through sneakers, injection drug use), *Salmonella* (sickle cell disease), *M tuberculosis* (foreign-born populations, HIV).

**Symptoms/Exam**

- Local erythema, edema, or tenderness. May have draining sinus tract.
- With spinal disease, if there is adjacent epidural abscess superior to the L1-L2 vertebrae, there can be spinal cord involvement and neurologic sequelae.

**Diagnosis**

- **Probing to bone at the base of an ulcer in diabetic patients.**
- **X-ray:** May demonstrate bony erosions or periosteal inflammation if >2 weeks of infection. If this is normal and suspicion remains for osteomyelitis, should pursue MRI.
- **MRI:** 90% sensitive, 95% specific. May show abnormal marrow edema and enhancement and surrounding soft tissue infection. Particularly useful for diagnosing vertebral osteomyelitis due to ability to visualize spinal cord (Figure 11.8).
- **Microbiology:** Obtain bone culture at debridement or by needle aspiration; sinus tract cultures are not reliable and may represent skin contaminants. With hematogenous osteomyelitis, blood cultures may obviate the need for bone biopsy.

**A****B****C**

**FIGURE 11.8. *Candida albicans* lumbar spondylodiscitis.** MRI of the lumbar spine shows diffuse bone marrow infiltration plus endplate erosion level at L3 and L4 (A, B, and C) characterized by low signal intensity on the T1-weighted image and high signal intensity on the T2-weighted image, with enhancement in affected bodies and cystic enhanced lesions in epidural and paraspinal regions after administration of gadolinium (red arrows). (Source: Chen CH, et al. *Candida albicans* lumbar spondylodiscitis in an intravenous drug user: a case report. *BMC Res Notes.* 2013;6:529.)

## Management

- After debridement of necrotic bone (with cultures taken), empiric antibiotics should be chosen to cover the likely pathogens (see above). Cover for polymicrobial infection in patients with DM-associated osteomyelitis of the foot.
- Antibiotics should be tailored to identified organism and given for 6 weeks unless infected bone is entirely removed. In most cases this requires IV therapy to deliver adequate antibiotic dosing to area of infection.

## Skin and Soft Tissue Infection

Table 11.9 outlines the etiology, clinical presentation, and treatment of common soft tissue infections.

TABLE 11.9. Skin and Soft Tissue Infection

ORGANISM	SOURCE OF ORGANISM	CLINICAL FEATURES	TREATMENT (EXAMPLES)
Group A streptococcus and occasionally groups B, C, and G	Skin flora	Cellulitis, erysipelas	Amoxicillin, cephalaxin, clindamycin
<i>S aureus</i>	Skin flora	Furunculosis, abscess, cellulitis	Doxycycline, TMP-SMX, clindamycin
<i>Vibrio vulnificus</i> , other <i>Vibrio</i> spp	Shellfish or seawater exposure, especially in cirrhosis	Hemorrhagic bullae	Ceftazidime, doxycycline
<i>Mycobacterium marinum</i>	Fish tanks	Nonhealing ulcer, nodular lymphangitis	Clarithromycin + rifampin OR ethambutol
<i>Pseudomonas</i>	Hot tubs, freshwater exposure	Folliculitis or ecthyma gangrenosum in neutropenia (ulcerating hemorrhagic bullae)	Quinolones if susceptible
<i>Francisella tularensis</i> (tularemia)	Ticks, rabbits	Regional lymphadenopathy, pneumonia	Doxycycline (mild), streptomycin (severe)
<i>Pasteurella</i>	Animal bites or scratches	Rapidly progressing cellulitis	Amoxicillin/clavulanate
<i>Sporothrix schenckii</i>	Thorned plants	Nodular lymphangitis	Itraconazole
Pityriasis rosea	—	Round, pink scaling patches; "Christmas tree" distribution on the back	UV light; topical steroids and antihistamines for itching

### KEY FACT

MRI has high sensitivity and specificity for osteomyelitis. However, bone biopsy is the most accurate way to provide microbiologic diagnosis.

### KEY FACT

To prevent DM-associated osteomyelitis, patients should be taught to examine their feet on a daily basis.

### KEY FACT

Do not delay antibiotics for osteomyelitis when a patient is clinically unstable or bacteremic; for clinically stable patients, await bone biopsy and culture data.

### KEY FACT

For small abscesses (<5 cm) with minimal surrounding erythema, I&D that baby! No need for antibiotics.

### QUESTION

A 71-year-old man with type 2 DM and hypertension presents to the hospital with 4 weeks of worsening lumbar back pain and 1 week of fatigue, anorexia, and low-grade fevers. Lumbar x-rays are unremarkable but MRI of the lumbar spine shows enhancement of the L4-L5 disc space and involvement of the superior endplate of the L5 disc and inferior endplate of the L4. What is the most likely diagnosis?

**KEY FACT**

If a patient has skin inflammation with hemodynamic instability, rapid progression, pain out of proportion to exam, physical exam with necrosis / bullae / crepitus, it is important to consider a deeper tissue infection such as necrotizing fasciitis and obtain urgent surgical consultation.

**DIABETIC FOOT INFECTION**

Neuropathy, hyperglycemia, and peripheral arterial disease make the management of diabetic foot infections complicated. Neuropathy predisposes to traumatic and pressure-induced injuries, while microvascular disease prevents wound healing, immune surveillance, and antibiotic delivery to infected tissues.

- **Organism:** Often polymicrobial, including gram-positive, gram-negative organisms, anaerobes and resistant organisms such as MRSA, pseudomonas.
- **Empiric inpatient antibiotic therapy** should cover all of these. All require wound care. Osteomyelitis (probing to bone) or other deep tissue involvement warrants surgical intervention due to difficulty with antibiotic delivery preventing sterilization.

**TOXIC SHOCK SYNDROME**

Toxic shock syndrome (TSS) is associated with **exotoxins** released by certain strains of *S aureus* or group A streptococci (rarely groups B, C, or G). May occur in the setting of concurrent infection (osteomyelitis, occult abscesses, erysipelas, necrotizing fasciitis or myositis) or simply in the setting of colonization of a mucosal, postoperative, or burn-wound surface.

- **Streptococcal TSS:** More commonly associated with invasive streptococcal infections.
- **Staphylococcal TSS:** Usually associated with vaginal/surgical wound colonization, tampons, nasal packing in the absence of invasive infection.

**Symptoms/Exam**

- Fever, hypotension, diffuse sunburn-like macular rash that may subsequently desquamate, evidence of end-organ damage (ARDS, renal insufficiency, coagulopathy, abnormal LFTs, confusion), isolation of staph (less frequent)/strep species in culture data.
- TSS is only rarely preceded by streptococcal pharyngitis.

**Management**

- Aggressive volume resuscitation and surgical debridement of deep-seated infection (if present) and necrotic tissue are critical. Administer empiric broad-spectrum antibiotics.
- If the appropriate organism is isolated, narrow therapy to penicillin + clindamycin for streptococci or nafcillin/oxacillin + clindamycin for methicillin-sensitive staphylococci. For MRSA, vancomycin + clindamycin.

**DERMATOPHYTES**

Fungi in the genera *Trichophyton*, *Microsporum*, and *Epidermophyton* can cause infection of body (corporis), scalp (capitis), cruris (groin), pedis (foot). See the Dermatology chapter for images of common dermatophyte infections.

**ANSWER**

A

Pyogenic bacterial osteomyelitis, likely due to a gram-positive organism such as *S aureus* or a streptococcal species. This occurs most commonly in the lumbar spine in areas of degenerative change, which provide a locus for bacterial seeding during an episode of transient bacteremia. In the spine, this process typically involves the disc space and spreads out to the vertebrae in contrast to TB spinal osteomyelitis (Pott disease), which typically spares the disc space.

**Symptoms/Exam:**

- **Corporis:** Pruritic erythematous scaling oval patch or plaque with central clearing.
- **Capitis:** Patch or plaque affecting scalp or beard and often associated with alopecia. Can be both inflammatory (pruritic, erythematous scaling) or noninflammatory (less redness/pruritus and more isolated hair loss).
- **Cruris:** Pruritic erythematous scaling oval patch or plaque with central clearing on proximal thigh, perianal, perineal, or gluteal regions; typically spares scrotum.
- **Pedis:** Erythematous scaling or erosive changes between digits. May alternatively be hyperkeratotic or vesiculobullous.

- **Diagnosis:** Can be confirmed with KOH preparation revealing segmented hyphae. Some types of fungus also show blue-green fluorescence under a Wood's lamp. Culture is most sensitive.
- **Management:** Primarily topical antifungals (azoles); systemic antifungals used only tinea capitis (griseofulvin or terbinafine) or extensive/refractory tinea corporis/cruris/pedis. Topical treatment is ineffective in capitis as organism located within the hair; systemic treatment is often prolonged 2 to 8 weeks.

## SCABIES

- Scabies presents as a pruritic erythematous rash particularly between webbed areas of hands and feet.
- **Symptoms/Exam:** May see pathognomonic burrows.
- **Diagnosis:** Generally clinical but may scrape lesions and see mites on microscopic evaluation.
- **Management:** Treat with **permethrin cream**. Ivermectin first line only in crusted scabies. Wash clothing and linens in hot water. Place other items in airtight plastic bags for several days.

## Viral Infection

### VARICELLA-ZOSTER VIRUS

1° infection with varicella-zoster virus (VZV) causes chickenpox. Reactivation of latent infection leads to herpes zoster, or “shingles.” Immunosuppressed patients can have more severe disease.



#### KEY FACT

Remember that the chickenpox and zoster vaccines are live and should not be given to highly immunocompromised patients.

#### Symptoms/Exam

- **Chickenpox:** The incubation period is **10 to 20 days**. Presents with prominent fever, malaise, and a pruritic rash starting on the face, scalp, and trunk and spreading to the extremities. The rash is initially maculopapular and turns into vesicles (“dewdrops on a rose petal”) and then into pustules that rupture, leading to crusts. **Multiple stages are present simultaneously.**
- **Herpes zoster:** Dermatomal tingling or pain followed by rash.

#### Differential

- **Smallpox:** Lesions are deeper and painful; all lesions occur at the same stage.
- **Disseminated HSV:** Especially in the setting of a skin disorder; diagnose by lesion PCR.

#### Diagnosis

- Clinical diagnosis. Confirm by scraping of lesions and sending for VZV PCR (most sensitive test, sensitivity highest if sample vesicular lesions; culture and direct immunofluorescent assay [DFA] are less sensitive).
- PCR of CSF for diagnosis of CNS infection.

#### Management

- **Acyclovir, valacyclovir, and famciclovir** ↓ the duration and severity of disease and may prevent complications in adult chickenpox (if treated within **24 hours**) and shingles (if treated within **72 hours**).
- Varicella-zoster immune globulin (**VariZIG**) may prevent complications in immunocompromised or pregnant patients who have no history of VZV but have been exposed to someone with active disease.

### Prevention

- **Chickenpox:** Vaccine can be given up to 3 days after exposure to patients with active lesions. This live attenuated vaccine should not be given to immunosuppressed patients.
- **Herpes zoster:**
  - Vaccine (Zostavax) does not always prevent disease but reduces both number and severity of episodes. This is also a live vaccine.
  - **Postherpetic neuralgia** is most common in elderly patients and may be mitigated by starting antivirals **within 72 hours** of rash onset. The effect of steroids is less clear.
  - **Ophthalmic zoster** may lead to blindness; patients with lesions on the tip of the nose should have an ophthalmologic consult.
  - **Ramsay Hunt syndrome:** Presents with vesicles on the ear, facial palsy, loss of taste on the anterior two-thirds of the tongue, and vertigo. Tinnitus/deafness may occur.

### EPSTEIN-BARR VIRUS

Infectious mononucleosis is caused by the Epstein-Barr virus (EBV). Commonly seen in late adolescence and early adulthood, particularly in college or military populations. The clinical course is generally benign, with patients recovering in 2 to 3 weeks.

#### Symptoms/Exam

- Presents with the triad of **fever, sore throat** (may be severe), and **generalized lymphadenopathy**, often with an abrupt onset.
- Patients may have a viral-like prodrome as well as retro-orbital headache or abdominal fullness (from hepatosplenomegaly).
- Exam reveals lymphadenopathy (especially of the posterior cervical nodes), pharyngitis, and splenomegaly.
- A maculopapular rash occurs in 10% of patients (especially in those given amoxicillin for presumed strep throat), and palatal petechiae may be seen.

#### Differential

- **CMV:** Symptoms are usually systemic. Diagnose with compatible clinical syndrome and CMV serum PCR or  $\oplus$  CMV IgM.
- **1° HIV infection:** Fever, lymphadenopathy, pharyngitis, maculopapular rash, and, less commonly, aseptic meningitis.
- **Streptococcal pharyngitis:** Presents with fever, tender submandibular or anterior cervical lymphadenopathy, and pharyngotonsillar exudates with no cough. Splenomegaly is not seen. Diagnose with a rapid streptococcal test and throat culture if the antigen test is  $\ominus$ .

#### Diagnosis

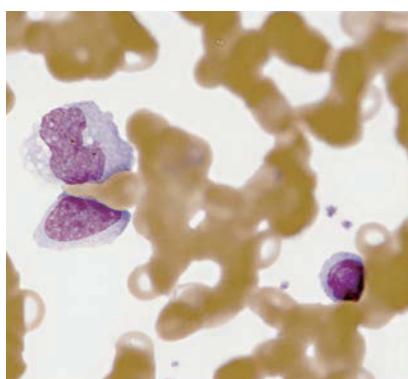
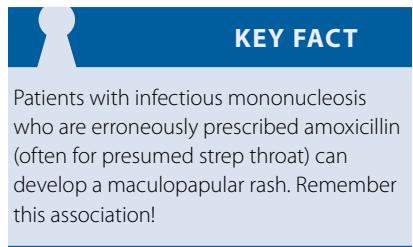
- Labs reveal neutropenia; **atypical lymphocytes** (Figure 11.9) in 70% of cases; thrombocytopenia; and mildly  $\uparrow$  LFTs.
- Specific serologic diagnosis:
  - Heterophile antibodies (Monospot test).
  - VCA (viral capsid antigen) IgM and IgG.

#### Management

No treatment is necessary in the majority of cases. Avoid contact sports.

#### Complications

- Autoimmune hemolytic anemia: Rare, treated with glucocorticoids.
- Splenic rupture: Also rare but may occur in weeks 2 to 3; patients should avoid contact sports and heavy lifting.



**FIGURE 11.9. Atypical lymphocytosis in a patient with infectious mononucleosis.** These reactive T lymphocytes are large with eccentric nuclei and bluish-staining RNA in the cytoplasm. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 174-2.)

## Fungal Infection

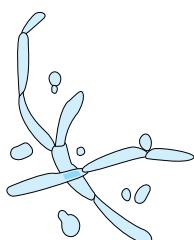
See Figure 11.10 for typical forms of fungi that might be seen in tissues examined by histopathology. Common fungal infections are discussed below.

### CANDIDIASIS

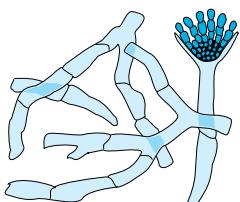
The opportunistic yeast *Candida* is a commensal found on the skin, GI tract, and female genital tract. **Superficial infection** is common among diabetics. Risk factors for **deep or disseminated infection** include **immune compromise** (HIV, malignancy, neutropenia, or steroids), multiple or prolonged **antibiotic** treatment, indwelling catheter, TPN and/or **invasive procedures**. *C albicans* is the most common pathogen.

#### Diagnosis

- **Candiduria:** Yeast in urine usually represents colonization and not infection. Seen in patients with Foley catheters or antibiotic use.

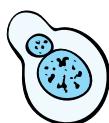


*Candida albicans*



*Aspergillus fumigatus*

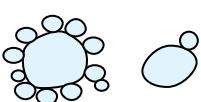
#### Endemic mycoses:



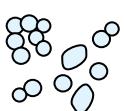
*Cryptococcus neoformans*



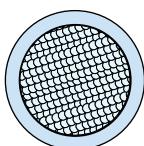
*Blastomyces dermatitidis*



*Paracoccidioides brasiliensis*



*Histoplasma capsulatum*



*Coccidioides immitis*

FIGURE 11.10. Characteristic forms of fungi in human tissue (37° C). (Redrawn with permission from Bhushan V, Le T. First Aid for the USMLE Step 1: 2005. New York: McGraw-Hill, 2005: 191.)



### QUESTION

A 37-year-old man is admitted to the hospital for progressive chest pain and odynophagia. His exam is notable for some oral plaques and wasting. A rapid HIV test returns  $\oplus$ , and a CD4 count is 130 cells/ $\text{mm}^3$ . What is the most appropriate therapy for this patient?

**KEY FACT**

*Candida* in the sputum is often a contaminant.

**KEY FACT**

All patients with candidemia should have an ophthalmologic exam to rule out candidal endophthalmitis.

**KEY FACT**

Echinocandins do not have adequate penetration of CNS or urine so should not be used to treat meningitis, endophthalmitis, UTI.

- **Intertrigo (“diaper rash”):** Pruritic vesiculopustules rupture to form macerated or fissured beefy-red areas at skin folds. Satellite lesions may be present. Seen in both immunocompetent and immunosuppressed patients.
- **Oral thrush:** Presents with burning sensations of the tongue or mucosa with white, curdlike patches that can be scraped away to reveal a raw surface. Seen in patients with AIDS or malignancy, in those who use inhaled steroids for asthma and in those with Sjögren disease. Diagnosis can be confirmed with a KOH preparation or Gram stain.
- **Candidal esophagitis:** Presents with dysphagia, odynophagia, and substernal chest pain. Seen in patients with AIDS, leukemia, and lymphoma. Diagnosed by the endoscopic appearance of white patches or from biopsy showing mucosal invasion. May develop concurrently with HSV or CMV esophagitis.
- **Candidemia and disseminated candidiasis:** Diagnosed through cultures of blood, body fluids, or aspirates. Candidemia may lead to fever, hypotension, shock, or endophthalmitis (need fundoscopic exam), osteomyelitis, arthritis, or endocarditis.

**Management**

- **Candiduria:** Most cases do not need treatment; if necessary to treat (neutropenic, s/p renal transplantation, or upcoming urinary tract procedures), use fluconazole.
- **Intertrigo and oral thrush:** May be treated with topical antifungals (nystatin and clotrimazole creams or nystatin suspension swish and swallow).
- **Esophagitis:** Systemic therapy with fluconazole.
- **Candidemia:**
  - Fluconazole: If patient is less ill or if urine or CNS infection suspected (echinocandins do not penetrate these regions).
  - Echinocandin: If patient is neutropenic or moderately/severely ill or there is possibility of fluconazole resistant organism.
- Resistance to fluconazole: *C albicans* is usually susceptible to fluconazole. Patients who have been on fluconazole prophylaxis may have resistant *C albicans* or non-albicans species (eg, *Candida glabrata*, *Candida krusei*) and should initially be treated with an echinocandin (eg, caspofungin) until guided by susceptibility testing.
- Vascular catheters: Replace vascular catheters at a new site.

**ASPERGILLOSISS**

*Aspergillus fumigatus* and other species are widespread in soil, water, compost. See Table 11.10 for *Aspergillus* syndromes.

**ENDEMIC MYCOSIS**

The endemic fungi include *Cryptococcus*, *Coccidioides*, *Histoplasma*, and *Blastomycetes*. They have several features in common:

- Exposure by inhalation.
- Often cause self-limited pulmonary disease in immunocompetent host; have potential to disseminate in immunocompromised host.
- Often treated with azoles for mild disease and amphotericin for severe disease.

**A****ANSWER**

Fluconazole and initiation of ART. The findings in this patient with advanced HIV suggest esophageal candidiasis. His CD4 count is too high to be associated with CMV disease, and the presence of oral lesions consistent with *Candida* makes this diagnosis most likely.

**Cryptococcosis**

*Cryptococcus neoformans* is an encapsulated budding yeast found worldwide in soil and bird (pigeon) droppings. Risk factors for the disease are HIV-related immunosuppression, Hodgkin disease, leukemia, advanced liver disease, and steroid use. *C neoformans* is the most common fungal infection in AIDS patients (usually associated with a CD4 count of <100 cells/mm<sup>3</sup>) and is the most common cause of fungal meningitis in all patients (Figure 11.11).

TABLE 11.10. *Aspergillus* Syndromes

SYNDROME	PATIENT	SIGNS/SYMPTOMS	DIAGNOSIS	TREATMENT
<b>Allergic bronchopulmonary aspergillosis</b>	Underlying asthma, CF	Episodic bronchospasm, fever, and brown-flecked sputum	Eosinophilia, ↑ serum IgE, cutaneous response to <i>Aspergillus</i> antigens and $\oplus$ serum <i>Aspergillus</i> IgG precipitins CXR with patchy, fleeting infiltrates	Systemic corticosteroids plus itraconazole $\times$ 8 months improves lung function and $\downarrow$ steroid requirements
<b>Aspergilloma</b>	Previous TB, sarcoid, emphysema	Asymptomatic; hemoptysis, chronic cough, weight loss	CXR and CT may show a rim of air around a fungus ball in a preexisting pulmonary cavity	Surgical excision for massive hemoptysis Antifungals play a limited role
<b>Invasive aspergillosis</b>	Neutropenia, advanced AIDS, diabetes, and chronic granulomatous disease, and those on high-dose steroids or immunosuppressants	Dry cough, pleuritic chest pain, and persistent fever	CXR and CT may show wedge-shaped lesions from tissue infarction, an <b>air-crescent sign</b> from cavitation of a necrotic nodule, or a <b>halo sign</b> of a necrotic nodule with surrounding hemorrhage Galactomannan assay, $\oplus$ sputum or bronchial washing cultures Definitive diagnosis: biopsy demonstrating tissue invasion	Voriconazole (less effective alternatives are amphotericin or echinocandins) or caspofungin

### Symptoms/Exam

- Meningitis:** Mental status changes, headache, cranial nerve palsies. **HIV patients usually lack obvious meningeal signs.**
- May also cause atypical pneumonia (pulmonary infection is usually asymptomatic) or skin lesions (umbilicated papules resembling molluscum contagiosum), or may involve the bone, eye, or GU tract.

 **KEY FACT**  
Cryptococcemia (a  $\oplus$  serum CrAg or blood culture) indicates disseminated disease.

### Diagnosis

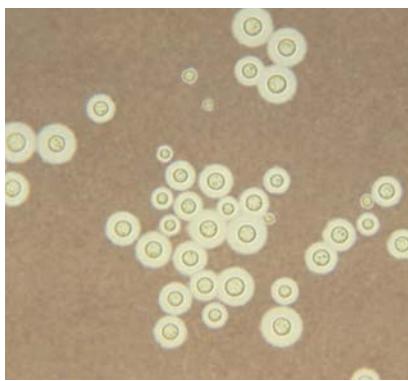
- LP:** Patients often have high opening pressure ( $>25$  cm H<sub>2</sub>O), low glucose, high protein, and lymphocytic pleocytosis. **Patients with more advanced immunosuppression may have a bland CSF profile even with meningitis.** India ink or Gram stain of CSF (Figure 11.11) may show budding yeast with a thick capsule (both are  $<50\%$  sensitive).
- Polysaccharide CrAg in serum or CSF:** CSF CrAg is highly sensitive for meningitis. Serum CrAg is also sensitive in AIDS patients with meningitis but is less sensitive in non-AIDS patients and in nondisseminated disease (ie, isolated pulmonary disease). A serum CrAg titer of  $>1:8$  typically indicates active disease.
- Fungal culture of blood** (*C. neoformans* can grow easily in blood culture unlike other endemic fungi), CSF, urine, sputum, or BAL.
- Imaging:** CT or MRI may show hydrocephalus or may occasionally reveal nodules (cryptococcomas, “cannon-ball” lesions).

 **KEY FACT**  
Unlike what is typically seen in bacterial meningitis, HIV patients with cryptococcal meningitis can have minimal symptoms and a bland CSF.

### Management

- For mild to moderate lung disease:** Treat with oral fluconazole at least 6 to 12 months.
- For meningitis, cryptococcemia, or severe lung disease:** Treat with induction of amphotericin plus 5-flucytosine for at least 2 weeks with transition to long-term fluconazole.

 **QUESTION**  
A 23-year-old man with untreated HIV and a CD4 count of 55 cells/mm<sup>3</sup> presents with headache and malaise. His head CT is normal, and LP reveals an opening pressure of 35 cm H<sub>2</sub>O, a WBC count of 6 (30% PMNs), a glucose level of 55 mg/dL, and a protein level of 79 mg/dL. What is the most appropriate test to make the diagnosis?



**FIGURE 11.11. *Cryptococcus neoformans* in CSF stained with India ink.** (Source: Centers for Disease Control and Prevention.)

### KEY FACT

CSF CrAg is highly sensitive for meningitis. Serum CrAg is also sensitive in AIDS patients with meningitis but is less sensitive in non-AIDS patients.

- Patients with HIV need **long-term maintenance therapy** with oral fluconazole. It may be reasonable to discontinue fluconazole once adequate treatment course is completed and if the CD4 count  $\uparrow$  to  $>200$  cells/mm $^3$  for  $>6$  months in response to antiretroviral therapy (ART).
- **Key management point:** In cryptococcal meningitis, the most common cause of morbidity and mortality is  $\uparrow$  intracranial pressure (ICP). Always perform ICP measurement with initial LP. If pressures  $\uparrow$  or neurologic symptoms develop, serial LPs or CSF drainage are often needed to maintain ICP at a safe level.

### Coccidioidomycosis

*Coccidioides immitis* is found in arid central California, southwestern United States, northern Mexico, and Central and South America. It is found in soil, and outbreaks occur after earthquakes or dust storms. Risk factors include exposure to soil and the outdoors (construction workers, archaeologists, farmers).

#### Symptoms/Exam

- **1° infection (“valley fever,” “desert rheumatism”):**
  - Usually presents with self-limited flulike or community-acquired pneumonia symptoms with fever, dry cough, pleuritic chest pain, and headache, often accompanied by **arthralgias, erythema nodosum, or erythema multiforme**. Occurs 1 to 3 weeks after exposure. CXR may be normal or may show unilateral infiltrates, nodules, or thin-walled cavities.
  - Some patients (5%) may develop chronic pneumonia, ARDS, or persistent lung nodules.
- **Disseminated disease (1%):** Chronic meningitis, skin lesions (papules, pustules, warty plaques), osteomyelitis, or arthritis.

#### Diagnosis

- **Serologic tests:**
  - Immunodiffusion assay—qualitative serologic test best used for initial screening.
  - Complement fixation assays—quantitative test that can be used to follow treatment response. Titers  $\geq 1:32$  indicate more severe disease and a higher risk of dissemination.
- **Histology** may show giant **spherules** in infected tissues.
- **Cultures** of respiratory secretions or aspirates of bone and skin lesions may grow the organism (*Coccidioides* is highly infectious to lab workers—alert the lab if testing).

#### Management

- Treatment may not be necessary for acute disease but is reasonable in patients at risk for dissemination.
- Fluconazole should be given for disseminated disease, including meningitis; titers (complement fixation) are useful in monitoring treatment response. Many patients will need lifelong suppressive therapy with fluconazole after meningitis. Amphotericin is utilized for severe coccidioidal infections that are refractory to azole agents or for women during first trimester.

A

### ANSWER

CSF cryptococcal antigen (CrAg). The presence of headache and an  $\uparrow$  CSF opening pressure in a patient with advanced HIV infection should be diagnosed as cryptococcal meningitis until proven otherwise. The CSF can often appear relatively normal.

### Histoplasmosis

*Histoplasma capsulatum* is found in the **Mississippi and Ohio River valleys**. The organism is found in moist soil and in bat and bird droppings. Risk factors include exploring caves and cleaning chicken coops or attics.

#### Symptoms/Exam

- **1° infection:** Most patients are asymptomatic. However, patients may present with fever, dry cough, and substernal chest discomfort. CXR may show patchy infiltrates

that become nodular or exhibit multiple small nodules and hilar or mediastinal adenopathy. Some patients may develop chronic upper lobe cavitary pneumonia or mediastinal fibrosis (dysphagia, SVC syndrome, or airway obstruction).

- **Disseminated disease:** Presents with **hepatosplenomegaly**, adenopathy, **painless palatal ulcers**, meningitis, pancytopenia from bone marrow infiltration, adrenal insufficiency from adrenal infiltration.

### Diagnosis

- **Urinary antigen test** is most useful in HIV/AIDS patients with disseminated disease. Less sensitive with isolated pulmonary disease and intact immune system.
- Serologic tests (complement fixation and immunodiffusion assays) are more likely  $\oplus$  in immunocompetent patients.
- **Histology with silver stain** of bone marrow, lymph node, or liver is often the key diagnostic.
- Cultures of blood or bone marrow can be  $\oplus$  in disseminated disease.

### Management

- Treatment is not needed for acute mild pulmonary disease.
- Itraconazole for moderate or amphotericin for severe acute diffuse pulmonary infection, chronic cavitary pneumonia, or disseminated histoplasmosis. As with other endemic fungi, treatment should be continued until CD4 recovery in patients with HIV.

### Blastomycosis

*Blastomyces dermatitidis* is found in the **central United States** (as is *Histoplasma*) as well as in the upper Midwest and Great Lakes regions. Risk factors include exposure to woods, streams.

- **Symptoms/Exam:** Acute pneumonia. May lead to warty, crusted, or ulcerated **skin lesions** or to osteomyelitis, epididymitis, or prostatitis. Can disseminate without immunosuppression.
- **Diagnosis:** Biopsy or aspirate material shows large yeast with **broad-based budding**; microscopy and culture of respiratory secretions.
- **Management:** Treat those with moderate-severe pneumonia, immunocompromise or extrapulmonary manifestations. Use itraconazole for mild to moderate disease, or amphotericin induction followed by itraconazole for severe disease.



### MNEMONIC

**Remember the B's of Blastomycosis microscopy—**  
**Broad-Based Budding**

### Mucormyces

Invasive fungal infection associated with immunocompromise from diabetes, burns, hematologic malignancies with neutropenia. Rhinocerebral mucormyces is the most common manifestation. Patients will present with vision changes, headache, epistaxis; exam will reveal black necrotic tissue. Diagnosis is made by biopsy and culture, and a combination of aggressive surgical debridement and amphotericin is the treatment of choice.

## Nontuberculous Mycobacteria

Nontuberculous (atypical) mycobacteria (NTMs) are natural inhabitants of water and soil. They can cause clinical disease in both immunocompetent and immunocompromised patients and are often difficult to diagnose and treat.

### Symptoms/Exam

- **Mycobacterium avium:** Three presentations are most frequently seen:
  - **Cavitary upper lobe lesions:** Classically in middle-aged men with underlying pulmonary disease (COPD). Presents similarly to *M tuberculosis*.



### QUESTION

A 47-year-old African American construction worker in central California presents with recent development of widespread cutaneous nodules. Exam reveals many raised, slightly painful nodules throughout the upper and lower extremities, and a biopsy shows spherules on pathology. What is the most likely diagnosis?

### KEY FACT

Think of pulmonary *M avium* in an elderly, nonsmoking woman with cough, malaise, and midlung nodular bronchiectasis on CXR or CT.

### KEY FACT

To distinguish nontuberculous *Mycobacterium* infection (which should be treated) from colonization (which may not require treatment), you usually need at least two  $\oplus$  sputum culture (preferably morning) specimens or one  $\oplus$  culture obtained from BAL.



### ANSWER

This patient has disseminated coccidioidomycosis and should be treated with systemic antifungals such as fluconazole. Risk factors for dissemination include non-Caucasian ethnicity and pregnancy. Skin biopsy may show spherules, and this patient's outdoor exposure in central California makes coccidioidomycosis a likely diagnosis.

- **Midlung nodular bronchiectasis:** Classically in elderly underweight women with bronchiectasis, particularly of the right middle lobe and lingula (Lady Windermere syndrome).
- **Disseminated MAC:** Seen HIV/AIDS patients with CD4 count  $<50$  cells/ $\text{mm}^3$  and can cause a systemic disease with fever, abdominal pain, lymphadenopathy, hepatosplenomegaly, and bone marrow infiltration.
- ***Mycobacterium kansasii*:** Primarily a pulmonary pathogen presenting in a manner similar that of *M tuberculosis*. Patients may or may not be immunocompromised and often have underlying lung disease. This is rarely a colonizing organism.
- ***Mycobacterium marinum*:** The 1° presentation consists of skin ulcers and nodular lymphangitis in patients with exposure to freshwater and saltwater, including marine organisms, swimming pools, and fish tanks.
- **Rapidly growing mycobacteria (*Mycobacterium abscessus*, *fortuitum*, and *cheloneae*):** *M abscessus* is the most virulent of these pathogens, causing nodular or cavitary pulmonary disease and often causing skin or soft tissue infections. *M fortuitum* and *M cheloneae* typically cause localized or disseminated (immunocompromised) skin and soft tissue infections.

### Differential

**Cavitary or nodular lung disease:** *M tuberculosis*, mycoses (coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis), *Nocardia*, aspergillosis, neoplasms.

### Diagnosis

- **Pulmonary disease:** All three of the following criteria must be satisfied:
  - **Clinical criteria:** Compatible signs and symptoms (cough, fatigue, fever, weight loss) with reasonable exclusion of other diseases.
  - **Radiographic criteria:** CXR with persistent or progressive infiltrates with cavitation and/or nodules or CT with multiple small nodules or multifocal bronchiectasis.
  - **Bacteriologic criteria:** Isolation of NTM from at least two separate sputum samples or a single bronchoscopy or tissue biopsy with growth from a sterile site.
- **Nodular lymphangitis:** Very common in children. Uncommon in adults. A  $\oplus$  culture from biopsy.

### Management

Treatment requires multiple drug regimens for prolonged courses of therapy (for MAC typically a regimen of macrolide, rifamycin, and ethambutol or for *M kansasii* a regimen of isoniazid, rifampin, and ethambutol). See the Skin and Soft Tissue Infection section above for treatment of *M marinum*. Many of these organisms (particularly the rapidly growing mycobacteria) are resistant to multiple antimicrobial agents. Consultation with a specialist is recommended.

## Tuberculosis

In the United States, *M tuberculosis* is most commonly found among immigrants from developing countries. Can also be seen in US-born population when enough risk factors for exposure—which include homelessness, incarceration, malnutrition, and crowded living conditions—are present.

### Symptoms/Exam

- **1° TB:** Usually asymptomatic with no radiographic signs, but **progressive 1° infection** develops in 5% of patients (usually infants, elderly persons, and the immunosuppressed).

- LTBI:** Patients are infected (and are usually skin test  $\oplus$ ) but do not have symptoms of active disease. Bacilli are contained by granuloma-forming T cells and macrophages.
- Active TB/reactivation disease:** Develops in approximately 10% of LTBI patients, 5% within the first 2 years of infection and 5% over the rest of their lives. **Risk factors for reactivation** include recent infection/immigration from an endemic country (within 2 years), HIV, hematologic malignancy, immunosuppressive medications (eg, highest risk from anti-TNF agents), diabetes, silicosis, malnutrition, and tobacco use.
- Pulmonary TB:** Presents with subacute cough (initially dry and then productive, sometimes with blood-streaked sputum) as well as with malaise, fever, sweats, and weight loss. Exam is normal or reveals apical rales, rhonchi, or wheezing.
- Extrapulmonary TB:** Lymphatic (painless cervical lymph node swelling) and pleural disease are most common. Other sites of infection may be seen (including meningitis, osteomyelitis, and arthritis), especially in patients with advanced HIV. Fever may be seen with more extensive disease or miliary (hematogenous dissemination) disease.
- Figure 11.12 shows the evolution of pulmonary TB from initial infection to reactivation.


**KEY FACT**

Be aware of TB reactivation risk in patients taking anti-TNF immunosuppressants.

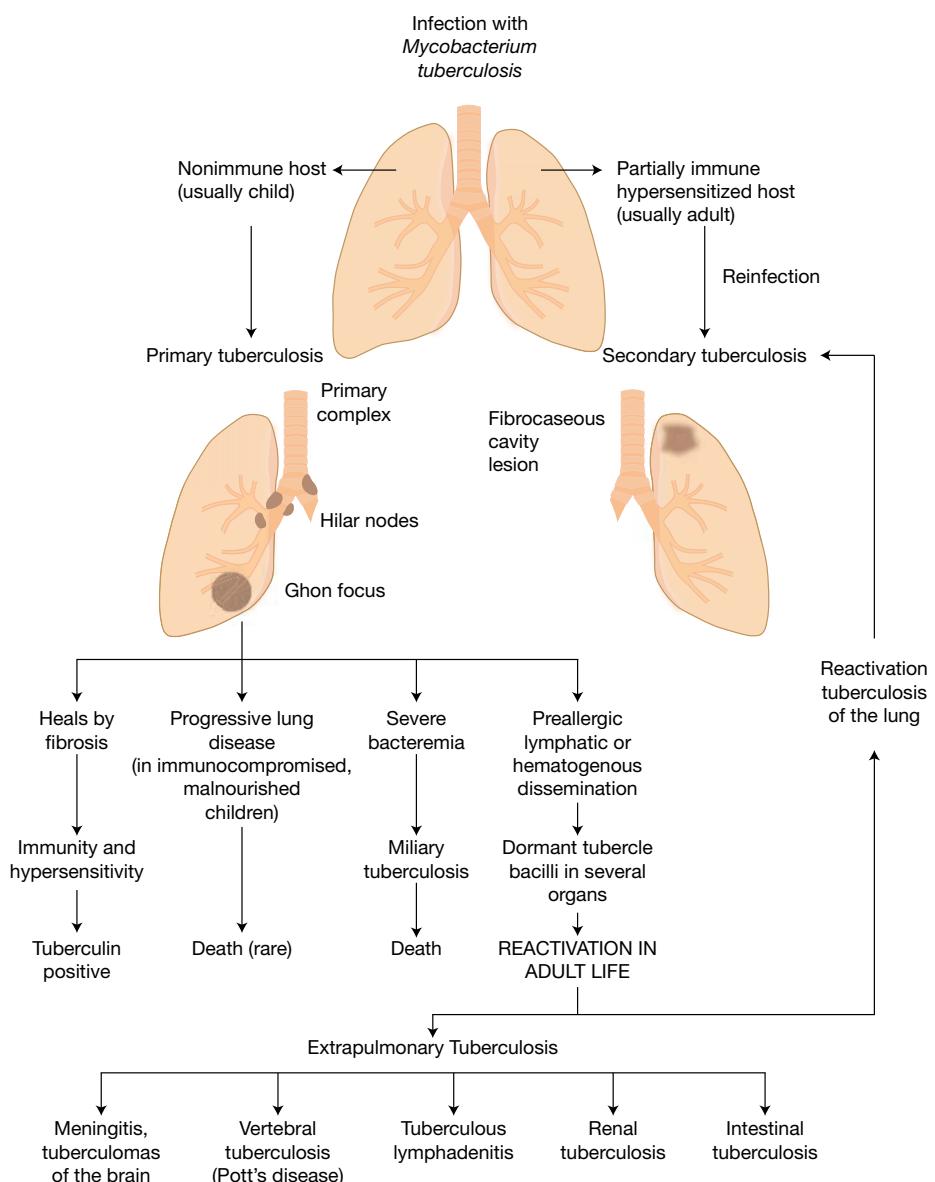
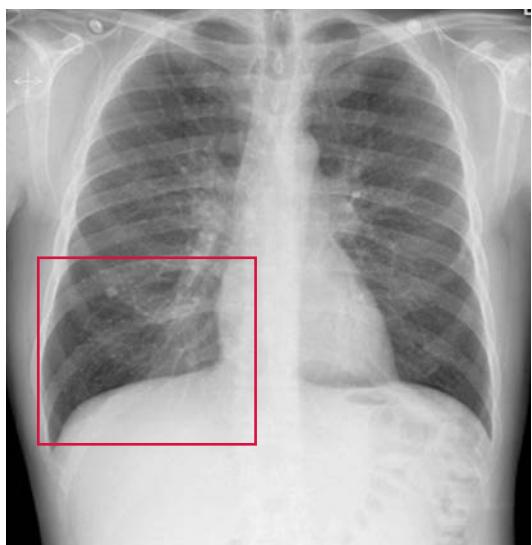


FIGURE 11.12. Evolution of pulmonary tuberculosis. (Modified with permission from Chandrasoma

P, Taylor CR. Concise Pathology, 2nd ed. Originally published by Appleton & Lange. Copyright © 1995 by The McGraw-Hill Companies, Inc.)

### Diagnosis

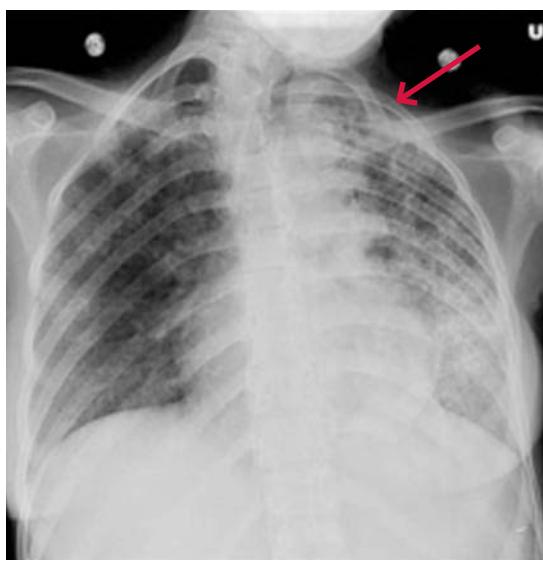
- Radiographic findings in active pulmonary TB show infiltrates, nodules (including hilar), cavities (especially the apical or posterior segments of the upper lobes or the superior segments of the lower lobes), and calcifications (Figure 11.13). Patients with advanced HIV and elderly patients may have normal or atypical radiographs.
- Sputum smears are most sensitive in patients with cavitary disease (Figure 11.14) and less sensitive in highly immunosuppressed patients, especially with HIV. When smears are  $\oplus$ , bacilli are visualized by acid-fast stain.
- Cultures of sputum, blood, or tissue are the **gold standard** (acid-fast staining characteristics depend on concentration so can have smear  $\ominus$  but culture  $\oplus$  disease) but may take weeks to months to grow. Sensitivities from cultures help guide treatment.



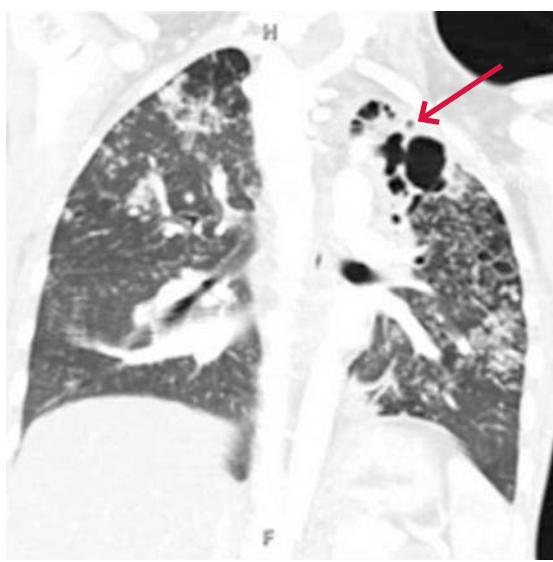
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B



C



D

**FIGURE 11.13. Pulmonary tuberculosis.** (A) Frontal CXR demonstrating diffuse, 1- to 2-mm nodules due to miliary TB. (B) A zoomed-in view corresponding to the area delineated by the red box in Image A. (C) Frontal CXR demonstrating left apical cavitary consolidation (red arrow) and patchy infiltrates in the right and left lung in a patient with reactivation TB. (D) Coronal reformation from a noncontrast chest CT in the same patient as Image C, better demonstrating left apical cavitary consolidation (red arrow) and other areas of parenchymal abnormality corresponding to the endobronchial spread of TB. (Reproduced with permission from USMLE-Rx.com.)

- Nucleic acid amplification and/or hybridization tests are adjuncts to smear and culture for rapid identification of TB in respiratory smears (and can sometimes be used in, although are not FDA approved, for extrapulmonary sites). This should be used in patients who you have a moderate to high suspicion for active disease. Sensitivity is lower if smear is  $\ominus$ .

### Management

- Hospitalized patients with suspected active TB should be placed in **respiratory isolation**. Confirmed cases should be reported to public health authorities.
- Begin treatment with four drugs (unless patient has history of drug-resistant TB or prior TB treatment):** Isoniazid (INH), rifampin (RIF), pyrazinamide, and ethambutol  $\times$  2 months, followed by INH and rifampin for remaining 4 or 7 months. A course of 7 months (or longer) is given for patients with persistently  $\oplus$  sputum cultures after initial therapy, cavitary lung findings, miliary TB, osteomyelitis, or meningitis. Modify antibiotic regimen once susceptibility results are available.
- In patients on protease inhibitors, non-nucleoside reverse transcriptase inhibitors, itraconazole, methadone, or other medications metabolized by the liver, **rifabutin** may be used instead of rifampin because it is associated with less cytochrome P-450 induction.
- Corticosteroids:** Consider in tuberculous meningitis or pericarditis where the inflammation in closed spaces after treatment could have significant consequences.
- Strongly consider using directly observed therapy** to maximize compliance.

### Prevention

- Patients who are at risk for reactivation disease should be screened regardless of age (“a decision to screen is a decision to treat”). **Screening of LTBI includes:**
  - Tuberculin skin testing:** Identifies patients with latent infection but is not close to 100% sensitive or specific; false-negative results are seen in elderly, malnourished, and immunosuppressed patients as well as in those with overwhelming TB infection. False-positive results can be caused by environmental mycobacteria. Table 11.11 outlines CDC guidelines governing tuberculin skin test positivity.
  - Quantiferon-TB Gold assay:** Measures the release of  $\gamma$ -interferon in whole

TABLE 11.11. CDC Guidelines for Tuberculin Skin Test Positivity

$\geq 5$ MM OF INDURATION (FOR PATIENTS AT HIGHEST RISK OF REACTIVATION)	
HIV	
Immunosuppression due to organ transplants or other medications (prednisone $\geq 15$ mg/day for $\geq 1$ month)	
Close contacts of TB cases	
CXR with fibrotic changes consistent with prior TB	
$\geq 10$ MM OF INDURATION	
Recent immigrants ( $\leq 5$ years) from developing countries	
Residents or established employees of jails, long-term care facilities, or homeless shelters	
Patients who inject drugs	
Patients with chronic illnesses such as silicosis, diabetes, CKD; malignancy (leukemia, or lymphoma, head and neck or lung cancers); underweight	
$\geq 15$ MM OF INDURATION (FOR PATIENTS AT LOWEST RISK OF REACTIVATION)	
Patients with no risk factors for TB	
New employees of high-risk institutions (at work entry)	

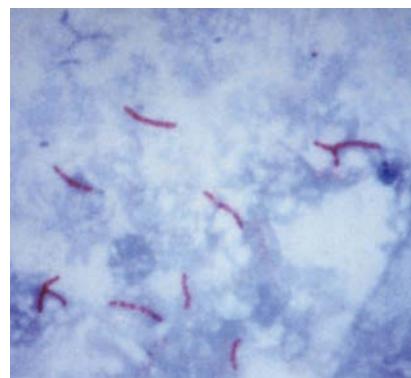


FIGURE 11.14. *Mycobacterium tuberculosis* in an acid-fast (Ziehl-Neelsen) stain. Magnified 1000 $\times$ . (Source: Centers for Disease Control and Prevention/Dr. George P. Kubica.)

#### KEY FACT

You should not consider previous BCG vaccination status when interpreting a reactive PPD.

#### KEY FACT

Once a PPD is positive, it will remain positive.



#### QUESTION

A 35-year-old woman who emigrated from India 2 years ago has a PPD as part of her routine physical and is found to have 20 mm of induration. She feels well and has no fever, cough, or weight loss but notes that she received the BCG vaccine as a child. What are the appropriate next steps for this woman?

blood in response to stimulation by synthetic peptide mixtures simulating two proteins secreted by *M tuberculosis*. Sensitivity is similar to that of PPD but specificity is ↑, and it does not require a follow-up visit for reading (as is required by PPD skin testing).

- After + skin test or quantiferon gold assay: CXR to rule out active pulmonary disease.
- **Treatment of LTBI:** INH QD or high dose twice weekly × 9 months or with RIF QD × 4 months. Combination once weekly INH/rifapentine × 3 months via directly observed therapy is another option. The use of combination rifampin/pyrazinamide for 2 months has been associated with severe and fatal hepatitis and should be avoided.

### Complications

- Treatment failure can be due to medication nonadherence but also consider poor drug absorption or drug-resistant disease.
- Adverse effects of antituberculous drugs are listed in Table 11.12.

## Immunocompromised Host

For further discussion of specific immunodeficiencies, please see the Allergy and Immunology chapter.

### ASPLENIA-RELATED INFECTION

**Postsplenectomy sepsis** has a short viral-like prodrome followed by abrupt deterioration and shock. Encapsulated organisms involved include *S pneumoniae* (>50%), *N meningitidis*, and *H influenzae*.

TABLE 11.12. Adverse Effects of Antituberculous Drugs

AGENT	ADVERSE EFFECTS	MONITORING
Rifamycin (rifampin)	GI upset, hepatitis (cholestatic), rash, drug-drug interactions, orange body fluid	Baseline LFTs and monthly check, skin check If rash or severe hepatitis occurs in response to TB treatment, discontinue all hepatotoxic drugs and reintroduce one at a time every 3-4 days while monitoring symptoms and LFTs
Isoniazid	Peripheral neuropathy, hepatitis (transaminitis), rash	LFTs, skin check
Pyrazinamide	↑ uric acid/gout, hepatitis (highest risk of the TB meds), rash, GI upset	Uric acid, LFTs, skin check
Ethambutol	Optic neuritis	Visual acuity and color vision

A

### ANSWER

Evaluate for active disease (eg, history and with CXR) and then treat for latent tuberculosis infection (LTBI) or active disease, if this is noted on CXR. Her BCG status does not affect the interpretation of PPD or decision to treat.

## Prevention

- Vaccinate against *S pneumoniae*, *H influenzae* type b (unvaccinated older individuals), and *N meningitidis*. Vaccinate  $\geq 2$  weeks before elective splenectomy or  $>2$  weeks after surgery.
- Give a supply of antibiotics to be taken as **self-administered therapy** for fever (eg, amoxicillin to be taken at the onset of fever, followed by immediate evaluation in urgent care).

## TRANSPLANT MEDICINE

Infection now accounts for 50% of deaths in solid organ transplant. The infectious risk depends on multiple factors, including type of organ transplanted, donor characteristics, type of immunosuppression, and presence of graft versus host disease. However, Table 11.13 provides a general outline of infectious risk.

## FEBRILE NEUTROPENIA

See the Oncology chapter.

**TABLE 11.13. Post-Transplant Infection**

### MONTH 1

#### Nosocomial infections

- Surgical site infection
- Hospital-acquired pneumonia
- Catheter-related blood stream infection
- Clostridium difficile*

### MONTHS 2-6

#### Opportunistic infection

- Viral
  - CMV: More common in seronegative recipients of seropositive donor; may present with fever, leukopenia/thrombocytopenia, infection of transplanted organ or pneumonia, GI disease
  - EBV: B lymphocyte proliferation leading to PTLD; presents with fever and extranodal mass or lymphadenopathy
  - Polyomavirus (BK virus): Nephropathy
  - HBV, HCV

#### Bacterial/mycobacterial

- *Legionella*
- *Listeria*
- *Nocardia*
- TB

#### Fungal

- *Aspergillus* (lung and stem cell transplant)
- *Candida* (liver and stem cell transplant)
- PCP

#### Protozoa/helminths

- Toxoplasmosis
- *Strongyloides*

### MONTH 6 AND BEYOND

#### Community-acquired infection + additional infections based on the type and degree of post-transplant immunosuppression used



### QUESTION 1

A 42-year-old woman who underwent a lung transplant 1 year ago is being evaluated for a new lung nodule. A CT-guided lung biopsy grows weakly acid-fast bacteria in a branching-rod pattern. Which of the following is the next most appropriate step in management?



### QUESTION 2

A 57-year-old man who underwent heart transplant 6 months earlier is admitted for night sweats and weight loss. He was seronegative for cytomegalovirus and EBV; his donor was seropositive. Exam and lab results are unremarkable. Imaging reveals a new pulmonary mass. What is the probable cause of this mass?



### QUESTION 3

A 23-year-old man presents to his primary care physician with fever, pharyngitis, and adenopathy. On history, he reports an unprotected sexual encounter that occurred 2 weeks ago. If this is 1° HIV, what is the most appropriate test to make the diagnosis?

**KEY FACT**

A patient should not be told they have HIV infection based on results of an ELISA alone; confirmatory Western blot assay is necessary.

**KEY FACT**

Monotherapy is not an option for HIV treatment even during pregnancy; treat with three drugs. No breastfeeding.

**KEY FACT**

Do not use CD4 count or HIV viral load as a factor in deciding when to initiate ART.

**A****ANSWER 1**

TMP-SMX for 3-6 months, potentially in combination with a second antibiotic depending on site of infection. This immunocompromised patient has a nodule that is growing *Nocardia*, a gram-positive branching bacterium that is weakly acid fast.

**A****ANSWER 2**

Post-transplant lymphoproliferative disorder (PTLD), which can be diagnosed by biopsy of the mass. PTLD is more common when donor and recipient are serodiscordant. Treatment involves reduction of immunosuppression.

**A****ANSWER 3**

HIV viral load and p24 antigen. 1° HIV should be considered in patients with this constellation of symptoms. Antibody response may take at least 1 to 3 months to develop, so viral load or antigen testing are the best tests to diagnose acute HIV.

**Human Immunodeficiency Virus**

Risk factors for HIV include unprotected sexual intercourse (more common with receptive anal sex due to mucosal abrasions causing transmission), injection drug use, maternal infection, needlesticks, and mucosal exposure to body fluids; also at risk are patients who received blood products before 1985. CD4 count measures the degree of immune compromise and predicts the risk of opportunistic infections.

**Symptoms/Exam**

- **1° HIV infection:** May be asymptomatic. Acute retroviral syndrome presents 2 to 6 weeks after initial infection with fever, sore throat, lymphadenopathy, and a truncal maculopapular rash or mucocutaneous ulcerations. Other signs and symptoms are nonspecific and include myalgias, arthralgias, weight loss, diarrhea, headache, aseptic meningitis.
- **Chronic HIV infection:** Constitutional symptoms (fatigue, fevers, night sweats, weight loss), diarrhea, and/or persistent lymphadenopathy. Suspect in patients with thrush, oral hairy leukoplakia, herpes zoster, seborrheic dermatitis, oral aphthous ulcers, or recurrent vaginal candidiasis.

**Differential**

Acute retroviral syndrome resembles infectious mononucleosis (EBV), acute CMV infection, aseptic meningitis, and syphilis.

**Diagnosis**

- **HIV-1/2 immunoassay:** Detect antiviral antibodies and p24 core antigen. Because false-positive results may occur (especially in low-risk populations being screened), confirm by HIV-1/2 antibody differentiation immunoassay. If confirmation testing is  $\ominus$ , ensure that HIV RNA viral load has been sent to detect acute HIV.
- **HIV RNA viral load:** Useful in window period (although this is small with new assays). Has high sensitivity even in patients who have not yet developed antibodies. False-positive results may occur, usually in the form of a low copy number (eg, <10,000 copies/mL); true-positive results in antibody-negative patients with acute infection are usually >100,000 copies/mL.

**Management**

- Current recommendations are to **start HIV treatment in all patients**. Genotype resistance testing is routinely performed in order to select ART regimen.
- Use three drugs—usually two nucleoside analogs (lamivudine, emtricitabine, abacavir, tenofovir or older options, AZT, d4T, ddI) plus one of the following:
  - Non-nucleoside analog (efavirenz or rilpivirine).
  - Protease inhibitor that may be ritonavir “boosted” (darunavir).
  - Integrase inhibitor (raltegravir, dolutegravir).
- **HIV screening:** All adolescents and adults aged 13 to 64 years are recommended to undergo testing at least once. People at high risk for HIV infection (those who have multiple sexual partners or a sexual partner with HIV, those who use injection drugs or exchange money/drugs for sex, and men who have sex with men) should undergo testing at least annually. All pregnant women, even if screened for HIV in previous pregnancy.
- **HIV prophylaxis:**
  - **Preexposure:** For HIV-uninfected individuals who practice high-risk behavior, consider daily tenofovir-emtricitabine. At baseline, patients should be evaluated for HIV infection, HBV infection, other STIs, pregnancy, osteoporosis, and renal disease. During preexposure prophylaxis, patients should undergo regular HIV, STI, and renal function monitoring.

- Postexposure:** After high-risk exposure to HIV, initiate tenofovir-emtricitabine + raltegravir or ritonavir-boosted darunavir as soon as possible (within 72 hours of exposure) and continue for 28 days.

### Complications

The development of effective ART has now made HIV infection a manageable chronic disease. However, affected patients are at risk for multiple complications from the disease or from its management. **Progressive immunosuppression** from HIV can lead to opportunistic infection and malignancy. Prophylactic measures against AIDS-related opportunistic infections are outlined in Table 11.14.

**Adverse effects from specific types of ART** include the following:

- Protease inhibitors: Hyperlipidemia, hyperglycemia, lipodystrophy, osteoporosis. Significant drug-drug interactions (especially with ritonavir or cobicistat).
- Indinavir: Kidney stones.
- Efavirenz: Neuropsychiatric effects.
- Stavudine, didanosine: Pancreatitis, peripheral neuropathy.
- Older nucleoside reverse transcriptase inhibitors (NRTIs): Lactic acidosis, hepatic steatosis.

#### KEY FACT

Don't be lured into selecting acyclovir, ganciclovir, or fluconazole as opportunistic infection prophylaxis in patients with AIDS. We do not routinely use prophylaxis for herpes, cytomegalovirus or *Cryptococcus*!

#### KEY FACT

Do not give the varicella or zoster vaccine to a patient with AIDS. Live vaccines can be given when CD4 >100 cells/mm<sup>3</sup>.

#### KEY FACT

Test for G6PD deficiency before beginning dapsone!

TABLE 11.14. Prophylaxis Against AIDS-Related Opportunistic Infections

PATHOGEN	INDICATIONS FOR PROPHYLAXIS	MEDICATION	COMMENTS
<i>Pneumocystis jiroveci</i> pneumonia (PCP)	CD4 count <200 or a history of oral thrush Prophylaxis may be stopped if CD4 count is >200 for ≥3 months on antiretroviral therapy (ART)	TMP-SMX or dapsone	Single-strength tablets of TMP-SMX are effective and may be less toxic than double-strength tablets
<i>Toxoplasma</i>	CD4 count <100 and <i>Toxoplasma</i> IgG + Prophylaxis may be stopped if CD4 count is >200 for ≥3 months on ART	TMP-SMX or dapsone + pyrimethamine or atovaquone	Covered by most PCP regimens except pentamidine and dapsone monotherapy
<i>Mycobacterium avium complex</i> (MAC)	CD4 count <50 Prophylaxis may be stopped if CD4 count is >100 for ≥3 months on ART	Azithromycin, clarithromycin	Azithromycin can be given once weekly
<i>Mycobacterium tuberculosis</i>	PPD >5 mm; history of a + PPD that was inadequately treated; close contact with a person with active TB <b>Need to rule-out active infection first</b>	INH sensitive: INH × 9 months (include pyridoxine)	For INH-resistant strains, use rifampin or rifabutin if organism is known to be sensitive
<i>Candida</i>	Frequent or severe recurrences or esophageal involvement	Fluconazole or itraconazole	
HSV	Frequent or severe recurrences	Acyclovir, famciclovir, valacyclovir	
<i>Pneumococcus</i>	All patients	Pneumococcal conjugate vaccine (13-valent) then pneumococcal polysaccharide vaccine (23-valent)	Repeat when CD4 count is >200
Influenza	All patients	Influenza vaccine	
HBV	All susceptible patients (ie, hepatitis B core antibody -)	Hepatitis B vaccine (three doses)	
HAV	All susceptible patients	Hepatitis A vaccine (two doses)	

- Abacavir: Skin hypersensitivity or Stevens-Johnson syndrome (more common if HLA-B5701  $\oplus$ ).
- Tenofovir: Renal toxicity, osteopenia/osteoporosis.
- **Immune reconstitution inflammatory syndrome:** This is an exuberant response to infection seen as the immune system recovers in response to ART. This most commonly occurs in response to mycobacterial or disseminated fungal infections. Treatment typically involves continuing ART; corticosteroids may be required to mitigate.

**Noninfectious long-term sequelae of chronic HIV infection:**

- Metabolic disorders: ART tends to  $\uparrow$  total and LDL cholesterol and worsen insulin resistance. Patients also with higher rates of osteopenia/osteoporosis.
- Cardiovascular disease: Higher rates in patients with HIV (possibly related to chronic inflammatory state).
- Neurologic conditions:
  - **Progressive multifocal leukoencephalopathy**—severe neurologic damage from reactivation of JC virus—occurs when CD4  $<50$  cells/mm $^3$  and is diagnosed with MRI demonstrating lesions *without* mass effect or enhancement or with brain biopsy, which is often forgone if CSF demonstrates JC virus DNA. Treatment is ART and  $\uparrow$  CD4 count.
  - **Contrast-enhancing mass lesions in AIDS with CD4  $<100$  cells/mm $^3$ :** Most likely toxoplasmosis or lymphoma. Give empiric treatment with pyrimethamine and sulfadiazine for 2 weeks with repeat imaging if patient is toxoplasma IgG  $\oplus$  (typically reactivation disease from prior exposure). Patients with improvement will be on this antibiotic regimen indefinitely. If no improvement, consider brain biopsy for lymphoma or alternative etiology.

**KEY FACT**

Give steroids in severe *Pneumocystis jiroveci* pneumonia if  $\text{PaO}_2$  is  $<70$  mm Hg at room air or A-a gradient  $>35$ .

**HIV-RELATED OPPORTUNISTIC INFECTION**

Table 11.15 outlines common HIV-related opportunistic infections with treatment guidelines.

**TABLE 11.15. Diagnosis and Treatment of Opportunistic Infections in HIV/AIDS**

DISEASE	CLINICAL PRESENTATION	DIAGNOSIS	1° THERAPY	ALTERNATIVE THERAPY	OTHER
<i>Pneumocystis jiroveci</i> pneumonia	Nonproductive cough, fever, and dyspnea Symptoms often progress over weeks CD4 count is often $<200$	CXR frequently shows bilateral interstitial infiltrates but may be normal Hypoxia with ambulation; $\uparrow$ LDH $\oplus$ $\beta$ -D-glucan Confirm with organism seen on silver-stained sputum sample or bronchoscopy	TMP-SMX If $\text{PaO}_2$ is $<70$ mm Hg at room air or A-a gradient $>35$ , add prednisone	Primaquine + clindamycin or atovaquone	Maintenance therapy should be continued following initial therapy

(continues)

TABLE 11.15. Diagnosis and Treatment of Opportunistic Infections in HIV/AIDS (continued)

DISEASE	CLINICAL PRESENTATION	DIAGNOSIS	1° THERAPY	ALTERNATIVE THERAPY	OTHER
<i>Mycobacterium avium complex</i>	Fever, night sweats, weight loss, fatigue, diarrhea, abdominal pain  Diffuse lymphadenopathy and hepatosplenomegaly may be seen  CD4 count is often <50	Pancytopenia, ↑ alkaline phosphatase. CT of the abdomen may reveal diffuse lymphadenopathy and hepatosplenomegaly  Diagnosed by culture of the organism from a sterile site (blood, lymph node, bone marrow, liver)	Clarithromycin + ethambutol ± rifabutin	Azithromycin + ethambutol ± rifabutin	Maintenance therapy should be continued following initial therapy
<i>Toxoplasma gondii</i> encephalitis	Fever, headache, altered mental status, seizure, and/or focal neurologic changes  Presentation may be very subtle  CD4 count is often <100	Head CT with contrast or MRI with ring-enhancing lesions (often multiple vs singular in CNS lymphoma)  <i>Toxoplasma</i> IgG is + in 95% of patients as it is a reactivation disease  LP may be normal or may show ↑ protein and mononuclear pleocytosis	Pyrimethamine + sulfadiazine	Pyrimethamine + clindamycin or TMP-SMX or pyrimethamine + atovaquone	Leucovorin should be given with pyrimethamine  Steroids should be given only if there is mass effect from intracranial lesions
<i>Cryptococcus neoformans</i>	<b>Meningitis</b>  Often subacute  <b>Pneumonia</b>  CD4 count is often <100	<b>CSF:</b> High opening pressure, ↑ protein, ↓ glucose, and lymphocytosis  In 25% of patients, studies may be normal  ⊕ CrAg; CSF culture ⊕  <b>Blood:</b> ⊕ CrAg; blood cultures ⊕	<b>Induction:</b> Amphotericin B plus flucytosine × 14 days  <b>Consolidation:</b> Fluconazole 400 mg QD × 10 weeks  <b>Maintenance:</b> Fluconazole 200 mg QD indefinitely	Liposomal amphotericin B plus flucytosine or fluconazole plus flucytosine	May require multiple LPs to relieve ↑ ICP  Chronic maintenance therapy may be discontinued after the completion of treatment with a CD4 count of >100 for 6 months on ART
CMV	<b>Retinitis:</b> Painless loss of vision, floaters  <b>Esophagitis:</b> Odynophagia  <b>Colitis:</b> Diarrhea (watery or bloody), abdominal pain  CD4 count is often <50	<b>Ophthalmologic exam:</b> Large plaques with perivascular exudates and hemorrhages  <b>Endoscopy:</b> Hemorrhages, ulcerations; confirm with biopsy	Ganciclovir	Valganciclovir, foscarnet, or cidofovir; consider intraocular ganciclovir implants for severe retinitis	Ganciclovir may cause bone marrow suppression

TABLE 11.15. Diagnosis and Treatment of Opportunistic Infections in HIV/AIDS (continued)

DISEASE	CLINICAL PRESENTATION	DIAGNOSIS	1 <sup>o</sup> THERAPY	ALTERNATIVE THERAPY	OTHER
Cryptosporidiosis	Persistent watery diarrhea Can cause HIV cholangiopathy CD4 count is <100	Must request stool exam for cryptosporidia (modified AFB, trichrome, or DFA); not seen on standard O&P exam	Initiation of ART is the only treatment shown to have benefit		Symptomatic relief with antimotility agents and electrolyte repletion

## Hospital-Acquired Infection

### CATHETER-RELATED INFECTIONS

The most commonly isolated etiologic agents are coagulase-negative staphylococci, *S aureus*, enterococci, and *Candida albicans*.

- **Symptoms/Exam:** Clinical findings are unreliable. Fevers, chills, malaise. Inflammation and purulence around the catheter and bloodstream infection are specific but not sensitive.
- **Diagnosis:**
  - **Blood cultures:** Obtain two sets of cultures, at least one of which is drawn percutaneously.
  - **Catheter cultures:** Should be performed only if CRBSI is suspected. The **semiquantitative (roll plate) method**, in which the catheter tip is rolled across an agar plate, is most commonly used. A **colony count of >15** following overnight incubation suggests catheter-related infection.
- **Management:**
  - Catheter removal is indicated in most cases of **nontunneled CRBSI**. For **tunneled catheters and implantable devices**, consider removal in the setting of severe illness, documented infection with virulent organisms (**especially S aureus, gram-negative rods, or Candida**) or if complications occur.
  - **Initial antibiotic therapy:** Treatment is usually **empiric** with vancomycin (to cover MRSA).
  - **Duration of treatment:** Patients with **uncomplicated bacteremia** should be treated for **10 to 14 days**; those with **complicated infections** (eg, persistently  $\oplus$  blood cultures after catheter removal, endocarditis, septic thrombophlebitis, osteomyelitis) should be treated for **4 to 6 weeks**.

### KEY FACT

TEE is a cost-effective means of ruling out endocarditis in *S aureus* CRBSI. TTE is less sensitive.

### KEY FACT

Candidemia in the setting of a tunneled or nontunneled catheter necessitates catheter removal in all circumstances.

### KEY FACT

*C difficile* is a common cause of otherwise unexplained leukocytosis in hospitalized patients.

### KEY FACT

Diarrhea that arises during antibiotic treatment may also be caused by adverse drug effects.

### CLOSTRIDIUM DIFFICILE COLITIS

Risk factors for *C difficile* colitis include antibiotic use, older age, health care exposure, cancer chemotherapy, bowel surgery, and multiple-organ failure. Diarrhea usually occurs after 1 week of antibiotic therapy but may arise up to 10 weeks later.

#### Symptoms/Exam

Presents with diarrhea (watery much more often than bloody), abdominal pain and distention, fever, and leukocytosis.

## Diagnosis

- **Detection of *C difficile* toxins:** Toxin assays are necessary because 5% of healthy patients and 25% of hospitalized patients have *C difficile* in their stools, but only one-third have toxin-mediated disease.
- **CT scans** often show marked colonic wall thickening and pericolonic inflammatory changes.
- **Endoscopy** shows friable, edematous colonic mucosa with raised yellow plaques (pseudomembranes).

## Management

- Stop antibiotics if possible.
- Avoid antidiarrheal agents and opiates.
- Contact isolation and hand hygiene using soap and water (alcohol-based products do not kill spores).
- For nonsevere disease, give PO or IV metronidazole (PO is preferred). For severe disease (albumin level <3 mg/dL, Cr >1.5 × premorbid level or WBC >15,000 cells/mm<sup>3</sup>), give PO vancomycin (**IV vancomycin is not effective**). For severe with complications (ICU, hypotension, shock, toxic megacolon), use IV metronidazole and PO vancomycin (consider vancomycin PR in ileus).
- Relapse treatment:
  - For first-time recurrences, treat again with the same regimen.
  - For refractory cases, consider tapering or pulse-dosing PO vancomycin treatment.

## Complications

Ileus, toxic megacolon, perforation (all may be accompanied by a ↓ in diarrhea), sepsis.

### INFECTION CONTROL PRECAUTIONS

Isolation and barriers are used to prevent the transmission of microorganisms from patients to other patients, visitors, and health care workers (Table 11.16).

## Tick-Borne Disease

### GENERAL CHARACTERISTICS

Table 11.17 outlines the predominant tick-borne diseases in the United States.

### LYME DISEASE

Prevalence of Lyme disease is based on the distributions of the tick vectors *Ixodes scapularis* (found in the Northeast and upper Midwest) and *Ixodes pacificus* (found in the West). This tick-borne illness is caused by *Borrelia burgdorferi* transmitted primarily by nymphal stages that are active in late spring and summer. Requires tick attachment for >24 hours.

Postexposure prophylaxis with one double dose of doxycycline (200 mg × 1) is recommended in patients where the local tick infection rate is ≥20% and where 1) the tick is estimated to have been attached for ≥36 hours and 2) prophylaxis can be started within 72 hours of tick removal.

### KEY FACT

For mild *C difficile* colitis, give PO or IV metronidazole (PO is preferred). For severe disease, give PO vancomycin.

### KEY FACT

In patients with active zoster, isolation depends on dissemination of disease and immune status. For patients with zoster that extends beyond a single dermatome or is otherwise disseminated, or for immunocompromised patients with local zoster, infection control measures include **both** airborne and contact precautions.

### KEY FACT

Doxycycline is treatment for all tick-borne illnesses except for *Babesia*.

### KEY FACT

The rash of early Lyme disease, erythema migrans, is often missed and resolves within 3 to 4 weeks without treatment.

### KEY FACT

The entity of chronic Lyme disease does not exist. Don't be lured into selecting this wrong answer!

### KEY FACT

*Ixodes scapularis* bites can lead to coinfection with Lyme disease, human granulocytic anaplasmosis, and/or babesiosis. Distinguish these two entities by the presence or absence of leukopenia (HGA) or anemia (babesiosis).

TABLE 11.16. Infection Control Measures

PRECAUTION	PARTICLE TYPE	BARRIERS TO BE USED	SHOULD BE USED FOR (EXAMPLES)
Standard	Transient flora from patients or surfaces	Hand washing; gloves for contact with all body fluids and mucosa Face shields and gowns if splashes of body fluids are possible	Everybody!
Airborne	Droplet nuclei ( $\leq 5 \mu\text{m}$ ) or dust particles that remain suspended for long distances	Negative-pressure rooms and use of surgical masks when transporting patients Health care workers should use fitted N-95 masks Consider face shields	TB, measles, SARS, vesicular rashes (chickenpox, zoster, smallpox)
Droplet	Large droplets that travel $<3$ feet and are generated by coughing, sneezing, talking, suctioning, or bronchoscopy	Private rooms and use of surgical masks when patients are transported Health care workers should use surgical masks	Meningococcal or <i>H influenzae</i> meningitis, influenza, pertussis
Contact	Direct and indirect contact	Private rooms (patients may be grouped together); limit patient transport Dedicated equipment (eg, stethoscopes) Health care workers should use gowns and gloves for all patients	Some fecally transmitted infections (HAV, <i>C difficile</i> ), vesicular rashes (chickenpox, zoster, smallpox), SARS

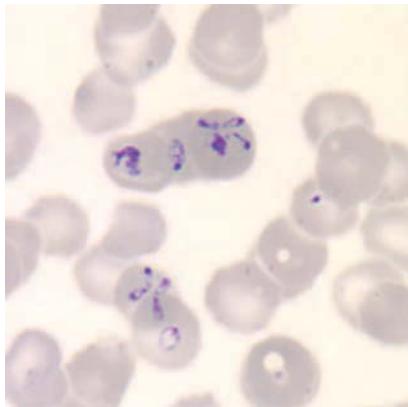
TABLE 11.17. Clinical Presentation and Treatment of Tick-Borne Diseases

DISEASE AND ORGANISM	TICK	LOCATION	CLINICAL FEATURES	TREATMENT	COMMENTS
Babesiosis ( <i>Babesia microti</i> )	<i>Ixodes scapularis</i>	Coastal New England and Long Island	Asymptomatic to fever, hepatosplenomegaly, and jaundice <b>Hemolytic anemia</b> and <b>thrombocytopenia</b> <b><i>Babesia</i> parasites look like <i>Plasmodium falciparum</i></b> signet-ring ("headphone") forms Less common: Intracellular forms may look like classic " <b>Maltese cross</b> " tetrads (see Figure 11.15)	Give clindamycin + quinine or atovaquone + azithromycin	Suspect coinfection with <i>Borrelia burgdorferi</i> (Lyme disease) and/or <i>Anaplasma phagocytophilum</i> (human granulocytotropic anaplasmosis) given similar geographical exposure and fact that can be carried in same tick

(continues)

TABLE 11.17. Clinical Presentation and Treatment of Tick-Borne Diseases (continued)

DISEASE AND ORGANISM	TICK	LOCATION	CLINICAL FEATURES	TREATMENT	COMMENTS
Lyme disease ( <i>Borrelia burgdorferi</i> )	<i>Ixodes scapularis</i> or, less commonly, <i>Ixodes pacificus</i>	Coastal New England, Long Island, mid-Atlantic, upper Midwest. Rarely in Pacific Northwest (pacificus)	Early localized: Presents like viral infection. <b>Erythema migrans</b> may be seen Early disseminated: Neuro or cardiac sequelae (Table 11.18) Late disease: Arthritis and chronic neurologic symptoms	<b>Early disease:</b> Doxycycline > amoxicillin x 14-21 days <b>Late disease:</b> Doxycycline, amoxicillin, or ceftriaxone (preferred for CNS, cardiac disease) for up to 28 days	Coinfection/alternative diagnosis with <b>babesiosis</b> , HGA possible
Human granulocytic anaplasmosis (HGA) ( <i>Anaplasma phagocytophilum</i> )	<i>Ixodes scapularis</i>	Northeast and upper Midwest	Flulike symptoms in the spring and summer, including fever Labs show <b>leukopenia</b> , <b>thrombocytopenia</b> , and ↑ <b>LFTs</b>  <b>Morulae</b> (Latin for mulberries), a cluster of organisms in WBCs, are seen on a peripheral blood <b>buffy-coat smear</b>	Doxycycline	A high fever with <b>leukopenia</b> , <b>thrombocytopenia</b> , and ↑ <b>LFTs</b> may suggest coinfection with HGA in patients with Lyme disease
Human monocytic ehrlichiosis (HME) ( <i>Ehrlichia chaffeensis</i> )	Lone Star tick	Southern states such as Arkansas and Missouri	Flulike symptoms in the spring and summer, including fever Labs reveal <b>leukopenia</b> , <b>thrombocytopenia</b> , and ↑ <b>LFTs</b> Less commonly seen are <b>morulae</b> in peripheral blood <b>buffy-coat smear</b>	Doxycycline	Clinically indistinguishable from anaplasmosis but different geography. Called "spotless" Rocky Mountain spotted fever because of epidemiologic and clinical overlap
Rocky Mountain spotted fever ( <i>Rickettsia rickettsii</i> )	Mainly <i>Dermacentor</i> spp. (dog ticks)	Mid-Atlantic and South Central states	Flulike symptoms, including fever Thrombocytopenia, ↑ <b>LFTs</b> , and <b>hyponatremia</b> common A centripetal rash follows (first affects wrists and ankles; then spreads centrally)	Doxycycline	<b>Not</b> commonly found in the Rocky Mountain states <b>Normal</b> leukocyte count unlike HME



**FIGURE 11.15. Babesiosis on a blood smear.** Note the “Maltese cross” tetrads, which are pathognomonic for *Babesia*. (Source: Centers for Disease Control and Prevention. DPDx. Laboratory diagnosis of babesiosis.)

### KEY FACT

Asymptomatic patients with a tick attached for <24 hours do not need treatment for Lyme disease. Testing of ticks for infectious organisms is not recommended.



**FIGURE 11.16. Erythema migrans seen in Lyme disease.** Note the classic “bull’s eye” lesion, which consists of an outer ring where the spirochetes are found, an inner ring of clearing, and central erythema due to an allergic response at the site of the tick bite. (Source: Centers for Disease Control and Prevention/James Gathany.)

**TABLE 11.18. Lyme Disease Clinical Characteristics and Treatment**

STAGE	INCUBATION	SIGNS/SYMPOMTS	DIAGNOSIS	TREATMENT
<b>Early localized infection</b>	3-30 days	<b>Erythema migrans (EM)</b> (Figure 11.16) Fever, myalgias, and lymphadenopathy	Clinical	Doxycycline
<b>Early disseminated infection</b>	Days to weeks after EM	Skin: EM-like lesions but smaller and often multiple  Neurologic: Cranial neuritis, peripheral neuropathy, and/or aseptic meningitis  Cardiac: AV block, myopericarditis  Nonspecific musculoskeletal: Migratory myalgias, arthralgias, fatigue, malaise	ELISA with confirmatory Western blot	Doxycycline; ceftriaxone in meningitis or myocarditis
<b>Late Lyme disease</b>	Months to years after tick exposure	MSK: Arthritis of large joints  Neurologic: Subacute encephalopathy (memory, sleep, or mood disturbances) and peripheral sensory polyneuropathy	ELISA with confirmatory Western blot  PCR of synovial or CSF fluid	Doxycycline; ceftriaxone in neurologic symptoms

## Travel Medicine

### GENERAL GUIDELINES

Most cases of fever in returned travelers are due to common illnesses such as influenza, viral URI, pneumonia, and UTI. Life-threatening infections that are treatable if diagnosed early include *Falciparum* malaria, typhoid fever, hepatitis, and meningo-coccemia (consider these in all returned travelers with fever).

### Differential

- **Malaria** (see below).
- **Typhoid fever:** Presents with fever, malaise, and abdominal discomfort, often without other GI symptoms. Exam reveals splenomegaly, pulse-temperature dissociation, and evanescent rose spots. Can cause pancytopenia, LFT abnormality. Diagnose by blood, stool, BM cultures growing *Salmonella*; treat with ciprofloxacin or cephalosporin (if quinolone resistance).
- **Hepatitis:** HAV and HEV are transmitted by the fecal-oral route and may have nonspecific prodromes; may be febrile unlike in acute HBV/HCV infection. HBV and HCV are transmitted by sexual contact, shared needles, or blood transfusions. See the Gastroenterology and Hepatology chapter for further details.

- **Dengue:** Mosquito-borne and endemic in equatorial and subtropical areas. Patients have abrupt onset of fever, retro-orbital headache, and myalgias. Thrombocytopenia common and can have transaminitis. Exam shows a blanching rash. Diagnose with serology. Treatment is supportive.
- **Chikungunya:** Mosquito-borne. Fever, polyarthralgia, and polymyalgia. Often persistent musculoskeletal symptoms following infection. Diagnose with serology. Treatment is supportive.
- **Zika virus:** Fever, maculopapular pruritic rash, conjunctivitis, arthralgia. May be associated with congenital microcephaly, stillbirth and Guillain-Barré syndrome. Diagnose with PCR or serology. Treatment is supportive.
- **Leptospirosis:** Associated with recreational water exposure. May be biphasic, with fever, chills, and headache that resolve but are followed 1 to 3 days later by subconjunctival suffusion, a maculopapular rash, hepatosplenomegaly, and aseptic meningitis. Severe cases (Weil syndrome) have jaundice, renal failure, pulmonary hemorrhage, and hypotension. Diagnose with blood culture or anti-leptospiral IgM. Treat with penicillin or doxycycline (watch patients for **Jarisch-Herxheimer reactions**).
- **Amebiasis (*Entamoeba histolytica*):** May cause bloody dysentery or liver abscesses. Diagnose by stool microscopy showing cysts or trophozoites with ingested RBCs. Colonoscopy shows typical flask-shaped ulcers. Serologic tests are sensitive for diagnosing liver abscess. Treat with metronidazole followed by paromomycin to eradicate stool cysts. **Amebic liver abscesses do not require drainage.**
- **Acute HIV and other STIs.**
- **Traveler's diarrhea:** Caused by enterotoxigenic *E coli* (>50%), *Campylobacter*, and—to a lesser extent—*Shigella*, *Salmonella*, and parasites (*Giardia*, *Entamoeba*, *Cryptosporidium*). Onset is usually within 1 week of arrival, with watery diarrhea lasting 2-4 days; patients are **usually afebrile**. Dysentery with bloody diarrhea and fever may be seen with *Shigella* or *Entamoeba*.

### Prevention

- Avoid untreated water, ice cubes, undercooked foods (“boil it, cook it, peel it, or forget it”), stray or wild animals, swimming in freshwater, and insect bites (use insect repellents containing 30% to 35% DEET or permethrin to coat mosquito netting or clothes).
- **Safe sex.**
- **Vaccines for most travelers to developing countries.**
- Malaria prophylaxis if indicated.

### MALARIA

A common cause of fever in the tropics and in returned travelers or immigrants. *Plasmodium falciparum* is the most dangerous species and has a high prevalence in sub-Saharan Africa. Other species include *Plasmodium vivax*, *malariae*, *ovale*, and *knowlesi*.

### Symptoms/Exam

- Incubation period between 1 week and 1 to 2 months.
- Fever, chills, malaise, headache, myalgias, and GI symptoms occur primarily when parasitized RBCs burst open, eventually leading to cyclic symptoms every 48 or 72 hours.
- Signs include hemolytic anemia (indirect hyperbilirubinemia, hemoglobinuria), splenomegaly, thrombocytopenia, transaminitis, renal failure and DIC.
- Mature *P falciparum* parasites (schizonts) bind to vascular endothelium, leading to capillary obstruction and ischemia. If left untreated, this can lead to cerebral malaria (seizures, coma), pulmonary edema, nephritis, and renal failure. *Falciparum* malaria also leads to high rates of parasitized RBCs, causing severe anemia.

### KEY FACT

Think *Giardia* in a patient with a history of fresh water exposure and persistent bloating, diarrhea, and malabsorption. Diagnose with O&P and treat with metronidazole.

### KEY FACT

Treat traveler's diarrhea with hydration, antimotility agents (avoid in dysenteric cases), and antibiotics to shorten disease duration (ciprofloxacin x 1-3 days; azithromycin).

### QUESTION 1

An 85-year-old man recently hospitalized for pneumonia presents with 4 days of loose stools. He is normotensive and tachycardic; laboratory evaluation shows leukocytosis (18,000 cells/mm<sup>3</sup>) and Cr 1.5 mg/dL (baseline, 0.8 mg/dL). *Clostridium difficile* toxin assay returns  $\oplus$ . What is the most appropriate initial step in management?

### QUESTION 2

An 18-year-old man in Connecticut presents to his primary care physician with erythematous “bull’s eye” rash on his leg. Five days ago he went hiking but does not recall a tick bite. What is the next most appropriate step in management?

### QUESTION 3

A 24-year-old woman develops a high fever with night sweats without associated symptoms 4 days after returning from a 2-week vacation to Thailand. Labs show a hematocrit of 28%. She did not take any chemoprophylaxis during travel and does note mosquito bites. What is the most likely diagnosis?

**KEY FACT**

A blood smear showing a banana-shaped gametocyte or RBCs infected with multiple signet-ring forms is diagnostic for *P falciparum* infection, the most severe form of malaria.

**MNEMONIC**

**P** *Vivax* and *P Ovale* may lead to **V**ery **O**ld infections, presenting months or years after individuals leave an endemic area. Be sure to include primaquine at the end of treatment regimens to eradicate the chronic liver stages.

**A****ANSWER 1**

Oral vancomycin for severe *C difficile* given leukocytosis >15,000 cells/mm<sup>3</sup> and Cr >1.5 × baseline. Metronidazole IV could be added if the patient becomes hypotensive, critically ill, or has signs/symptoms of toxic megacolon.

**A****ANSWER 2**

Oral doxycycline for 10 to 14 days for early localized Lyme disease. No need for serologic testing when story is consistent with Lyme exposure (hiking in the Northeast) and skin exam reveals erythema migrans. It is common for patients to not recall a tick bite.

**A****ANSWER 3**

*Plasmodium falciparum* malaria, which can be confirmed with a thick and thin smear. The short incubation period, lack of malaria prophylaxis, and ↓ hematocrit (from lysis of RBCs) make malaria the most likely etiology.

**Diagnosis**

- Order blood smears in all febrile travelers or returned immigrants from endemic areas. Giemsa- or Wright-stained **thick and thin smears** are the best diagnostic tests.
- *P falciparum* must be distinguished from other species (Figure 11.17) because it requires hospital admission. It is also associated with travel to Africa, severe disease, and symptoms that occur within 1 month of travel.
- *P vivax* is as widespread as but generally less virulent than *P falciparum* (Figure 11.18). *P malariae* and *P ovale* are much less common causes of malaria.

**Management**

- *P vivax*, *P ovale*, and *P malariae*: Treat with chloroquine. *P vivax* and *P ovale* should also be treated with primaquine to eradicate chronic liver stages (if patients have normal G6PD levels); these can recur otherwise.
- *P falciparum*:
  - Assume **chloroquine resistance** and treat with quinine plus doxycycline, quinine plus sulfadoxine/pyrimethamine, mefloquine, or atovaquone/proguanil. Artemisinin therapy is drug of choice in severe disease.
  - **Repeat blood smears at 48 hours** to document a >75% ↓ in parasitized RBCs. Exchange transfusion may be used for severe malaria or in the presence of >10% to 15% parasitemia.

**Prevention**

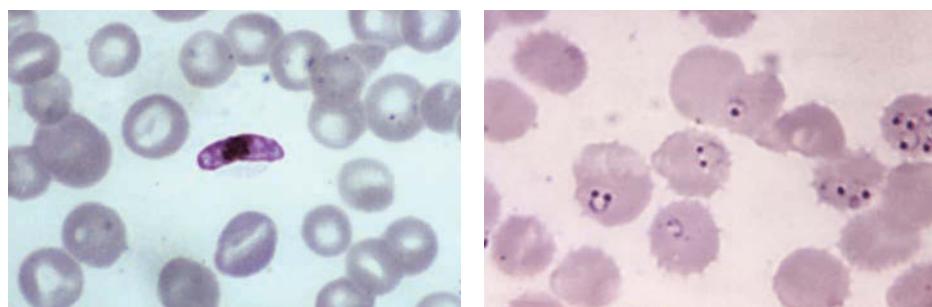
- Avoid mosquito bites (use bed netting, window screens, insecticides, and insect repellents with 30%-35% DEET).
- Chemoprophylaxis: Chloroquine is effective in Central America, Haiti, and parts of the Middle East. For most other areas, the CDC recommends mefloquine or atovaquone/proguanil. For Southeast Asia, use doxycycline or atovaquone/proguanil, as resistance to all other antimalarials is common.

**STRONGYLOIDES**

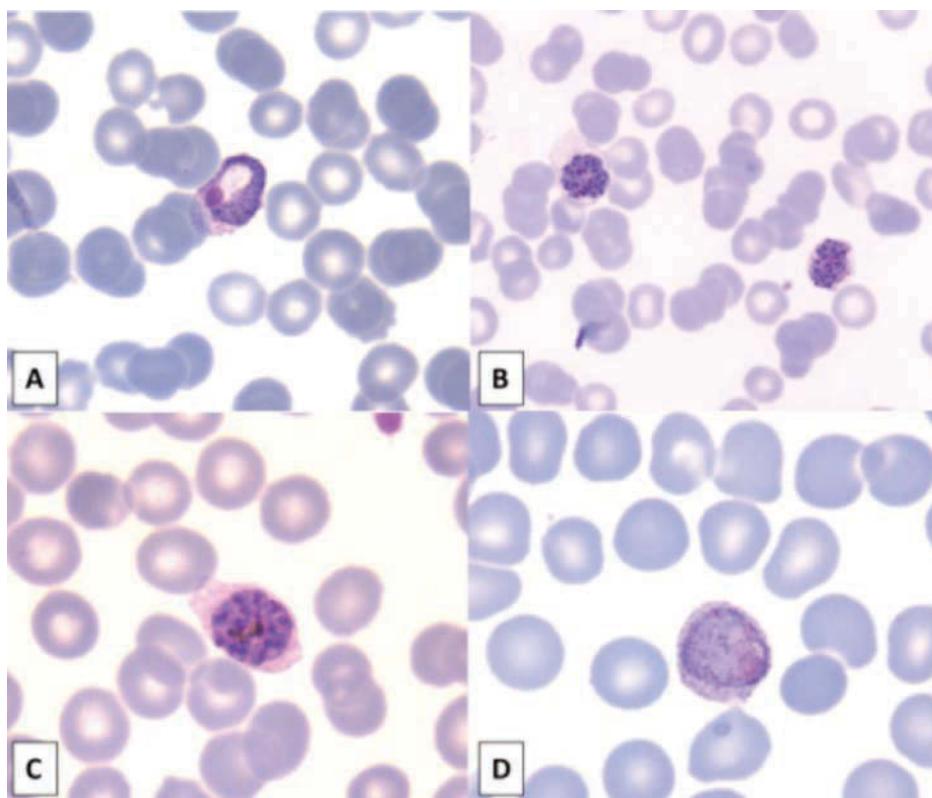
The helminth *Strongyloides stercoralis* is endemic in warm climates such as the southeastern United States, Central America, the Caribbean, Africa, and Asia.

**Symptoms/Exam**

- **Normal hosts:**
  - May be asymptomatic or present with vague epigastric pain, nausea, bloating, diarrhea, or weight loss due to malabsorption.



**FIGURE 11.17. *Falciparum* malaria on a thin blood smear.** (A) “Banana-shaped” gametocyte. (B) Ring-shaped trophozoites. (Image A reproduced with permission from USMLE-Rx.com. Image B source: Dr. Mae Melvin/Centers for Disease Control and Prevention.)



**FIGURE 11.18. Plasmodium vivax in Giemsa-stained thin blood smear with all developmental stages present in peripheral blood.** (A) Growing amoeboid trophozoite in enlarged red blood cell (RBC) with eosinophilic stippling (Schuffner dots). (B) Immature schizonts with clumps of brown pigment almost filling the enlarged RBCs. (C) Mature schizont with merozoites (about 14) and clumped pigment. (D) Macrogametocyte with diffuse brown pigment and eccentric compact chromatin. (Source: Loupa CV, et al. Autochthonous Plasmodium vivax malaria in a Greek schoolgirl of the Attica region. *Malar J*. 2012;11:52.)

- Serpiginous papules or urticaria (“larva currens”) may be seen around the buttocks, thighs, and lower abdomen as larvae migrate from the rectum and externally autoinfect the host.
- Immunocompromised hosts:
  - Hyperinfection or disseminated strongyloidiasis can develop. Worms leave the GI tract and travel to the lungs and elsewhere.
  - Tracking of enteric bacteria (gram-negative rods, enterococci) into bloodstream can lead to bacteremia, meningitis, or pneumonia.

### Diagnosis

- ELISA to detect IgG. Stool studies or duodenal aspirates can be tested for ova and parasites (should check at least two stool samples). In hyperinfection, larvae may be seen in sputum, bronchoalveolar lavage (BAL), CSF, and urine.
- CXR may show transient or diffuse, persistent pulmonary infiltrates (hyperinfection).

### Management

Ivermectin > thiabendazole or albendazole. Discontinue steroids and other immunosuppressive agents.

### KEY FACT

Consider hyperinfection with *S stercoralis* in patients with vague abdominal complaints or fleeting pulmonary infiltrates plus eosinophilia, or in immunosuppressed patients who develop systemic gram-negative or enterococcal infection.

**KEY FACT**

In up to 50% of fevers of unknown origin, the cause is not diagnosed; most of these cases resolve spontaneously. Do not be tempted to treat empirically with steroids or antibiotics without a diagnosis!

**KEY FACT**

Postexposure antibiotic prophylaxis is recommended for anthrax or tularemia exposure; use doxycycline or ciprofloxacin. Postexposure vaccination should be utilized for smallpox exposure.

**KEY FACT**

Most cutaneous cases of anthrax resolve spontaneously without significant sequelae, but 10% to 20% of untreated cutaneous cases may result in death.

**Fever of Unknown Origin**

A fever of unknown origin is a **temperature of  $>38.3^{\circ}\text{C}$  (100.9°F)** that lasts at least **3 weeks** and remains undiagnosed despite evaluation for **more than two outpatient visits** or **three hospital days**. Etiologies vary depending on the patient's age, immune status, and geographic location. In the United States, infection (33%), cancer (25%), and, to a lesser extent, autoimmune diseases (13%) are responsible for most identified cases. Infection is likely if the patient is older or from a developing country, as well as in the setting of nosocomial, neutropenic, or HIV-associated fever.

**Management:** Empiric antibiotics or steroids are discouraged unless patient is severely ill or neutropenic.

**Bioterrorism Agents**

Table 11.19 outlines infectious agents that could potentially be used in acts of bioterrorism.

TABLE 11.19. **Bioterror Agents, Manifestations, and Treatments**

AGENT/DISEASE	CLINICAL FINDINGS	DIAGNOSTIC TESTING	IMMEDIATE INFECTION CONTROL	TREATMENT
Inhalational anthrax	Nonspecific flulike illness followed by abrupt onset of fever, chest pain, and dyspnea; progression to shock and death	Culture or PCR of blood, tissue, or fluid	Standard precautions	Ciprofloxacin or doxycycline + 1-2 other agents
Cutaneous anthrax (most common form of anthrax)	A pruritic maculopapule that ulcerates between days 1 and 3, progressing to vesicles and a painless black eschar with extensive nonpitting edema (Figure 11.19) Can progress to systemic illness if untreated	Gram stain (gram + rods), culture or PCR of vesicle fluid	Standard precautions; contact precautions if uncontained copious drainage	Ciprofloxacin or doxycycline
Pneumonic plague ( <i>Yersinia pestis</i> )	Severe acute respiratory distress with fever and hemoptysis, cyanosis, GI symptoms, and progression to shock and death	Gram-negative rods or coccobacilli with a "safety pin" appearance in sputum, blood, or lymph nodes	Standard and droplet precautions	Gentamicin, streptomycin
Smallpox	Severe flulike prodrome followed by a generalized papular rash that begins on the face and extremities and uniformly progresses to vesicles and pustules	Clinical diagnosis	Standard, droplet, airborne, and contact precautions	Supportive care

(continues)

**TABLE 11.19.** **Bioterror Agents, Manifestations, and Treatments (continued)**

AGENT/DISEASE	CLINICAL FINDINGS	DIAGNOSTIC TESTING	IMMEDIATE INFECTION CONTROL	TREATMENT
Viral hemorrhagic fever (eg, Ebola)	Fever with mucosal bleeding, petechiae, thrombocytopenia, and hypotension	Clinical diagnosis Specific studies depend on timing and include PCR, viral antigens, IgM ab	Use of sharps safety devices and safe work practices, hand hygiene, barrier protection, and appropriate waste handling	Supportive care Novel therapies in development
Tularemia ( <i>Francisella tularensis</i> )	Influenza-like illness with fever, rigors, myalgia, and sore throat followed by substernal discomfort, dry cough, pleuritis, or pneumonitis	Gram-negative coccobacilli in sputum or blood PCR of fluid or tissue	Standard precautions	Gentamicin, streptomycin

(Data from the California State Department of Health, Sacramento, CA, and the Centers for Disease Control and Prevention, Atlanta, GA.)



**FIGURE 11.19.** **Cutaneous anthrax.** Lesion on the forearm caused by *Bacillus anthracis* begins as an ulceration that progressively turns black, hence the term *anthrax*, the Greek name for coal. (Reproduced with permission from USMLE-Rx.com.)

## NOTES

## CHAPTER 12

# Nephrology

Talia R. Kahn, MD, MPH  
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		of the Kidney	
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**KEY FACT**

For the boards, you should be given the plasma osmolality, which should be the same as the calculated osmolality unless there is an osmolar gap due to an unmeasured osm, usually from a toxic alcohol ingestion.

**KEY FACT**

The vast majority of clinically significant hyponatremias will have a  $P_{osm}$  of <280 mOsm/kg. The main reason to check plasma osmolality in the setting of hyponatremia is to exclude pseudohyponatremia (severe hyperlipidemia, severe hyperproteinemia, hyperglycemia, or mannitol infusion).

## Sodium Disorders

### HYPONATREMIA

#### Symptoms/Exam

- Symptoms of hyponatremia are related to the rate and severity of the decline in  $\text{Na}^+$ .
- Can include nausea/vomiting, confusion, lethargy, seizures, and coma. May be asymptomatic.

#### Differential

An algorithm for the evaluation and differential diagnosis of hyponatremia is given in Figure 12.1.

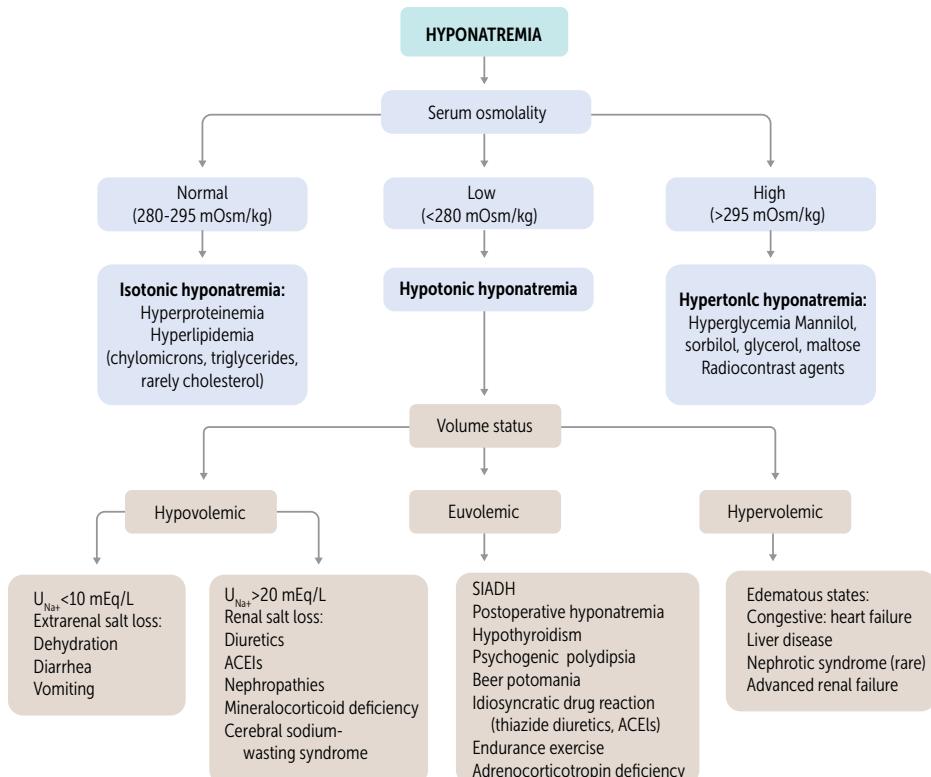
#### Diagnosis

- **Step 1:** In most cases of hyponatremia, the plasma osmolality will be given to you and will be the same as the calculated osmolality, but the following equation to calculate osmolality can be used to confirm:

$$\text{Plasma osmolality } (P_{osm}) = (2 \times \text{Na}^+) + (\text{BUN}/2.8) + (\text{glucose}/18)$$

- **Step 2:** For hypotonic hyponatremias, determine volume status:

- On clinical exam, look for volume overload ( $\uparrow$  JVP, S3 gallop, ascites, edema) or volume depletion (dry mucous membranes, flat JVP).
- A urine  $\text{Na}^+$  ( $U_{\text{Na}^+}$ ) of <10 mEq/L suggests low effective arterial circulation.
- A fractional excretion of  $\text{Na}^+$  ( $Fe_{\text{Na}^+}$ ) of <1% is a more accurate predictor of low volume status than  $U_{\text{Na}^+}$  alone.  $Fe_{\text{Na}^+} = [(U_{\text{Na}^+} \times P_{\text{Cr}})/(P_{\text{Na}^+} \times U_{\text{Cr}})] \times 100$  where  $P_{\text{Cr}}$  = plasma creatinine,  $P_{\text{Na}^+}$  = plasma sodium,  $U_{\text{Na}^+}$  = urine sodium and  $U_{\text{Cr}}$  = urine creatinine.



**FIGURE 12.1. Algorithm for the evaluation of hyponatremia.** (Reproduced with permission from USMLE-Rx.com.)

- Step 3: Measure urine osmolality.  $U_{\text{osm}} > P_{\text{osm}}$  or  $U_{\text{osm}} > 100 \text{ mOsm/kg}$  essentially rules out 1° polydipsia or a reset osmostat and reflects impaired renal water excretion.

### Management

Rate at which  $\text{Na}^+$  should be corrected depends on how quickly it dropped and on the chronicity of the patient's symptoms:

- Acute symptomatic hyponatremia:**  $\text{Na}^+$  should be corrected until symptoms resolve, but do not exceed  $\uparrow 4$  to  $6 \text{ mEq/L}$  in the first 6 hours. If the patient has seizures, altered mental status, or other severe symptoms (eg, severe nausea, vomiting, headache), hypertonic (3%) saline is often required.
- Chronic symptomatic hyponatremia:**  $\text{Na}^+$  should be corrected more slowly ( $4$ - $6 \text{ mEq/L}$  per day).
- Chronic asymptomatic hyponatremia:** No immediate correction is required; fluid management as outlined above often suffices.
- Fluid management depends on volume status** (Figure 12.2). In cases of euvolemic hyponatremia, it can be helpful to calculate the electrolyte free-water clearance (EFWC) to determine whether the patient is excreting free water in the urine, and whether free-water restriction alone will correct the hyponatremia. This calculation, however, is unlikely to be tested on the boards.

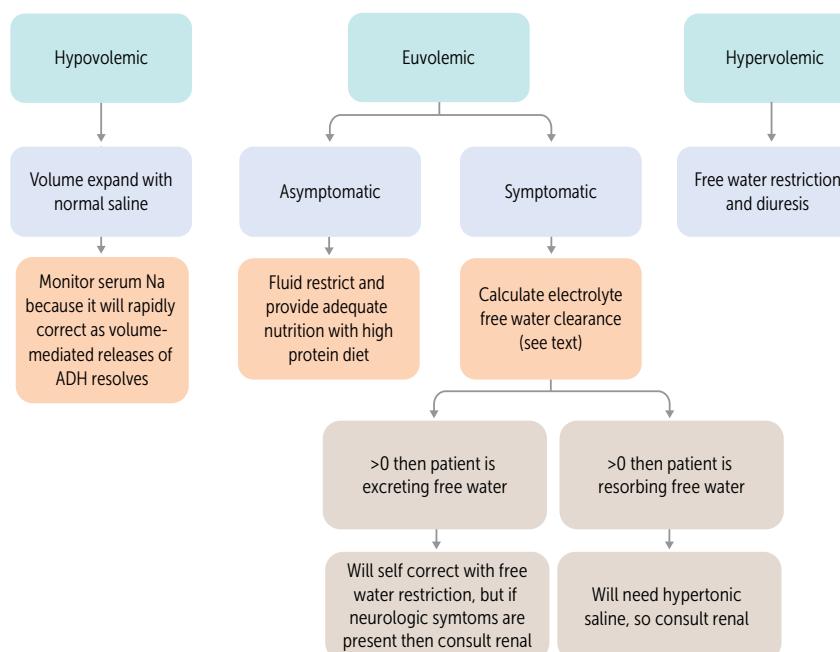
$$\text{EFWC} = \text{Urine volume} \times [(1 - (U_{\text{Na}^+} + U_{\text{K}^+})) / P_{\text{Na}^+}]$$

EFWC tells you how much free water is being excreted in the urine. If the result is  $\ominus$ , this means the kidney is maximally holding on to water and there is a high ADH stimulus. In this scenario, free water restriction alone is unlikely to be sufficient enough to correct the hyponatremia.

### SIADH

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) can be identified with the following three findings:

- ADH is being released ( $\uparrow \text{ADH}$ ): Reflected by  $U_{\text{osm}} > P_{\text{osm}}$ .
- $P_{\text{osm}}$  is low ( $<280 \text{ mOsm/kg}$ ).
- Euvolemia.



**FIGURE 12.2. Algorithm for the treatment of hyponatremia.** (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

### KEY FACT

For euvolemic hyponatremias, urine osmolality can help distinguish SIADH (concentrated urine) from psychogenic polydipsia (dilute urine). SIADH has  $\uparrow$  urine osmolality ( $U_{\text{osm}} > 100 \text{ mOsm/kg}$ ,  $U_{\text{Na}} > 20$ , or  $U_{\text{osm}} > P_{\text{osm}}$ ) as the kidneys are resorbing water. In contrast, 1° polydipsia has  $\downarrow$  urine osmolality ( $U_{\text{osm}} < 50 \text{ mOsm/kg}$ ) because the kidneys function normally and can excrete excess water.

### KEY FACT

In acute symptomatic hyponatremia,  $\text{Na}^+$  should be corrected until symptoms resolve, but do not exceed 4 to 6 mEq/L in the first 6 hours. In chronic symptomatic hyponatremia,  $\text{Na}^+$  should be corrected 6 mEq/L/day.

### KEY FACT

To prevent osmotic demyelination syndrome (central pontine myelinolysis), which is characterized by dysarthria, dysphagia, and paralysis, do not  $\uparrow$  sodium more than 4 to 6 mEq/L over a 24-hour period.



### QUESTION

A 65-year-old healthy woman presents with a community-acquired pneumonia and is found to have euvolemic hyponatremia (serum  $\text{Na}^+ 124 \text{ mEq/L}$ ) with normal mental status. Urine osmolality ( $430 \text{ mOsm/kg H}_2\text{O}$ ) is much higher than serum osmolality ( $260 \text{ mOsm/kg}$ ). What is the most likely etiology of her hyponatremia and what would constitute first-line management?

**KEY FACT**

The “big four” causes of SIADH: Any CNS disorder, any pulmonary disorder, cancer (primarily small cell lung cancer), and medications (especially psychiatric agents, such as SSRIs). Pain and nausea also stimulate secretion of ADH.

**KEY FACT**

If SIADH is treated with normal saline, hyponatremia will worsen.

**KEY FACT**

Tolvaptan, an AVP receptor antagonist, is good for refractory euvolemic hyponatremias.

**KEY FACT**

Hypernatremia is almost always due to free-water deficits (and only rarely due to ↑ in body sodium). Because hypernatremia leads to thirst, most patients who become hypernatremic have restricted access to water (eg, dementia patients who are bedridden or ICU/ventilated patients).

**KEY FACT**

Patients with DI have extremely dilute urine, with no change in urine output even if fluid intake is ↓. If  $U_{osm}$  is low in a hypernatremic patient, consider DI.

**KEY FACT**

Giving DDAVP to an individual with central DI should ↓ urine output and ↑ urine osmolality.

**ANSWER**

First, the patient has low serum osmolality (defined as <280 mOsm/kg), confirming hypotonic hyponatremia. Second, her urine osmolality > serum osmolality, suggesting ADH secretion. Third, she is euvolemic, which means that the ↑ ADH secretion is inappropriate, likely stemming from her pneumonia. Treatment consists of free-water restriction; if the condition is refractory, consider adding oral salt tabs, treating with demeclocycline or, alternatively, tolvaptan—an AVP receptor antagonist.

Remember the “big four” causes of SIADH: any CNS disorder, any pulmonary disorder, medications, and cancer (especially small cell cancer).

- **CNS disorders:**

- Head trauma: SAH, subdural hematoma.
- Infection: Meningitis, encephalitis, brain abscess.
- Other: Tumors, CVA, MS, Guillain-Barré syndrome.

- **Pulmonary disorders:** Small cell lung cancer (ectopic ADH), pneumonia, lung abscess, TB, pneumothorax.

- **Drugs:** Chlorpropamide, TCAs, haloperidol, phenothiazine, SSRIs, amiodarone, carbamazepine, thiazides.

- **Malignant neoplasia.**

- **Other:** Pain, nausea.

**Diagnosis**

**One of exclusion**—other euvolemic causes of hyponatremia, including adrenal insufficiency (AI) and hypothyroidism, must be ruled out.

**Management**

Generally requires **water restriction**. However, in the case of life-threatening hyponatremia, you can use hypertonic saline and a loop diuretic. For chronic SIADH, use tolvaptan, an AVP receptor antagonist. Consult nephrology prior to using hypertonic saline or tolvaptan.

**HYPERNATREMIA****Symptoms/Exam**

- Usually occurs in the setting of ↓ access to water (eg, in dementia or in bedridden patients or ICU/ventilated patients). Hyperosmolality results in cellular dehydration and **CNS symptoms** (lethargy, weakness, irritability, altered mentation, seizures, coma).
- **Volume depletion** presents as dry mucous membranes, hypotension, and low urinary output.

**Differential**

As with the algorithm for hyponatremia, think of the differential for hypernatremia in terms of volume status (Figure 12.3).

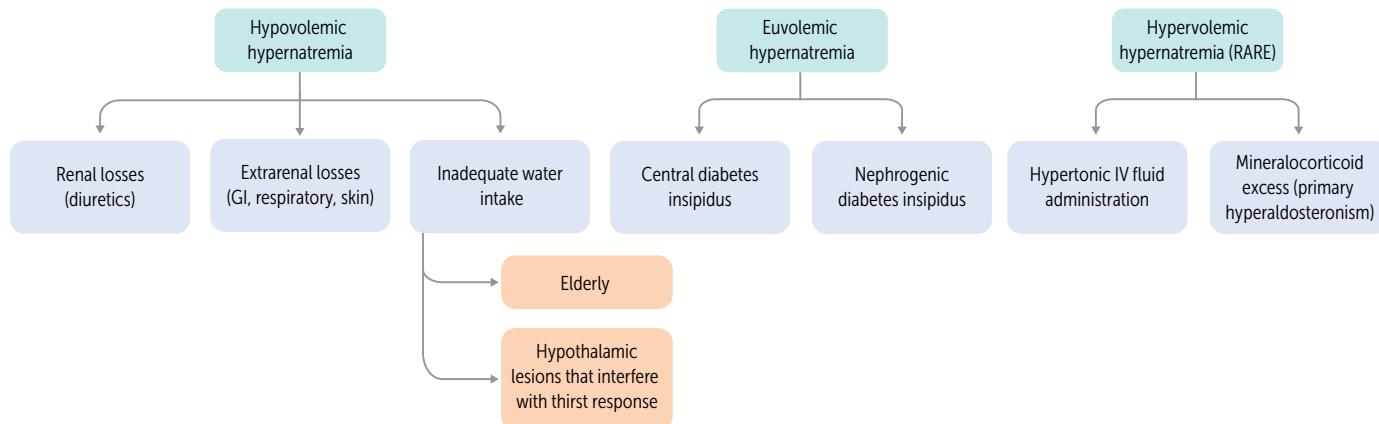
See the Endocrinology chapter for further details on central diabetes insipidus (DI) and nephrogenic DI.

**Diagnosis**

- Based on clinical presentation.
- Measure  $U_{osm}$  (should be high in hypovolemia).
- **Water restriction test:** Urine remains inappropriately dilute in both central and nephrogenic DI.
- **DDAVP challenge test** (desmopressin, a type 2 vasopressin receptor agonist, is comparable to synthetic ADH): Urine becomes concentrated in central DI but not in nephrogenic DI.

**Management**

- Replace free-water deficit using hypertonic fluid (D5W or free-water boluses). The rate of correction should be approximately 0.5 mEq/L/hr or 12 mEq/L in a 24-hour period to avoid cerebral edema.



**FIGURE 12.3. Algorithm for the evaluation of hypernatremia.** (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

- If the patient is hypotensive and volume depleted, isotonic saline should be used initially; hypotonic saline or water (D5W or free-water boluses) can be used once tissue perfusion is adequate.
- Optimal rates of correction for hypernatremia are not clearly defined. Ten to 12 mEq/L per day for chronic hypernatremia (>48 hours) is reasonable, but less important for acute hypernatremia (which can be corrected rapidly).
- In central DI, treat with desmopressin and tell patients to drink until they are no longer thirsty.

**KEY FACT**  
Free water is the initial treatment of choice to correct the water deficit of hypernatremia.

## Potassium Disorders

### HYPERKALEMIA

#### Symptoms/Exam

May be asymptomatic or may present with symptoms ranging from muscle weakness to ventricular fibrillation (VF).

#### Differential

- Extracellular K<sup>+</sup> shift: Metabolic acidosis (often DKA), insulin deficiency.
- Cell breakdown: Rhabdomyolysis, tumor lysis syndrome, hemolysis, pseudohyperkalemia (hemolysis, excessive tourniquet time, severe leukocytosis or thrombocytosis), succinylcholine.
- Inhibition of Na<sup>+</sup>/K<sup>+</sup> ATPase: Digoxin toxicity, β-blockers.
- ↓ aldosterone: Oliguric renal failure, ACEIs or ARBs, Addison disease, K<sup>+</sup>-sparing diuretics, heparin, NSAIDs, ketoconazole, trimethoprim, and pentamidine.

**KEY FACT**  
Medications that can be associated with hyperkalemia include digoxin, β-blockers, K<sup>+</sup>-sparing diuretics, heparin, NSAIDs, ketoconazole, trimethoprim, and pentamidine.

#### Diagnosis

- Review the history, medications, and basic chemistry labs.
- Check an ECG as an indicator of severity.
  - Mild: Normal or peaked T-waves.
  - Moderate: QRS prolongation or flattened P-waves.
  - Severe: Ventricular fibrillation.

**QUESTION**  
A 60-year-old woman with type 2 DM and hypertension (HTN) has recurrent hyperkalemia (K<sup>+</sup> = 6 mEq/L). She is on lisinopril and metformin. The following are her test results: urine K<sup>+</sup> 20 mEq/L, urine osmolality 570 mOsm/kg, serum osmolality 290 mOsm/kg. The transtubular K<sup>+</sup> gradient (TTKG) for this patient is 1.7 (<5 reflects defect in excreting K<sup>+</sup> in urine). What is the most likely cause of her hyperkalemia?

- Order additional labs if indicated:
  - Tumor lysis syndrome: High LDH, uric acid, and phosphorus; low calcium.
  - Hypoaldosteronemic states: Check TTKG (a value <5 is suggestive of **hypoaldosteronemic state**):

$$\text{TTKG} = (\text{U}_{\text{K}^+}/\text{P}_{\text{K}^+}) / (\text{U}_{\text{Osm}}/\text{P}_{\text{Osm}})$$

where  $\text{U}_{\text{K}^+}$  = urine potassium and  $\text{P}_{\text{K}^+}$  = plasma potassium.

### Management

- Hyperkalemia requires emergent treatment if any of the following are present: ECG changes (cardiac conduction abnormalities or arrhythmias), symptoms or signs of hyperkalemia (muscle weakness or paralysis), or  $\text{K}^+$  level  $>6.5 \text{ mEq/L}$ .
- First  $\downarrow$  cardiac excitability: **IV calcium gluconate** and repeat every 5 minutes if ECG changes persist.
- Shift extracellular  $\text{K}^+$  into cells: **IV insulin (given with glucose);  $\beta_2$ -adrenergic agonists (eg, inhaled albuterol)**; and if metabolic acidosis is present,  $\text{NaHCO}_3$  ( $\uparrow$  the systemic pH with  $\text{NaHCO}_3$  leads to  $\text{H}^+$  release from the cells, which leads to  $\text{K}^+$  shift into the cells to maintain electroneutrality).
- Remove excess  $\text{K}^+$  from body: **Diuretics (furosemide), cation exchange resin (Kayexalate), dialysis**.
- Remove medications that cause hyperkalemia.

## HYPOKALEMIA

### Symptoms/Exam

- Symptoms usually occur when  $\text{P}_{\text{K}^+}$  is  $<2.5$  to  $3.0 \text{ mEq/L}$ .
- Presents with muscle cramps, weakness, rhabdomyolysis, ileus, and arrhythmias.

### Differential

- Intracellular  $\text{K}^+$  shift: Respiratory or metabolic alkalemia ( $\text{H}^+$  ions shift out of cells to provide a buffer to the high extracellular pH; to maintain electroneutrality,  $\text{K}^+$  shifts into the cells); insulin release (eg, after being treated for diabetic ketoacidosis with exogenous insulin; a carbohydrate load stimulates endogenous insulin release that can lead to refeeding syndrome).
- GI/skin  $\text{K}^+$  loss: Diarrhea, vomiting, tube drainage, high-volume sweating.
- Renal  $\text{K}^+$  loss: Diuretics, vomiting. Consider Liddle syndrome in the setting of low  $\text{K}^+$ , metabolic alkalosis, and HTN.
- Stimulation of  $\text{Na}^+/\text{K}^+$  ATPase:  $\beta$ -agonists (albuterol).
- $\uparrow$  mineralocorticoid (aldosterone): Hypersecretion of aldosterone from the adrenal glands leads to urinary  $\text{K}^+$  wasting; patients have HTN.  $1^\circ$  hyperaldosteronism (aka Conn syndrome; aldosterone-producing adrenal adenoma, adrenal hyperplasia), licorice, Liddle syndrome (mimics mineralocorticoid excess but presents with a low aldosterone level), Cushing syndrome,  $2^\circ$  hyperaldosteronism (renovascular disease causes  $\uparrow$  renin secretion and thus  $\uparrow$  in aldosterone).
- Other: Hypomagnesemia, periodic paralysis (classically associated with thyrotoxicosis).
- Mutations in tubular transport proteins that mimic diuretics: **Bartter syndrome** (tubular defect at ascending loop; effects are similar to a loop diuretic, high urinary calcium); **Gitelman syndrome** (acts like a thiazide diuretic; low urine calcium). Both syndromes lead to hypokalemia and metabolic alkalosis.



### ANSWER

Type 4 RTA (typically hypoaldosteronism) associated with DM and ACEI use, both of which can impair urinary  $\text{K}^+$  excretion.

## Diagnosis

- Review the history and medications.
- Check plasma renin and aldosterone levels if hyperaldosteronism is suspected.
- If the history suggests hypokalemic periodic paralysis, check TSH.

## Management

Replete with potassium chloride (only after initial repletion of magnesium, if hypomagnesemia is present as well).

### KEY FACT

Low magnesium and low potassium can occur simultaneously in situations such as vomiting, diarrhea, or medications (diuretics or tubular toxins, such as gentamicin, iophosphamide). These patients may be refractory to  $K^+$  replacement unless you first reverse their hypomagnesemia.

## Acid-Base Disorders

Figure 12.4 illustrates an overall approach toward the diagnosis and management of acid-base disorders.

### METABOLIC ACIDOSIS

There are **two main categories** of metabolic acidosis:

- Non-anion gap metabolic acidosis** (aka hyperchloremic metabolic acidosis): Characterized by a  $\downarrow$  serum  $HCO_3^-$ , which leads to an equivalent  $\uparrow$  in  $Cl^-$  to counterbalance this  $HCO_3^-$  drop.
- Anion gap metabolic acidosis:** Occurs with excess production of lactic acid or ketoacids, renal failure, and toxin ingestion.

### Non-Anion Gap Metabolic Acidosis (NAGMA)

NAGMA is also known as hyperchloremic metabolic acidosis, since there is an equivalent  $\uparrow$  in serum  $Cl^-$  to counterbalance the initial  $\downarrow HCO_3^-$ . Most commonly due to:

- GI losses:** Diarrhea leads to  $HCO_3^-$  wasting with subsequent  $Cl^-$  retention.
- Renal tubular acidosis (RTA).**
- Renal failure:** Failure to excrete normally produced acid.
- Normal saline (NaCl) fluid infusion:** Dilution of serum  $HCO_3^-$ , commonly seen in hospitalized patients.

## Diagnosis

The urine anion gap can help differentiate between GI losses and RTA (Figure 12.5):

$$\text{Urine anion gap} = (U_{Na^+} + U_{K^+}) - U_{Cl^-}$$

## Management

There are three types of RTA (Table 12.1 and Figure 12.6):

- Distal (type 1) RTA** presents with NAGMA, hypokalemia, recurrent kidney stones or hypercalciuria, and alkaline urine pH (urine pH is often  $>6$ ). Think Sjögren syndrome and amphotericin. Treat with bicarbonate.
- In proximal type 2 RTA ( $HCO_3^-$  wasting),** urine is acidic when at a steady state but is initially alkaline (high). Think multiple myeloma, acetazolamide, tenofovir, and heavy metal poisoning. Treat associated diseases and institute  $Na^+$  restriction. Any of the proximal type 2 RTA etiologies can lead to Fanconi syndrome, reflecting generalized proximal tubule dysfunction. **Think Fanconi syndrome if you see hypophosphatemia, hyperuricosuria, and glucosuria despite normal serum glucose levels.**
- High  $K^+$**  distinguishes type 4 RTAs from other subtypes. Think 1° AI and drugs (spironolactone, amiloride, triamterene, TMP, pentamidine). Treat with  $Na^+$  restriction and possibly furosemide.

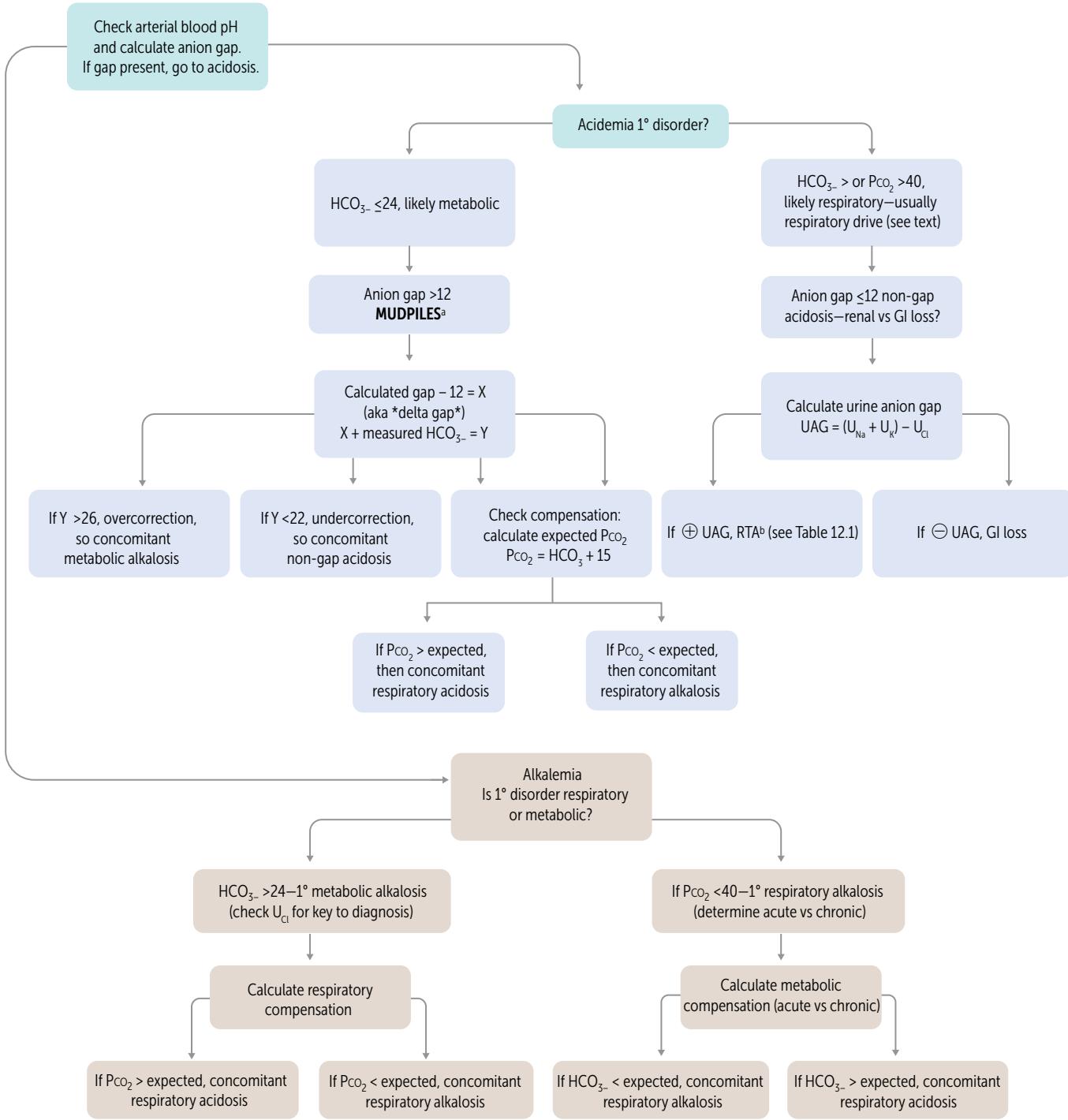
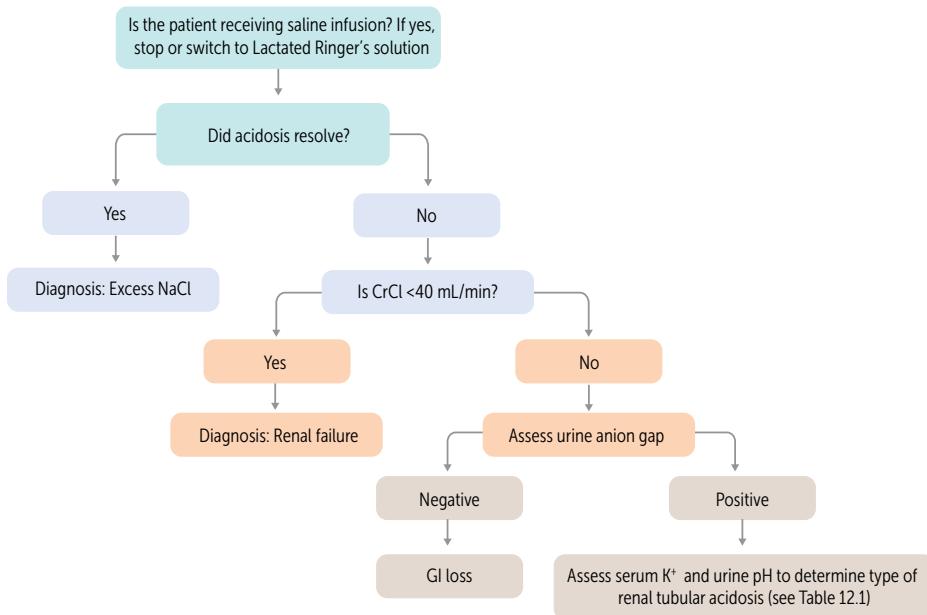


FIGURE 12.4. Approach to acid-base disorders. (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 12.5.** Approach to non-anion gap acidosis. (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

### Anion Gap Metabolic Acidosis (AGMA)

An ↑ anion gap signifies that there is extra acid in the body. This acid may be from the body's own production (lactic acid or ketoacids), an ingestion of an acid (salicylates), a metabolic byproduct of an ingested toxin (methanol, ethylene glycol, paraldehyde) or a drug that causes a lactic/ketoacidosis (salicylates, isoniazid, and iron).

#### Diagnosis

AGMA is quickly identifiable with routine chemistries (for anion gap) and clues from the clinical presentation. If AGMA is present, check:

- Toxicology screen, serum glucose, urine and serum ketones, lactate.
- Serum osmolality to allow for calculation of osmolar gap.

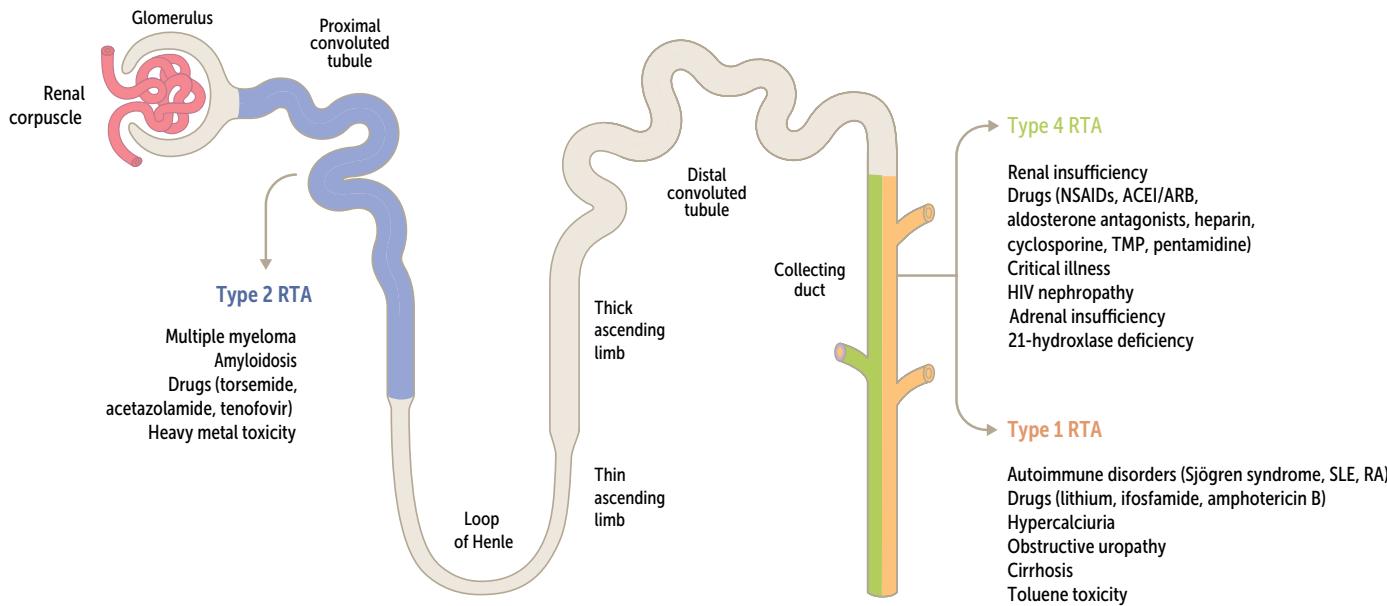
**TABLE 12.1.** Characteristics of Different Types of Renal Tubular Acidosis<sup>a</sup>

	TYPE 1 (DISTAL)	TYPE 2 (PROXIMAL)	TYPE 4
Basic defect	↓ distal acidification	↓ proximal $\text{HCO}_3^-$ reabsorption	Aldosterone deficiency or resistance
Urine pH during acidemia	>5.3	Variable: Usually <5.3, but can be high initially	Usually <5.3
Plasma $\text{HCO}_3^-$ , untreated	Very low (may be <10 mEq/L)	Moderately low (14-20 mEq/L)	Usually >15 mEq/L
Plasma $\text{K}^+$	↓ or normal	↓ or normal	<b>High <math>\text{K}^+</math></b>
Systemic complications	<b>Nephrocalcinosis and renal stones</b>	Rickets or osteomalacia	None

<sup>a</sup>What had been called type 3 RTA is actually a variant of type 1 RTA.

(Adapted with permission from Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 5th ed. New York: McGraw-Hill, 2001: 613.)

MNEMONIC
<b>Differential diagnosis of anion gap metabolic acidosis—MUDPILES</b>
<b>M</b> ethanol ingestion—windshield fluid, paint removers, retinal edema/blindness
<b>U</b> remia
<b>D</b> iabetic ketoacidosis
<b>P</b> araldehyde, propylene glycol ingestion (in benzodiazepine injections)
<b>I</b> soniazid, iron overdose (causes lactic acidosis and ketoacidosis)
<b>L</b> actic acidosis
<b>E</b> thylene glycol poisoning—radiator fluid/antifreeze, calcium oxalate crystals in urine
<b>S</b> alicylate ingestion—ASA toxicity, concomitant respiratory alkalosis



**FIGURE 12.6. Renal tubular acidosis.** (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

### KEY FACT

Both ethylene glycol and methanol have high osmolal gap. When you see severe AG acidosis and an osmolal gap >25 and neurologic symptoms with AKI/flank pain (calcium oxalate stones):

- Think **ethylene glycol** poisoning.
- Do UA to check for calcium oxalate crystals.
- Ask about radiator fluid/antifreeze ingestion.

Acute visual symptoms (retinal toxicity) or severe abdominal pain (pancreatitis):

- Think **methanol** poisoning.
- Do funduscopic exam.
- Ask about windshield fluid or paint remover ingestion.

Treatment of both conditions is fomepizole and hemodialysis.

### Management

Treat underlying disease process. For ethylene glycol and methanol ingestion, treat with fomepizole and hemodialysis.

### METABOLIC ALKALOSIS

Metabolic alkalosis is either due to loss of acid or bicarbonate retention. Urine chloride concentration, urine  $K^+$  concentration, and BP can help distinguish the causes (Figure 12.7).

There are three genetic defects in the kidney that result in metabolic alkalosis and may show up on the boards. Table 12.2 outlines these defects.

### RESPIRATORY ACIDOSIS

#### Symptoms/Exam

Presents with somnolence and altered mental status, depending on the severity of hypcapnia.  $Paco_2$  is inversely related to the respiratory rate ("won't breathe") and alveolar ventilation ("can't breathe").

#### Differential

- Often the answer is opiates; also consider anesthetics and sedatives.
- Consider concomitant respiratory problems: Central sleep apnea; obstructed upper airway, impaired respiratory muscle or chest wall function, impaired alveolar gas exchange.

#### Diagnosis

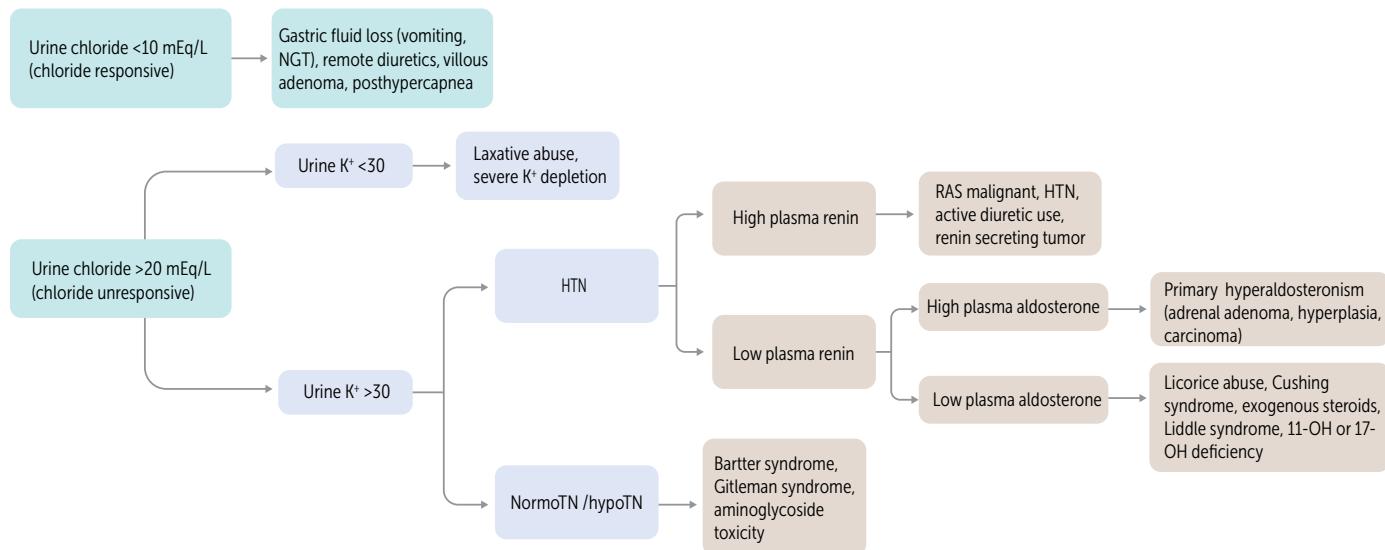
- An arterial pH of  $<7.40$  and an arterial  $Pco_2$  of  $>45$  mm Hg suggest 1° respiratory acidosis.
- Calculate the alveolar-arterial oxygen gradient to distinguish intrinsic pulmonary from extrapulmonary disease (see the "Pulmonary and Critical Care" chapter for details).

### KEY FACT

If urine  $Cl^-$  is low ( $<10$  mEq/L), the most common cause of the metabolic alkalosis is volume loss, and therefore will be volume-responsive.

### KEY FACT

Respiratory acidosis and respiratory alkalosis can **never** be present simultaneously; you can't hypoventilate and hyperventilate at the same time!



**FIGURE 12.7. Approach to metabolic alkalosis.** NGT, nasogastric tube; RAS, renal artery stenosis; NormoTN, normotension; hypoTN, hypotension. (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

- Compensation for acute versus chronic respiratory acidosis:
  - Acute: For every 10 mm Hg ↑ in  $\text{PCO}_2$ , plasma  $\text{HCO}_3^- \uparrow 1 \text{ mEq/L}$ .
  - Chronic (after 3-5 days): For every 10 mm Hg ↑ in  $\text{PCO}_2$ , plasma  $\text{HCO}_3^- \uparrow 3 \text{ mEq/L}$ .

### Management

- Naloxone is often empirically used for patients on opioids with somnolence and presumed respiratory acidosis.
- Noninvasive ventilation (eg, BPAP) to blow off  $\text{CO}_2$ .

## RESPIRATORY ALKALOSIS

### Symptoms/Exam

- Presents with tachypnea, lightheadedness, and altered mental status.
- Can result in hypocalcemia, leading to paresthesias, circumoral numbness, and carpopedal spasms.

**TABLE 12.2. Genetic Defects leading to Metabolic Alkalosis and Hypokalemia**

SYNDROME	CLASSIC DEFECT	PRESENTATION: ALL WITH METABOLIC ALKALOSIS ( $\downarrow \text{K}^+$ , $\uparrow \text{HCO}_3^-$ )
Bartter syndrome	A defect in NaCl reabsorption in the thick ascending loop of Henle ( <b>looks like furosemide</b> )	Renal salt wasting → normal BP Classically presents in childhood; normal serum magnesium
Gitelman syndrome	Defective $\text{Na}^+/\text{Cl}^-$ cotransporter in the distal tubule ( <b>looks like thiazide</b> )	Renal salt wasting → normal BP $\downarrow \downarrow$ magnesium Cramps and tetany (from low potassium and magnesium)
Liddle syndrome	$\uparrow$ epithelial $\text{Na}^+$ channel activity in the collecting tubule	<b>Renal salt retention → HTN</b> $\downarrow$ serum aldosterone levels



### QUESTION 1

A 30-year-old man presents to an acute care clinic with severe arm and leg cramping of 1 year's duration. He also has profound fatigue, chronic polyuria, and  $\uparrow$  nocturia. BP is 105/65 mm Hg and he has tetany. Labs are notable for  $\text{K}^+ 2.9 \text{ mEq/L}$ ,  $\text{Mg}^{2+} 1.5 \text{ mg/dL}$ , metabolic alkalosis, and normal urine chloride concentration. What is the most likely diagnosis?



### QUESTION 2

A woman with type 1 DM has intractable vomiting and is tachypneic, hypovolemic, and hyperglycemic. Serum  $\text{Na}^+ 126 \text{ mEq/L}$ ,  $\text{K}^+ 5.2 \text{ mEq/L}$ ,  $\text{Cl}^- 75 \text{ mEq/L}$ ,  $\text{HCO}_3^- 15 \text{ mEq/L}$ . Room air ABG with pH 7.52,  $\text{PCO}_2$  30 mm Hg,  $\text{PO}_2$  260 mm Hg. What is the underlying acid-base disturbance?

### Differential

- CNS mediated: Salicylate poisoning, pregnancy ( $\uparrow$  progesterone), sepsis, neurologic disease.
- Any lung problem leading to hyperventilation: eg, **pulmonary embolism**, hypoxia, mechanical overventilation.

### Diagnosis

- A pH of  $>7.45$  and a  $\text{PCO}_2$  of  $<35$  mm Hg constitute respiratory alkalosis.
- Compensation for acute versus chronic respiratory alkalosis:
  - Acute: For every 10 mm Hg  $\downarrow$  in  $\text{PCO}_2$ , plasma  $\text{HCO}_3^- \downarrow 2$  mEq/L.
  - Chronic (after 3-5 days): For every 10 mm Hg  $\downarrow$  in  $\text{PCO}_2$ , plasma  $\text{HCO}_3^- \downarrow 4$  mEq/L.

### Management

Correct the underlying disorder.

## MIXED ACID-BASE DISORDERS

See Figure 12.1 for an algorithm of acid-base disorders.

## TRIPLE ACID-BASE DISORDERS—THE “TRIPLE RIPPLE”

Defined as metabolic acidosis + metabolic alkalosis + respiratory acidosis or alkalosis. Classic causes are as follows:

- **Diabetic or alcoholic ketoacidosis:** NAGMA and AGMA (ketacidosis), metabolic alkalosis (vomiting and hypovolemia), compensatory respiratory alkalosis (reflected by low  $\text{PCO}_2$  and tachypnea that is compensating for DKA).
- **Salicylate toxicity:** 1° respiratory alkalosis (early on, salicylates directly stimulate the respiratory center in the brainstem), anion-gap metabolic acidosis (from salicylic acid), and metabolic alkalosis (vomiting). Look for a patient with reason for chronic pain such as osteoarthritis. Treat with urine alkalinization and dialysis.

### KEY FACT

If there is an early respiratory acidosis in the course of an intentional aspirin overdose, the patient may have also ingested another respiratory depressant (eg, an opioid).

A

### ANSWER 1

Gitelman syndrome.

## Nephrolithiasis

Nephrolithiasis is more common in men than in women. Eighty percent of stones are calcium oxalate.

### Symptoms/Exam

- Presents with flank pain  $\pm$  radiation to the groin.
- Urinary frequency, urgency, and dysuria.
- Exam reveals microscopic or gross hematuria.

### Diagnosis

- Collect and analyze the stone for crystalline properties: uric acid (pleiomorphic, yellow or reddish-brown), cystine (hexagonal shape), calcium phosphate (type 1 distal RTA, hyperparathyroidism), magnesium ammonium phosphate (struvite stones; look like coffin lids), calcium oxalate (less helpful since this is seen in multiple disorders).

A

### ANSWER 2

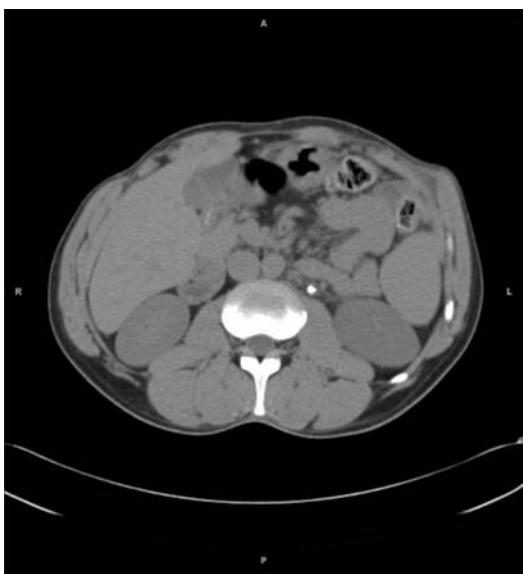
Mixed AGMA (from DKA), metabolic alkalosis (vomiting, hypovolemia), and compensatory respiratory alkalosis. Her  $\text{HCO}_3^-$  is much higher than expected for her degree of gap (indicating additional metabolic alkalosis from vomiting).

■ **Labs:**

- **UA:** To look for blood, assess urine pH (pH <5.5 is compatible with uric acid stone, since an acidic urine favors conversion of soluble urate salt to insoluble uric acid), and rule out UTI.
- **Plasma Ca<sup>+</sup>, phosphorus, uric acid, and electrolytes:** To assess renal function, acidosis, and hypokalemia. This helps in identifying conditions such as 1° hyperparathyroidism, hyperuricemia, and type 1 distal RTA.
- **PTH level:** 1° hyperparathyroidism can ↑ urinary Ca<sup>+</sup> excretion.
- **Imaging:**
- **Noncontrast helical CT** (Figure 12.8) or **ultrasound:** Both acceptable initial imaging studies, although ultrasound should be first-line in pregnant women and in other patients who should avoid radiation. Ultrasound may miss smaller stones and ureteral stones; CT is more sensitive than ultrasound in detecting stones but is associated with radiation exposure.
- Plain x-rays capture calcium-containing stones but miss uric acid stones.

### Management

- **Asymptomatic stones:** ↑ daily fluid intake.
- **Symptomatic stones:**
  - Most ≤5 mm will pass spontaneously with ↑ daily fluid intake. Consider calcium channel blockers (nifedipine) and α-blockers (tamsulosin) to encourage passage.
  - Stones >10 mm require invasive measures: Extracorporeal shock-wave lithotripsy or percutaneous nephrolithotomy is indicated for stone removal.
- Specific treatment guidelines are outlined in Table 12.3. Clues from the history are as follows:
  - **Recurrent UTIs:** Struvite (magnesium ammonium phosphate) stones.
  - **Prior malignancies:** Uric acid stones (tumor lysis).
  - **Malabsorption (eg, IBD, CF, short gut syndrome):** Oxalate stones.



**FIGURE 12.8. Ureteral stone.** CT scan showing a calcified stone in the left ureteropelvic junction and minimal periureteral fat stranding in a 38-year-old man with severe left flank pain radiating to the groin. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

A 24-hour urine collection (volume, pH, sodium, calcium, oxalate, phosphorus, citrate, uric acid, cystine, creatinine) is warranted for recurrent nephrolithiasis.

### KEY FACT

Struvite stones are caused by urea-producing bacteria (*Proteus*, *Klebsiella*, *Pseudomonas*), which leads to ↑ NH<sub>3</sub> production and a ↑ urinary pH to lower the solubility of phosphate. Struvite stones often form in the setting of foreign bodies and neurogenic bladder and have magnesium ammonium phosphate crystals that are shaped like coffin lids.

### KEY FACT

Calcium oxalate stones are commonly seen in hypercalciuria and hyperoxaluria (from GI disorders such as IBD because of fat malabsorption as fat binds to calcium leaving oxalate free to be deposited in the kidney).

### KEY FACT

All staghorn calculi need surgical removal.



### QUESTION 1

A 60-year-old woman presents to the ED 1 week after a fall in which she injured her back. In addition to being in a lot of pain, she has ringing in her ears and double vision. On exam, she is lethargic and is breathing rapidly and deeply. What is the most likely diagnosis?



### QUESTION 2

A 30-year-old man with a history of ulcerative colitis involving the small intestine presents with sudden onset of colicky flank pain that radiates to the groin with 10 to 30 RBCs/hpf on UA, suggesting kidney stone. What do you recommend to prevent recurrent stones?

TABLE 12.3. Types, Mechanisms, and Treatment of Kidney Stones

TYPE	MECHANISMS AND DISEASE ASSOCIATIONS	TREATMENT <sup>a</sup>	NOTES
Calcium oxalate	<b>Hypercalciuria:</b> Hyperparathyroidism, malignancy, granulomatous diseases <b>Hyperoxaluria:</b> Short gut syndrome, IBD <b>Hypocitraturia:</b> Metabolic acidosis from RTA, CKD, chronic diarrhea	<b>Ca<sup>++</sup> restriction is not helpful</b> (may lead to hyperoxaluria) Thiazides, potassium citrate <b>Low Na<sup>+</sup> diet</b>	Citrate is the 1° stone formation inhibitor
Uric acid	<b>Acidic urine (pH &lt;5.5):</b> A diet high in animal protein <b>Hyperuricosuria:</b> Gout, tumor lysis syndrome	<b>Allopurinol, potassium citrate to alkalinize urine</b>	
Cystine	<b>Hypercystinuria:</b> Cystinuria	Tiopronin (Thiola)	
Struvite	<b>Alkaline urine (pH &gt;6.5):</b> UTI with urease-splitting organisms (eg, <i>Proteus mirabilis</i> )	Treat the underlying infection	Recurrent UTIs may be due to a residual nidus of infection from the stone
Medication-related	Triamterene, acyclovir, indinavir, methotrexate		

<sup>a</sup>In addition to large-volume water intake.

## Acute Kidney Injury

There is no consensus definition for acute kidney injury (AKI). However, the Kidney Disease Improving Global Outcomes definition includes the following:

- ↑ in serum creatinine by ≥0.3 mg/dL within 48 hours; or
- ↑ in serum creatinine by ≥1.5 times baseline, which is known or presumed to have occurred within the prior 8 days; or
- Urine volume <0.5 mL/kg/hr for 6 hours.

A

### ANSWER 1

Overdose from salicylate, an ingredient in aspirin and other over-the-counter and prescription analgesics. Salicylate directly stimulates the respiratory center, leading to early ↓ in CO<sub>2</sub> and respiratory alkalosis, and cause a buildup of lactic acid and ketoacids, manifesting as an AGMA. The net effect is that most patients have either a 1° respiratory alkalosis or a mixed 1° respiratory alkalosis-1° AGMA.

A

### ANSWER 2

↑ fluid intake and a low-oxalate diet.

### Diagnosis

Start by reviewing the history and medications. Causes can be divided into prerenal, intrarenal and postrenal etiologies (Figure 12.9 and Table 12.4).

See Table 12.5 for a comparison of prerenal azotemia and ATN.

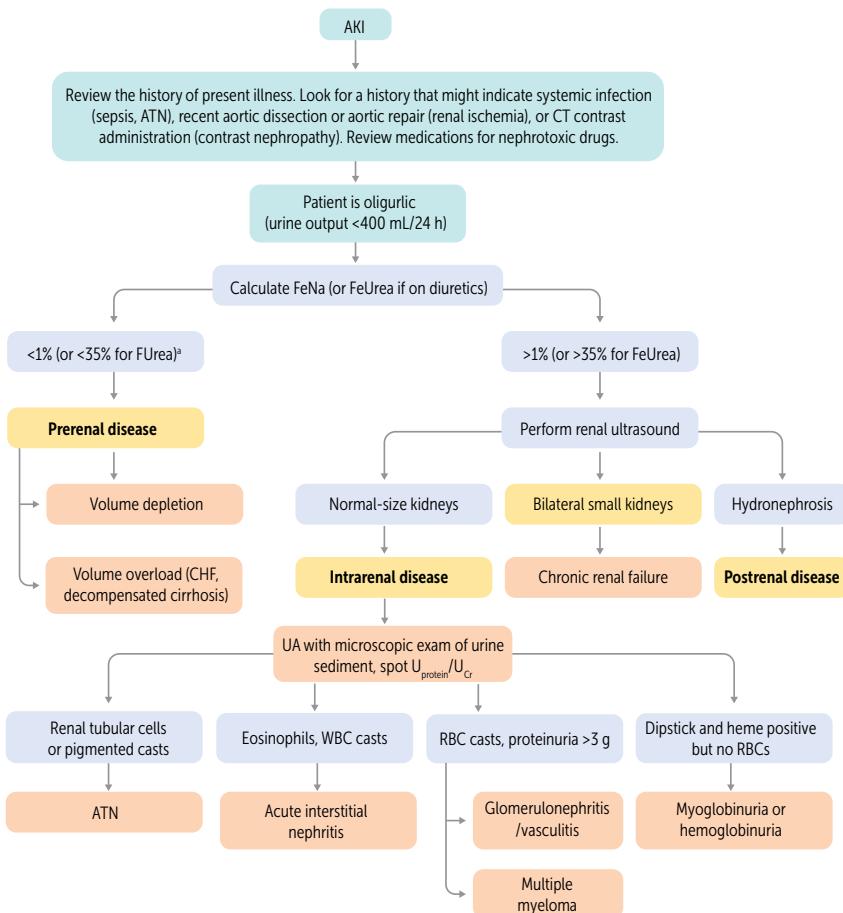
### Management

Treat the underlying cause or remove the offending agent:

- Volume depletion: Administer saline.
- Volume overload: Administer diuretics; perform afterload reduction if patient is in heart failure.
- ATN: Eliminate nephrotoxins; treat underlying cause.
- AIN: Eliminate offending drug; prescribe glucocorticoids.
- Support renal function through dialysis if necessary (see the mnemonic AEIOU). There is no role for “renal-dose” dopamine.

### Contrast Nephropathy

- Creatinine begins to rise within 24 to 48 hours postcontrast exposure, but may peak several days later.
- Risk factors: Underlying kidney disease, diabetes, heavy contrast volume, multiple myeloma, arterial contrast (as opposed to venous administration), volume depletion, sepsis.



**FIGURE 12.9.** Approach to AKI in oliguric patients. (Reproduced with permission from USMLE-Rx.com; illustration by Dr. Talia R. Kahn.)

**TABLE 12.4. Etiologies of AKI**

#### PRERENAL

- Volume depletion
- Circulatory shock
- Severe CHF
- Severe cirrhosis (hepatorenal syndrome)

#### INTRINSIC RENAL

##### Tubular injury—acute tubular necrosis (ATN):

- Ischemia
- Infection
- Renal artery occlusion
- Contrast dye
- Myeloma
- Heme pigment (rhabdomyolysis, hemolysis)
- Aminoglycosides
- Amphotericin B
- Methotrexate
- Hyperuricemia



#### KEY FACT

Checking urine sodium or calculating  $\text{Fe}_{\text{Na}}$  is reliable only when the patient is oliguric, does not have CKD and is not taking diuretics.



#### KEY FACT

Casts come from tubules. Clues to UA:

- Muddy brown (pigmented granular) casts or renal tubular epithelial cells: ATN (Figure 12.10).
- Red cell casts or dysmorphic RBCs: Glomerulonephritis.
- WBC casts: AIN, pyelonephritis.
- Waxy casts: Chronic kidney disease.
- Fatty casts: Free fat can coalesce into casts that look like "Maltese crosses" under polarized light, indicative of high urinary protein (nephrotic syndrome).
- Hyaline casts: Nonspecific and not indicative of disease. Can be seen with concentrated or low volume of urine (eg, dehydration, exercise).

(continues)

**KEY FACT**

NSAID-induced nephropathy may include the following:

- AKI from afferent arteriolar vasoconstriction in the setting of prerenal azotemia leading to ATN.
- AIN and minimal change disease.
- Analgesic nephropathy (papillary necrosis—chronic interstitial nephritis).

**MNEMONIC****Indications for emergent dialysis—****AEIOU**

**A**cidosis

**E**lectrolytes—hyperkalemia

**I**ngestions—severe acidemia (eg, lithium toxicity)

**O**verload—pulmonary edema

**U**remia

**KEY FACT**

Suspect contrast nephropathy in patients who have rising creatinine within 24 to 48 hours after contrast load. IV fluids may reduce the likelihood of contrast nephropathy in at-risk individuals, but care for established nephropathy is supportive.

**TABLE 12.4. Etiologies of AKI (continued)****INTRINSIC RENAL (continued)****Interstitial—acute interstitial nephritis (AIN):**

- **Allergic and drug reactions** (antibiotics, NSAIDs, COX-2 inhibitors, allopurinol, interferon, TMP, thiazides, phenytoin)
- **Infections** (HIV, toxoplasmosis, EBV, CMV, strep, legionella, candidiasis, histoplasmosis)
- **Autoimmune** (sarcoidosis, SLE)

**Glomerular—glomerulonephritis** (see separate section)**Crystals**

- Tumor lysis syndrome
- Cholesterol emboli syndrome (renal biopsy with cholesterol “washed out” in an atheroembolus, causing biconvex, needle-shaped clefts)
- Medication crystals (eg, acyclovir, ethylene glycol)

**POSTRENAL****Urinary tract obstruction**

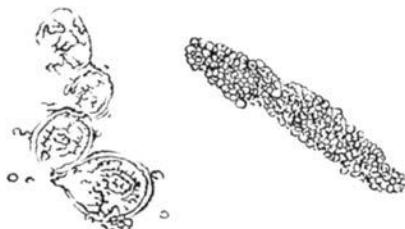
- Normal saline (1.0 mL/kg/hr) 6 to 12 hours before and after contrast administration (to prevent volume depletion) and holding NSAIDs may help ↓ the risk by reducing renal vasoconstriction. Consider using lower doses of contrast and spacing out studies requiring contrast (by >48–72 hours).
- $\text{Fe}_{\text{Na}}$  is low due to intrarenal vasoconstriction.

**Rhabdomyolysis**

- Rhabdomyolysis is a syndrome characterized by muscle necrosis that leads to myalgias, myoglobinuria (red-brown urine), and elevated CK levels.
- **Labs:** A serum CK >5000 U/L is the threshold required to develop AKI; **urine dipstick is positive for blood but no RBCs are seen on microscopy**; may also see hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia.
- **Risk factors:** Muscle trauma, ischemia or inflammation; toxins such as alcohol or cocaine; medications such as statins and reverse transcriptase inhibitors; prolonged immobilization; genetic disorders including McArdle disease.
- **Management:** Early aggressive volume repletion, urine alkalinization with sodium bicarbonate may help; dialysis may be necessary.

**TABLE 12.5. Prerenal Azotemia vs ATN**

	PRERENAL AZOTEMIA	ATN
$\text{Fe}_{\text{Na}}$	<1%	>1%
BUN/Cr	>20:1	10:1
$\text{U}_{\text{osm}}$	High	Similar to $\text{P}_{\text{osm}}$
Urine sediment	Bland	Muddy brown casts (see Figure 12.10)
Response to fluids	Rapidly improves	Poor; may take weeks to months for recovery, depending on the length and severity of the initial ischemic episode. Often requires dialysis in the interim



**FIGURE 12.10. Acute tubular necrosis.** Drawing of renal epithelial cells (left) and muddy brown cast (right). (Used with permission from Dr. Rudolph Rodriguez.)

## Urinary Tract Obstruction

Obstruction that leads to hydronephrosis of >2 weeks' duration is likely to cause permanent damage. A decline in glomerular filtration rate (GFR) and tubular function (leading to impaired ability to concentrate and dilute urine, as well as to transport solutes) can occur within hours after an acute obstruction, and may even persist for weeks after resolution of obstruction. More chronic obstruction can lead to tubular atrophy and nephron loss.

### Differential

- Upper tract obstruction: Nephrolithiasis, external compression from lymphadenopathy, GI/GU cancers and lymphoma, retroperitoneal fibrosis (radiation, drugs such as bromocriptine, malignancies such as lymphomas and sarcomas, IgG4 disease, infections such as TB and histoplasmosis, surgery).
- Lower tract obstruction: Benign prostate hyperplasia, pelvic cancers, neurogenic bladder.

### Diagnosis

- Labs show ↑ K<sup>+</sup>, acidosis, and ↑ creatinine.
- Fe<sub>Na</sub> is low (<1%) early after obstruction and higher later in the disease course.
- Foley catheter reveals a large postvoid residual if you are dealing with a bladder obstruction.
- Ultrasonography reveals hydronephrosis except in early obstruction or in cases of retroperitoneal fibrosis (Figure 12.11).**

### Management

- Relieve the obstruction via Foley catheter, nephrostomy tube, or ureteral stent.
- Volume and electrolyte repletion during postobstructive diuresis.

## Hepatorenal Syndrome (HRS)

Seen in severe liver disease with portal HTN. Intense renal salt and water retention leads to renal vasoconstriction and oliguric or anuric renal failure. See also the Gastroenterology and Hepatology chapter.



### KEY FACT

Renal failure in severe liver disease is not always HRS. HRS is a diagnosis of exclusion (normal renal ultrasound, absence of hematuria, no nephrotoxic drugs, no sepsis or signs of infection).



**FIGURE 12.11. Hydronephrosis.** Ultrasound examination of urinary tract revealed that the right kidney was hydronephrotic with dilated renal pelvis. (Source: Vaidyanathan S, et al. Pyonephrosis and urosepsis in a 41-year-old patient with spina bifida: Case report of a preventable death. *Patient Saf Surg*. 2012;6:10.)



### QUESTION

A 70-year-old man with type 2 DM was found down and CT with contrast showed ischemic bowel. Two days later, serum Cr rose from 1.2 mg/dL to 2.7 mg/dL with muddy brown casts on UA. What is the most likely etiology of his AKI?

### Diagnosis

- Type I: rapid, doubling of serum creatinine to  $>2.5$  or  $>50\%$  reduction in GFR in less than 2 weeks (evolves over days-weeks).
- Type II: slower decline in renal function (weeks-months), often seen with refractory ascites.
- Look for advanced hepatic failure and portal HTN.
- Additional features include the following:
  - **No other obvious cause of renal failure;** normal renal ultrasound; absence of hematuria ( $<50$  cells/hpf) and proteinuria ( $<500$  mg/24 hr); no nephrotoxic drugs; no sepsis or signs of infection.
  - **No improvement in renal function after volume expansion with albumin (1 g/kg) and diuretic withdrawal.**
  - A salt-avid state may be seen with very low urine  $\text{Na}^+$ .

### KEY FACT

HRS is a marker of severe liver disease that can be reversed only by liver transplantation.

### Management

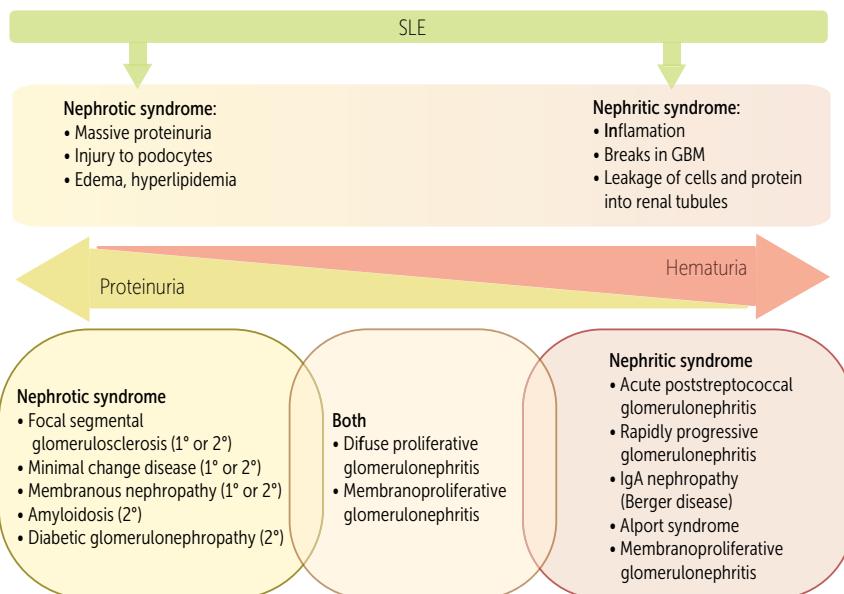
- **Albumin infusion.**
- **Splanchnic vasoconstrictors:** Vasopressin analogs (terlipressin, ornipressin), midodrine, octreotide.
- Transjugular intrahepatic portosystemic shunt (TIPS).
- Renal replacement therapy as a bridge to liver transplantation. Liver transplantation is the treatment of choice.

### Cholesterol Emboli Syndrome

See the Rheumatology chapter.

## Glomerular Diseases

The glomerular diseases are on a spectrum with nephrotic syndromes resulting primarily from injury to the podocytes and leakage of protein versus the nephritic syndromes resulting from breaks in the basement membrane and leakage of cells and protein (Figure 12.12).



A

### ANSWER

ATN from a combination of sepsis/hypotension and contrast-induced nephropathy.

**FIGURE 12.12. The spectrum of glomerular disease.** GBM, glomerular basement membrane. (Reproduced with permission from USMLE-Rx.com; modified from Turner NN, et al, eds. *Oxford Textbook of Clinical Nephrology*, 4th ed. United Kingdom: Oxford University Press; 2015, Fig. 45.2.)

## NEPHRITIC SYNDROME (GLOMERULONEPHRITIDES)

### Symptoms/Exam

Presents with HTN, edema, ± hematuria.

### Differential

See Figure 12.13 and Table 12.6.

Both IgA nephropathy and poststreptococcal glomerulonephritis frequently occur after a URTI, but gross hematuria of IgA nephropathy occurs “syn-pharyngitic” (at the same time as URI symptoms), whereas poststreptococcal glomerulonephritis patients develop dark urine 2 to 3 weeks after symptom onset.

### Diagnosis

- Urine microscopy shows **dysmorphic RBCs** and **RBC casts** (Figure 12.14).
- Renal biopsy is definitive.

### Management

See Table 12.7.

The four pulmonary-renal syndromes are granulomatosis with polyangiitis (used to be known as Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), microscopic polyangiitis, and anti-GBM disease (Goodpasture syndrome). They are all treated with steroids and cyclophosphamide. To differentiate them, remember:

- **Granulomatosis with polyangiitis:** Otitis, sinusitis, saddle nose, pulmonary infiltrates, granulomas on biopsy (hence the name),  $\oplus$  c-ANCA,  $\oplus$  antiproteinase 3 (anti-PR3).
- **Eosinophilic granulomatosis with polyangiitis:** Asthma, eosinophilia.
- **Microscopic polyangiitis:** No granulomas on biopsy,  $\oplus$  p-ANCA, less upper respiratory tract involvement.
- **Anti-GBM disease:** Pulmonary hemorrhage,  $\oplus$  anti–basement membrane antibodies.

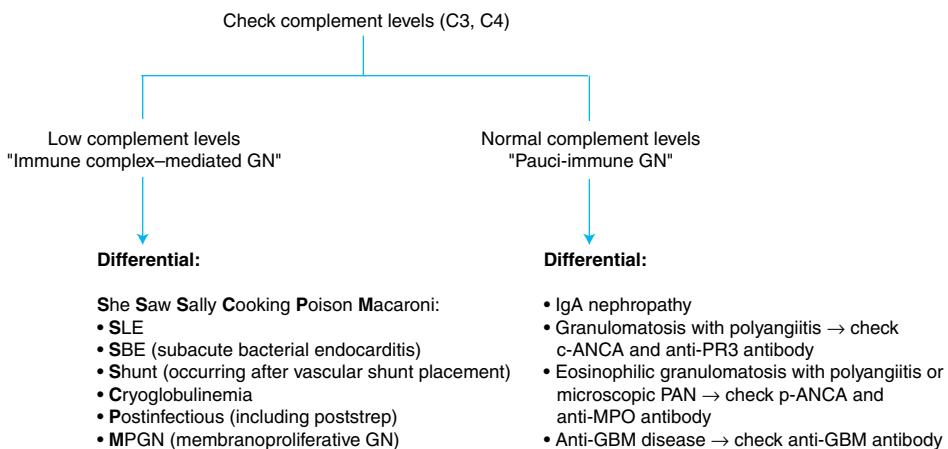


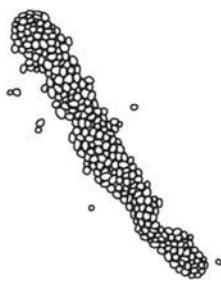
FIGURE 12.13. Differential diagnosis of glomerulonephritis.



### MNEMONIC

**The causes of glomerulonephritis can be broken down by complement levels. The main causes of low-complement glomerulonephritis are “C LESS”:**

- Cryoglobulins/hepatitis C (MPGN)**
- Lupus**
- Endocarditis**
- Streptococcal/infectious.** All other causes of glomerulonephritis have normal complement levels



**FIGURE 12.14. Red blood cell casts in urine.** (Used with permission from Dr. Rudolph Rodriguez.)

TABLE 12.6. Subtypes of Glomerulonephritis

SUBTYPE	RELEVANT SEROLOGIES	DISEASES
Immune complex	↓ C3, C4	Membranoproliferative glomerulonephritis, cryoglobulinemia, postinfectious glomerulonephritis, SLE, subacute bacterial endocarditis, shunt nephritis IgA nephropathy, usually with normal C3/C4
Pauci-immune	ANCA (anti-MPO, anti-PR3) Normal complements	Granulomatosis with polyangiitis (formerly Wegener granulomatosis), eosinophilic granulomatosis (Churg-Strauss syndrome), microscopic polyangiitis
Anti-GBM	Anti-GBM antibodies Normal complements	Anti-GBM disease, Goodpasture syndrome

TABLE 12.7. The Glomerulonephritides

DISEASE	PRESENTATION	DIAGNOSIS	TREATMENT
<b>IMMUNE COMPLEX GLOMERULONEPHRITIS</b>			
SLE	Any of the criteria for SLE (see Rheumatology chapter)  Lupus nephritis can be the presenting feature	Anti-dsDNA, anti-Sm antibodies $\oplus$	<b>Biopsy is essential for staging</b>  Steroids and cyclophosphamide or mycophenolate depending on severity  End-stage renal disease (ESRD) occurs in 8%-15% of cases
Postinfectious	<b>Occurs 2-3 weeks after pharyngitis or skin infection</b>  Classically seen with streptococcal infection, but may be triggered by others	$\uparrow$ ASO and anti-DNase B antibodies $\oplus$	Treat with diuretics  Give antibiotics if infection is still present  Renal failure typically resolves in 6 weeks
MPGN	<b>Cryoglobulin-related MPGN:</b> <b>Arthralgias, palpable purpura, history of HCV infection</b>  Microscopic hematuria with mild to heavy proteinuria  May be chronic or rapidly progressive	$\oplus$ cryoglobulins, RF  Check HBV, HCV, and HIV serologies  Low C3, C4	Treat HCV-related disease and cryoglobulinemia with $\alpha$ -interferon alone or in combination with ribavirin (if kidney function is not severely impaired)
IgA nephropathy	More common in <b>Asians</b> and Hispanics  Episodic hematuria with or without proteinuria ( <b>usually within 24 hours of URI</b> )  May be primary or secondary to HIV, cirrhosis, IBD, celiac disease	Renal biopsy <b>Normal C3</b>	<b>Mild disease: ACEIs/ARBs</b> <b>Progressive disease: Corticosteroids <math>\pm</math> cyclophosphamide</b>  Ten to 20% of cases progress to ESRD $\uparrow$ creatinine, proteinuria, HTN worsens the prognosis
Endocarditis	Episodic hematuria with or without proteinuria	Blood cultures, echocardiography  Low C3, C4	Antibiotics  The general rule is that if endocarditis is cured, renal impairment will be cured

(continues)

TABLE 12.7. The Glomerulonephritides (continued)

DISEASE	PRESENTATION	DIAGNOSIS	TREATMENT
<b>PAuci-IMMUNE/ANCA-POSITIVE GLOMERULONEPHRITIS</b>			
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	<b>Upper respiratory tract disease and nodular cutaneous lesions are common</b>  Rapidly progressive glomerulonephritis (RPGN)	c-ANCA and anti-PR3 antibody $\oplus$  Renal biopsy	Steroids with PO cyclophosphamide  <b>Plasmapheresis in cases of pulmonary hemorrhage</b>
Microscopic polyangiitis	Lower rate of upper respiratory tract than granulomatosis with polyangiitis  RPGN	p-ANCA and anti-MPO antibody $\oplus$  Renal biopsy	Steroids with PO cyclophosphamide
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)	<b>Asthma, allergic rhinitis, eosinophilia</b>  Peripheral neuropathy (mononeuritis multiplex) common	p-ANCA and anti-MPO antibody $\oplus$  Renal biopsy	Steroids with PO cyclophosphamide
<b>ANTI-GBM GLOMERULONEPHRITIS</b>			
Anti-GBM disease (formerly Goodpasture syndrome)	RPGN  May have pulmonary alveolar hemorrhage; dyspnea, cough  May have ANCA-associated vasculitis	Anti-GBM antibody $\oplus$  Renal biopsy	Corticosteroids + cyclophosphamide  Plasmapheresis

## NEPHROTIC SYNDROME

Can be primary or secondary (due to either an identifiable process or a systemic cause). The most common 1° causes are membranous nephropathy and focal segmental glomerulosclerosis. The most common 2° cause is DM.

### Symptoms/Exam

Has the following clinical features:

- Anasarca/peripheral edema.
- Hypoalbuminemia (serum albumin <3 g/dL).
- Hyperlipidemia.
- Proteinuria >3.5 g/day.
- Hypercoagulability.

### Differential

- **1° nephrotic syndrome:** Nephrotic syndrome without an identifiable systemic disease. It has four subtypes as described in Table 12.8.
- **2° nephrotic syndrome:** Nephrotic syndrome occurring in the presence of an identifiable systemic disease such as diabetes, amyloidosis, or multiple myeloma (Table 12.9). The same four 1° causes of nephrotic syndrome can occur in the presence of an identifiable process that causes glomerular disease:
  - **Minimal change disease:** 2° causes include lymphoproliferative disease, drugs (particularly NSAIDs), and infection (syphilis, TB, HIV).



### KEY FACT

Minimal change disease can be caused by NSAIDs. Other inciting drugs are lithium, penicillamine, pamidronate, sulfasalazine, and  $\gamma$ -interferon.



### KEY FACT

Treat HIV-associated nephropathy with antiretrovirals (on the test, don't choose steroids).

TABLE 12.8. Primary Causes of Nephrotic Syndrome

DISEASE	PRESENTATION	TREATMENT	CLINICAL COURSE
Minimal change disease	Sudden onset with heavy proteinuria More common in children Associated with atopic disease	Steroids	Responds to steroids but often relapses Renal failure is uncommon
Focal segmental glomerulosclerosis	↑ in African Americans	Steroids, cyclosporine; cyclophosphamide	Up to 50% develop ESRD within 5 years
Membranous nephropathy	Predilection to clotting—renal vein thrombosis	Observation with ACEIs/ARBs if slow progression Steroids; cyclosporine, tacrolimus, mycophenolate	Twenty-five percent spontaneously remit <b>"1/3 get better, 1/3 stay the same, 1/3 get worse"</b> Slow progression to renal failure
MPGN	Can present with either nephritic or nephrotic features Associated with HCV/cryoglobulins, HBV, HCV, subacute bacterial endocarditis, syphilis; autoimmune (SLE, Sjögren); malignancy	<b>Non-nephrotic: Observe</b> <b>Nephrotic or worsening renal function: Steroids</b>	Fifty percent die or progress to ESRD within 5 years of renal biopsy

TABLE 12.9. Systemic Diseases That Cause Nephrotic Syndrome

DISEASE	PRESENTATION	TREATMENT	CLINICAL COURSE	NOTES
Diabetic nephropathy	Onset 5-10 years after diagnosis in type 1 DM; more variable in type 2 <b>High prevalence of simultaneous DM retinopathy</b>	Glycemic control Target LDL <100 mg/dL Target BP <130/80 mm Hg <b>ACEIs/ARBs are first-line treatment</b>	Progresses from hyperfiltration to microalbuminuria to nephrotic to ESRD	The leading cause of ESRD in the United States BP control is very important in slowing GFR decline
Multiple myeloma	<b>More severe renal failure with cast nephropathy</b> May have tubular dysfunction, <b>Fanconi syndrome</b> (glycosuria, aminoaciduria, phosphaturia, bicarbonaturia)	See the Hematology chapter	Higher creatinine is correlated with worse survival Survival improves if stem cell transplantation is successful	Monoclonal gammopathy on SPEP/UPEP <b>Light chains will not be detected by urine dipstick for protein</b>
Amyloidosis	May have heavy proteinuria of >20 g/day <b>AL (1°): Amyloid Ig Light chain deposition;</b> associated with multiple myeloma/MGUS <b>AA (2°): Serum Amyloid A protein deposition;</b> associated with <b>chronic inflammation and infection</b>	<b>AL:</b> See the Hematology chapter <b>AA:</b> Control the underlying condition	Mean survival in 1° amyloidosis is months	

- **Focal segmental glomerulosclerosis:** 2° causes include **HIV** (collapsing variant), heroin, nephron loss (from HTN, reflux nephropathy, or sickle cell disease), obesity, and lymphomas.
- **Membranous nephropathy:** 2° causes include gold, penicillamine, NSAIDs, HBV, HCV, syphilis, captopril, solid tumors (lung, kidney, breast, GI tract), chronic graft versus host disease, and SLE.
- **Membranoproliferative glomerulonephritis:** 2° causes include **HCV**, HBV, SLE, Sjögren syndrome, and chronic infection (malaria, subacute bacterial endocarditis, chronic abscesses, chronic osteomyelitis).

## Diagnosis

- As above plus the following:
  - **UA:** In addition to proteinuria, **oval fat bodies** or “**Maltese crosses**” may be visualized under polarized light.
  - **24-hour urine protein:** The gold standard for quantifying the extent of proteinuria. Can use the spot urine protein-to-creatinine ratio (divide spot protein by creatinine to approximate 24-hour protein excretion in grams) for longitudinal follow up to assess response to therapy and recurrence.
  - Renal biopsy is definitive.
- Additional labs to search for 2° causes include HbA<sub>1c</sub>, SPEP/UPEP, and serology for HBV, HCV, HIV, and syphilis. However, these will only suggest a diagnosis; biopsy is necessary to prove disease.

## Management

In addition to treating underlying disease:

- Control volume status and peripheral edema with loop diuretics.
- Maintain good nutrition.
- Give ACEIs to slow proteinuria.
- Lipid lowering—generally target an LDL <100 mg/dL.
- Prophylactic anticoagulation on a case-by-case basis.

## Essential Hypertension

See the Cardiovascular Disease chapter.

## Secondary Hypertension

2° HTN is defined as BP refractory to a three-drug regimen that includes a diuretic. Comprises 5% of cases of HTN.

### Symptoms/Exam

Suspect a 2° cause of HTN if:

- Age at onset is <30 or >50 years.
- Rapid onset of severe hypertension occurs in <3 to 5 years.
- Hypertension is refractory to multiple medications.
- Spontaneous hypokalemia is seen.

### KEY FACT

Although chronic abscesses can lead to MPGN, they are also associated with amyloidosis. Consider AA-amyloidosis in patients with IVDU who have progressive renal disease and nephrotic-range proteinuria.

### KEY FACT

Biopsy is usually needed to make the diagnosis in nephrotic syndrome, whereas serology results may make the diagnosis in nephritic diseases.

### KEY FACT

Multiple myeloma may affect the kidney in many ways:

- Cast nephropathy (most common)—due to light chains
- Light chain deposition disease
- Amyloidosis → nephrotic syndrome
- Proximal tubule involvement → Fanconi syndrome
- Hypercalcemia
- Hyperuricemia
- Hypovolemia

### KEY FACT

Patients with nephrotic syndrome are hypercoagulable due to loss of anticoagulant proteins (eg, AT III, protein C, protein S) and thus have ↑ incidence of venous and arterial thrombi.

### KEY FACT

In diabetes, ACEIs/ARBs can delay progression of proteinuria to overt nephropathy.



### QUESTION

A 45-year-old woman with diffuse joint pain presents with edema and HTN. Labs include Cr, 3.7 mg/dL; albumin, 2.1 g/dL; ANA, 1:320; and ↓ complement levels. UA shows 3+ protein and dysmorphic RBCs. What is the most likely diagnosis?

**MNEMONIC****Differential diagnosis of 2° hypertension—****ABCDE****A**—Accuracy of the diagnosis, obstructive sleep **A**pnea, **A**ldosteronism**B**—Presence of renal artery **B**ruits (renal artery stenosis), **B**ad kidneys (renal parenchymal disease)**C**—Excess **C**atecholamines, **C**oarctation of the aorta, **C**ushing syndrome**D**—**D**rugs, **D**iet**E**—Excess **E**rythropoietin, **E**ndocrine disorders**Differential**

- Renal: **R**enovascular disease, **R**enal **P**arenchymal disease, polycystic kidney disease, Liddle syndrome, syndrome of apparent mineralocorticoid excess, hypercalcemia.
- Endocrine: Hyper- or hypothyroidism, hyperparathyroidism, 1° **H**yperaldosteronism, **C**ushing syndrome, **P**heochromocytoma, **A**cromegaly, congenital adrenal hyperplasia (see also the Endocrinology chapter).
- Drugs:
  - Estrogen (OCPs), testosterone, steroids, cyclosporine, tacrolimus, fludrocortisone, epoetin, pseudoephedrine, NSAIDs.
  - Nicotine, ethanol, cocaine.
- Neurogenic: ↑ ICP.
- Aortic coarctation, **O**bstructive **S**leep **A**pnea, polycythemia vera.

**Diagnosis**

See Table 12.10.

**Management**

See the Cardiovascular Disease chapter for a summary of antihypertensive medications.

**RENOVASCULAR HYPERTENSION**

↓ renal blood flow causes ↑ renin and aldosterone levels, eventually resulting in hypertension (Table 12.11). Fibromuscular dysplasia often occurs in younger patients (often women), while atherosclerosis is the cause in older patients (often men) and in those with other atherosclerotic disease.

**Symptoms/Exam**

Clinical features include the following:

- Age at onset <30 or >50 years.
- Rapid onset in <3 to 5 years.

**TABLE 12.10. Tests for the Evaluation of Secondary Hypertension**

<b>BASIC TESTS</b>	<b>SCREENING STUDIES TO OBTAIN IF CLINICAL PRESENTATION IS SUGGESTIVE</b>
TSH Hematocrit to screen for polycythemia vera Serum K <sup>+</sup> (↓ K <sup>+</sup> suggests 1° aldosteronism) Serum creatinine and/or BUN for renal failure CXR to look for coarctation	<b>Renovascular disease:</b> ACEI radionuclide scan, renal duplex Doppler flow studies, or CT or MRI angiography <b>Pheochromocytoma:</b> 24-hour urine assay for creatinine, metanephrines, and catecholamines, or plasma-free metanephrines and normetanephrines <b>Cushing syndrome:</b> Overnight dexamethasone suppression test or 24-hour urine cortisol and creatinine <b>1° aldosteronism:</b> Plasma aldosterone-renin activity ratio

**ANSWER**

SLE with glomerulonephritis.

**TABLE 12.11. Features of the Two Most Common Causes of Renovascular Hypertension**

	ATHEROSCLEROSIS OF RENAL ARTERY (MORE COMMON)	FIBROMUSCULAR DYSPLASIA
Affected gender	<b>Men, especially with diabetes</b>	Women
Age	<b>&gt;50 years</b>	<b>&lt;40 years</b>
Total occlusion	Common; often bilateral renal artery stenosis	Rare; often bilateral
Ischemic atrophy	Common	Rare
Angioplasty	Less amenable	Highly amenable
Cure rate	Poor	Good

- Severe HTN despite an appropriate three-drug regimen, especially in patients with diffuse atherosclerotic disease.
- Flash pulmonary edema.
- Hypokalemia.
- Continuous abdominal bruit.
- ↑ in serum creatinine after initiation of ACEI treatment.

### Diagnosis

Imaging (duplex ultrasonography, MRA, CT angiography, angiography) reveals >75% stenosis (Figure 12.15). Sensitivity and specificity are operator dependent.



**FIGURE 12.15. Renal artery stenosis.** 3D MRA study of a 66-year-old hypertensive patient with ↑ plasma creatinine on ACE-inhibitor therapy. (Source: Maceira AM, et al. Cardiovascular magnetic resonance in systemic hypertension. *J Cardiovasc Magn Reson*. 2012;14(1):28.)



### QUESTION

A 24-year-old woman presents with several years of BP readings in the 160s/80s refractory to thiazide, lisinopril, and metoprolol. She has a continuous abdominal bruit, and K<sup>+</sup> is 3.0 mEq/L. What is the most likely cause of her HTN?

### Management

- **Medical therapy:** Control cardiovascular risk factors; give antihypertensive medications. Revascularization is helpful only for hemodynamically significant stenosis.
- **Percutaneous transluminal angioplasty (PTA)** is effective for fibromuscular dysplasia.
- **PTA/stent** may be effective for atherosclerotic patients.
- Benefit of surgical intervention is unclear.

## Chronic Kidney Disease

Permanent loss of renal function or renal injury (eg, albuminuria) of >3 months' duration. **End-stage renal disease** is defined as permanent loss of renal function that requires renal replacement therapy; GFR is <15 mL/min.

### KEY FACT

When you see large kidneys on ultrasound, think amyloidosis, early DM, lymphomatous infiltration, or HIV nephropathy.

### Diagnosis

Stages of CKD is outlined in Table 12.12. Staging the severity of CKD helps with management, including risk stratification for progression and for major complications of CKD. Staging is done using three categories: cause of disease, six categories of GFR (G stages), and three categories of albuminuria (A stages).

### Management

- **Proteinuria is the most important predictor of progression of renal disease.**
- ACEIs/ARBs are the drugs of choice for proteinuria and/or HTN.
- Target BP <130/80 mm Hg: After first-line ACEIs/ARBs, treat with diuretics ( $\uparrow$  Na<sup>+</sup> retention in CKD patients).
- Target LDL <100 mg/dL.
- Protein restriction is controversial.

**TABLE 12.12. Chronic Kidney Disease Prognosis Determined by GFR and Albuminuria<sup>a</sup>**

STAGE	GFR (ML/MIN/1.73 M <sup>2</sup> )	STAGE		
		A1 ALBUMINURIA <30 MG/G	A2 ALBUMINURIA 30-300 MG/G	A3 ALBUMINURIA >300 MG/G
G1	90	Normal or $\uparrow$	1 <sup>b</sup> (least severe)	2
G2	60-89	Mild $\downarrow$	1 <sup>b</sup>	2
G3a	45-59	Mild to moderate $\downarrow$	1	2
G3b	30-44	Moderate to severe $\downarrow$	2	3
G4	15-29	Severe $\downarrow$	3	3
G5	<15	Kidney failure	4+	4+ (most severe)

<sup>a</sup>Prognosis illustrated by frequency of monitoring (number of visits per year); 1 visit per year being the least severe prognosis, and 4+ visits being the most severe prognosis.

<sup>b</sup>If CKD. CKD is defined as abnormalities of kidney structure or function of >3 months' duration, affecting health.

(Modified from KDIGO 2012 Clinical Practice Guideline. *Kidney International Supplements*. 2013;3(1):63-72.)

### ANSWER

Renovascular HTN from bilateral fibromuscular dysplasia, leading to 2° hyperaldosteronism, 2° HTN, and hypokalemia.

## Complications

- **Anemia:**
  - Erythropoietin injections if hemoglobin is <10 g/dL; a target hemoglobin of >13 g/dL is associated with higher mortality.
  - Replete iron stores if ferritin is <100 ng/mL or transferrin saturation ( $T_{sat}$ ) is <20% (IV iron can be used in hemodialysis patients).
- **Renal osteodystrophy:** Phosphate control is typically initiated with a calcium-based phosphate binder ( $\text{CaCO}_3$  or calcium acetate). 1,25-OH vitamin D (calcitriol) may be used to control PTH.
- **Hyperkalemia:** Dietary restriction, diuretics.
- **Acidosis:**  $\text{NaHCO}_3$  supplementation to prevent  $\ominus$  bone balance.
- Mineral bone disease:  $2^{\circ}$  hyperparathyroidism (low Ca, high Phos). Low phosphorus diet.
- **Pericarditis** (can present as a rub, chest pain, or ECG abnormalities): Initiate dialysis or  $\uparrow$  dialysis dose.
- **Cardiovascular disease.**
- **Vascular catheter-related infections:**
  - *Staphylococcus aureus* is the most likely cause, followed by coagulase-negative *Staphylococcus*.
  - Treat empirically with broad-spectrum antibiotics such as a third- or fourth-generation IV cephalosporin; add coverage for MRSA in the setting of high local prevalence.
  - Remove the catheter in the presence of a fungal/*S aureus/Pseudomonas* infection, severe sepsis, endocarditis, metastatic infection, infection of catheter exit site, or persistent bacteremia.
- **Peritoneal catheter-associated peritonitis:**
  - *S aureus, Staphylococcus epidermidis*, enteric gram-negative rods, and fungi are the dominant organisms.
  - Look for a cloudy appearance to peritoneal fluid, fever, or abdominal pain.
  - Diagnose with Gram stain (>100 WBCs/ $\mu\text{L}$  in peritoneal fluid) and culture of peritoneal fluid.
  - Treat with antibiotic infusion into the peritoneum. For severe cases, add IV antibiotics  $\pm$  catheter removal.
  - If culture grows anaerobes, or multiple organisms, suspect  $2^{\circ}$  peritonitis due to perforated abdominal viscus (although the presence of fungus may simply be due to long-term broad-spectrum antibiotic use, not necessarily a perforation).
- **Transplant-related problems: Acute rejection occurs in the first 6 months** after transplant:
  - Usually asymptomatic with a serum creatinine elevation or rarely with fever, malaise, oliguria, graft pain, or tenderness to palpation.
  - Ultrasound shows  $\uparrow$  graft size with loss of corticomedullary junction, prominent hypoechoic pyramids, and  $\downarrow$  echogenicity of the renal sinuses.
  - Treatment is based on biopsy findings:
    - Cellular rejection  $\rightarrow$  Augment immunosuppression.
    - Ab-mediated rejection or mixed cellular and Ab-mediated  $\rightarrow$  Remove or inhibit circulating anti-donor Abs.

### KEY FACT

Peritoneal catheter-associated peritonitis is diagnosed by the presence of >100 WBCs/ $\mu\text{L}$ . In contrast, spontaneous bacterial peritonitis uses >250 PMNs/ $\mu\text{L}$  as a diagnostic cutoff.

### KEY FACT

Deafness, hematuria, and a family history of kidney disease should make you suspect Alport syndrome.

### KEY FACT

Think of medullary sponge kidney in a patient with episode painless hematuria who has nephrocalcinosis on ultrasound.

## Genetic Disorders and Congenital Diseases of the Kidney

Table 12.13 presents the relationship of various genetic disorders to congenital kidney diseases.

TABLE 12.13. Genetic Disorders and Congenital Diseases of the Kidney

DISEASE	PRESENTATION	DIAGNOSIS	TREATMENT
Alport syndrome	<b>Hematuria</b> , nephrotic-range proteinuria, progressive CKD <b>Sensorineural deafness, ocular defects</b>	Renal biopsy reveals a thickened GBM with splitting and splintering of the lamina densa	Renal transplantation
Autosomal dominant polycystic kidney disease (ADPKD)	Massive kidney enlargement due to multiple cyst formation; back/flank pain, kidney stones, hematuria <b>Can present with fever and flank pain and have infected cysts without abnormal UA or culture</b> <b>HTN; mitral valve prolapse; hepatic cysts</b> <b>Intracranial aneurysms (familial clustering)</b>	Family history of ADPKD The diagnosis depends on patient age, genotype, and the number of cysts on renal ultrasound	ACEIs or ARBs for HTN Renal transplantation for ESRD <b>Treatment of infected cysts is antibiotics for 2-4 weeks</b>
Medullary sponge kidney	Asymptomatic or <b>presents with hematuria, kidney stones, UTIs</b>	IVP Retention of contrast media in the collecting ducts of the medulla, leading to a "bouquet of flowers" appearance Ultrasound or CT may also be used (medullary nephrocalcinosis)	Benign clinical course

# CHAPTER 13

## Neurology

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		Focal (Partial) Seizures	448
		Status Epilepticus	449

## Neurodiagnostic Testing

### KEY FACT

In suspected meningitis, obtain a head CT before LP if the patient is >50 years of age, has HIV, or has a focal neurologic deficit (including papilledema or altered mental status) or seizure.

### KEY FACT

The yield of electroencephalography in a patient with new-onset seizure is low, with only ~ 30% sensitivity. Sleep-deprived electroencephalography may have ↑ sensitivity but is seldom performed.

### LUMBAR PUNCTURE

- Brain imaging (eg, head CT) to evaluate for mass effect and herniation risk is only indicated prior to lumbar puncture (LP) for patients with: papilledema, focal neurologic signs, or immunosuppression. Imaging of the spine should precede LP in patients with spinal cord signs or symptoms.
- Coagulopathy is a contraindication to LP.

### ELECTROENCEPHALOGRAPHY

Conditions with notable electroencephalography (EEG) findings include the following:

- **Metabolic encephalopathy:** Hepatic encephalopathy is the classic metabolic coma. The EEG typically shows generalized periodic triphasic waves.
- **HSV encephalitis:** look for the classic periodic lateralizing epileptiform discharges originating over one or both temporal lobes.
- **Prion disease:** In Creutzfeldt-Jakob disease, look for generalized periodic epileptiform discharges.

### BRAIN IMAGING

- **Computed tomography (CT):** CT imaging of the brain is inferior to MRI for most pathology but is the imaging study of choice for investigating acute hemorrhage (eg, subarachnoid hemorrhage [SAH], epidural hematoma) and bone pathology (eg, skull or vertebral fractures).
- **Magnetic resonance imaging (MRI):** The best imaging modality for most diseases of the brain and spinal cord, including neoplastic, vascular, demyelinating, infectious, and structural diseases (eg, spondylosis of the spine).
- **Cerebral angiography:** The gold standard for investigating vascular abnormalities of the CNS, including stenosis, aneurysms, arteriovenous malformations (AVMs), and cerebral vasculitis. **Venography** is the gold standard for diagnosing venous sinus thrombosis.

### KEY FACT

Board exam questions may give you a clue to Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy by providing evidence of demyelination on nerve conduction studies.

### ELECTROMYOGRAPHY/NERVE CONDUCTION STUDIES

- **Electromyography (EMG):** Examines spontaneous and voluntary muscle activity by using a needle electrode placed directly into the muscle. Useful for studying and differentiating radiculopathies (spinal root injuries), motor neuron disease, neuropathies, neuromuscular junction diseases, and myopathies.
- **Nerve conduction study (NCS):** Obtained by stimulating peripheral nerves and recording either sensory or motor responses along the course of the nerve.

## Headache

Table 13.1 lists alarm symptoms, which should prompt further investigation (eg, imaging, basic labs, LP), and potential urgent diagnoses in patients with headache.

**TABLE 13.1. Alarm Features in Patients with Headache**

ALARM FEATURE	POTENTIAL URGENT DIAGNOSES
Abrupt-onset, severe headache	Intracranial bleed
Visual complaints	Malignancy, infection, bleed, giant cell arteritis
Fever	Meningitis, encephalitis, brain abscess
Jaw claudication	Giant cell arteritis
Worsening with Valsalva or cough	↑ ICP from malignancy or bleed
Papilledema	↑ ICP from malignancy or bleed; pseudotumor cerebri, cerebral venous thrombosis
History of malignancy	Brain metastasis
Focal neurologic deficit or seizure	Bleed, malignancy, CNS infection
Scalp tenderness	Zoster
Onset of headache after age 40-50 years	Malignancy, CNS infection
Neck pain	Carotid or vertebral dissection

## MIGRAINE HEADACHE

Roughly 10% to 20% of the US population have experienced migraine headaches, with 80% of cases beginning before age 30 years. Most patients are **young women** (the female-to-male ratio is 3:1). **Ninety percent of patients have a strong family history.** Subtypes are as follows:

- **Migraines without aura:** Remember the **POUND** mnemonic.
- **Migraines with aura:** Associated with focal neurologic deficits, including motor, sensory, language, brainstem (ataxia, vertigo, and slurred speech), and visual disturbance.

### Symptoms/Exam

- **Benign, recurrent headaches** that classically produce **unilateral pulsating pain** associated with symptoms such as **photophobia**, phonophobia, anorexia, **nausea**, and vomiting.
- Episodes typically last 4 to 72 hours, and patients often report improvement with resting in a **dark, quiet room**.
- Patients with migraines without aura have **normal neurologic exams**.

### Diagnosis

- Look for the features of the **POUND** mnemonic.
- Look for strong family history.
- Neuroimaging is **not recommended** for patients with stable migraine headaches without neurologic deficits.

### Management

- Divided into two categories: **Abortive therapy** for the migraine itself (taken only at the time of the migraine) and **prophylactic therapy** for preventing future attacks (taken daily).
- **Abortive therapy** includes the following:
  - First-line therapy is NSAIDs.



### MNEMONIC

#### **Symptoms of migraines—**

#### **POUND**

Pulsating

One day

Unilateral

Nausea

Disabling

Can diagnose migraine in patients with >3 of these criteria without further evaluation.



### KEY FACT

The typical migraine patient is a woman <30 years of age with a unilateral headache associated with nausea or photophobia, a strong family history of migraines, a normal neurologic exam, and **no** preceding aura.



### KEY FACT

Tension headache is usually a nonthrobbing, bilateral head pain that is generally not associated with nausea, vomiting, or prodromal visual disturbances.



### QUESTION

A 25-year-old woman presents with episodic left-sided headaches that have occurred a few times a month for the past year. The headaches usually resolve over 1 to 2 days and do not respond to decongestants, antihistamines, or acetaminophen, but they worsen with movement and improve when the patient rests in a quiet, dark room. Her mother has a history of similar headaches. Exam reveals facial tenderness on palpation. What is the most likely diagnosis?

**KEY FACT**

Avoid estrogen-containing OCPs in women with migraines with auras as this can ↑ the risk of stroke.

**KEY FACT**

Opioid or butalbital-containing medications should be avoided in patients with migraines and tension headache as they can lead to dependency.

**KEY FACT**

Muscle relaxants, benzodiazepines, and botox injections are not effective abortive or prophylactic treatments.

**KEY FACT**

The classic presentation of cluster headache is that of a **young man who smokes cigarettes** with an identifiable pattern of recurring headaches that last a half hour to 2 hours; often occur at bedtime or are **triggered by alcohol**; and are accompanied by unilateral eye pain or tearing. Abort cluster headaches with high-flow O<sub>2</sub> or triptans.

**ANSWER**

Migraine without aura. Typical features include worsening of symptoms with movement, limitation of activities, photophobia, and phonophobia. Cluster headaches last <2 hours and occur more often in men.

- Second-line are **triptans**: 5-HT<sub>1</sub> serotonin receptor agonists (eg, sumatriptan, frovatriptan, eletriptan, naratriptan, almotriptan, rizatriptan, zolmitriptan) produce vasoconstriction. **Contraindicated** in patients with vascular disease (eg, CAD, peripheral vascular disease), **brainstem migraines**, **hemiplegic migraines**, and in pregnant women.

- **Other abortive agents:**

- **Ergotamine:** Avoid in patients with vascular disease and in pregnant women.
- **Antiemetic:** Prochlorperazine (antidopaminergic), promethazine.
- Diphenhydramine to prevent dystonic reaction from antidopaminergic.
- IV ketorolac.
- Steroid: Short course may be helpful.

- **Prophylactic therapy** indicated for frequent severe migraines (eg, >4 episodes per months or lasting longer than 12 hours):

- **First-line medications:** TCAs (eg, amitriptyline), β-blockers (eg, propranolol), and **anticonvulsants** (eg, valproic acid, topiramate).
- **Second-line medications:** Calcium channel blockers (eg, verapamil).
- **Behavioral measures:** Proper sleep hygiene and avoiding food triggers (eg, tyramine, nitrates, dairy products, xanthines).
- **Menstrual migraine prophylaxis:** Low-dose estrogen therapy during menstruation, NSAIDs, triptans, or oral magnesium.

**TENSION HEADACHE**

Most prevalent 1° headache disorder characterized by the lack of disabling features.

**Symptoms**

- Tightness or pressured bilateral headaches that is mild to moderate in severity.
- Not associated with nausea, vomiting, photophobia, or phonophobia.

**Diagnosis**

- Exclude the diagnosis of migraine.
- Chronic tension-type headaches (>14 days/month) require a brain MRI to exclude other etiologies.

**Management**

- Abortive therapy: Acetaminophen, aspirin, and NSAIDs.
- Prophylactic therapy: Amitriptyline is used to treat chronic tension headache ( $\geq 15$  days/month) and episodic tension headache (1-14 days/month) that cause severe disability. Venlafaxine and mirtazapine may be used as alternative.

**CLUSTER HEADACHE**

Classically occurs in **young men** 20 to 40 years of age; the male-to-female ratio is 5:1 (Table 13.2). A family history of similar headaches is uncommon.

**Symptoms**

- Cardinal feature is **periodicity** with “cluster” of headaches for weeks (often during the spring or fall season) followed by long period of remission (months to years).
- A typical attack is characterized by abrupt onset and severe **unilateral periorbital pain** with associated **ipsilateral autonomic symptoms**.
- Attack frequency ranges from one every other day to eight per day; each attack typically lasts 15 to 180 minutes.

**TABLE 13.2. Cluster Headache Versus Migraine**

	MIGRAINE	CLUSTER HEADACHE
Typical patient	Young woman	Young man
Triggered by alcohol	No	Yes
Periodicity	No	Yes
Aura	Yes (with classic form, ~ 20%)	No
Rhinorrhea, congestion	No	Yes
Response to O <sub>2</sub>	No	Yes

**Exam**

- Patients are restless and agitated and often pace the room (vs migraine patients).
- Autonomic symptoms: Tearing, conjunctivitis, eyelid edema, forehead flushing, sweating, nasal discharge, and/or ptosis (eg, **Horner syndrome**) ipsilateral to the location of eye pain.

**Differential**

Clues to distinguish cluster headaches from migraines are shown in Table 13.2.

**Management**

- As with migraines, treatment includes abortive and prophylactic therapies.
- Abortive therapy** includes **two first-line options**:
  - O<sub>2</sub> inhalation: Give 5 to 10 L/min for 10 to 15 minutes.
  - Triptans.
- Second-line abortive therapy: Ergotamine and intranasal lidocaine.
- Prophylactic medications:**
  - Start once cluster headaches begin, but do not use during remissions since months to years may elapse between clusters.
  - First line is **verapamil**.
  - Other options include: **Prednisone taper**, lithium, valproate, and pericranial nerve blocks.

**TRIGEMINAL NEURALGIA (TIC DOULOUREUX)**

A **unilateral** facial pain syndrome affecting middle-aged and elderly patients, most commonly occurs in the sixth decade. Onset in young patients should raise suspicion for an underlying disorder (eg, MS, brainstem neoplasm).

**Symptoms/Exam**

- Characterized by abrupt-onset, short-duration (seconds-long) episodes of severe, **unilateral, lancinating electrical pain**, typically **radiating along the jaw** in the distribution of the second and third divisions of CN V (the trigeminal nerve).
- Attacks are often **triggered by sensory stimuli** to the face (eg, touch, wind, shaving, chewing).
- Neurologic exam is **normal**.

**Management**

- First-line therapy is **carbamazepine**.
- Alternatives include oxcarbazepine, valproate, phenytoin, baclofen, lamotrigine, gabapentin, and benzodiazepines.
- Surgical decompression of the trigeminal nerve root is considered after there is no response to multiple trials of a single agent or multiple agents.

**KEY FACT**

Cluster headache patients are often hyperactive during a headache (pacing), whereas migraine patients tend to retreat to a dark, quiet room.

**KEY FACT**

Unlike in patients with classic migraine, patients with cluster headache should undergo brain MRI to rule out structural lesions.

**QUESTION**

A 40-year-old man presents with a severe, throbbing left retro-orbital headache associated with left-sided rhinorrhea and ptosis. The headaches started 3 weeks ago and have occurred at 7 AM and 7 PM daily, lasting 30 to 60 minutes each. The patient had similar symptoms a year ago that lasted for 6 weeks. His vital signs, funduscopic exam, and neurologic exam are normal. MRI of the brain and cervical spine are normal, as is his LP. What is the most likely diagnosis, and how should he be treated?

**KEY FACT**

Suspect trigeminal neuralgia in a 50-year-old man with attacks of severe, unilateral electrical jaw pain triggered by light touch or shaving.

**KEY FACT**

In a patient with trigeminal neuralgia who is <40 years of age or who has any neurologic deficits (including sensory deficits), brain imaging is warranted to exclude a mass lesion, infiltrative, or demyelinating disorders (eg, MS).

**FIGURE 13.1. Papilledema.**

Fundoscopic exam revealing optic nerve edema and hemorrhage in an obese young woman with idiopathic intracranial hypertension. (Used with permission from Dr. Nicholas Mahoney.)

**A****ANSWER**

This patient has episodic cluster headache. Acute treatments to abort the attack include triptans, ergots, and high-flow O<sub>2</sub>. Prednisone, anticonvulsants, or calcium channel blockers may also be indicated as prophylactic treatments for patients with frequent episodes.

**IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOR CEREBRI)****Symptoms/Exam**

- Consider idiopathic intracranial hypertension (pseudotumor cerebri) in **young, obese women** with headache.
- Related to chronically ↑ ICP, possibly in association with **medications** (tetracycline, OCPs, isotretinoin, steroids, lithium, phenytoin, tamoxifen, retinoic acid, vitamin A) or with SLE, Behçet syndrome, and uremia.
- Headaches are classically diffuse, worse in the morning or with Valsalva maneuvers, and are often accompanied by transient visual blurring, peripheral vision loss, total blindness, or diplopia from CN VI palsies.
- Headaches may also be associated with pulsatile tinnitus.
- On exam, look for **papilledema** (Figure 13.1), diplopia, and peripheral visual acuity.
- Keys to differentiating idiopathic intracranial hypertension from other headache syndromes are outlined in Table 13.3.

**Diagnosis**

Evaluation should include:

- MRI: To exclude other causes. Is often normal, but can show optic globe flattening or empty sella turcica.
- LP: **Opening pressure of >250 mm H<sub>2</sub>O**, normal protein and glucose, and no cells.

**Management**

- First-line therapy: **Acetazolamide**, a carbonic anhydrase inhibitor, or topiramate. Both ↓ CSF production and ICP.
- Treat underlying cause: Stop medications associated with pseudotumor and recommend **weight loss**.

**MEDICATION REBOUND HEADACHE**

- **Overuse of analgesic medications** (eg, acetaminophen, NSAIDs, butalbital/ASA/caffeine, isometheptene/dichloralphenazone, narcotics, triptans, ergotamines, barbiturates) for ≥10 days per month for headache syndromes can paradoxically produce refractory chronic daily headache, or medication rebound headache.
- First-line management consists of weaning off the offending analgesic medications. Often requires a slow taper of the analgesic to prevent withdrawal symptoms.

**TABLE 13.3. Classic Case Presentations of Headache Syndromes**

MIGRAINE	CLUSTER HEADACHE	TRIGEMINAL NEURALGIA	PSEUDOTUMOR CEREBRI
A 25-year-old woman resting uncomfortably in a dark, quiet room complains of unilateral head pain associated with nausea and photophobia. The headache was preceded by an aura of flashing colored lights.	A 32-year-old man pacing the ED has severe unilateral periorbital pain associated with tearing of the ipsilateral eye and nose. He has had three attacks per day over the past week, each occurring at the exact same time every day and lasting 20-40 minutes. The headache began after the patient drank alcohol at a party.	A 58-year-old woman presents with attacks of brief, unilateral, severe electrical sensations radiating along the jaw.	A 22-year-old obese woman presents with a 2-month history of progressive headaches. The headaches were initially associated with intermittent blurry vision but are now accompanied by a progressive ↓ in visual acuity.

## Vertigo

An illusion of movement; room spinning, or a sense of falling, rocking, spinning, or being pushed or pulled. Should be distinguished from other sensations of dizziness:

- **Presyncope:** A feeling of impending loss of consciousness (LOC), which manifests as lightheadedness. Usually due to postural changes rather than to arrhythmia or structural heart disease. Cardiac dysfunction, respiratory distress, and anxiety can also cause a similar sensation of lightheadedness. See the Cardiovascular Disease chapter for further details.
- **Disequilibrium:** Unsteadiness with standing or walking. Common in older patients; often multifactorial.
- Tinnitus, hearing loss, ear fullness/pain, or recent upper respiratory tract infection (URTI) suggests inner ear (peripheral vestibular) dysfunction.

### Exam

- Orthostatic vital signs: If abnormal, would point away from diagnosis of vertigo.
- Thorough neurologic exam to look for evidence of CNS pathology.
- Table 13.4 lists specific maneuvers to differentiate central versus peripheral vertigo.

### Diagnosis

MRI is required when you suspect a central cause (Table 13.5), because the bony artifact in the posterior fossa region on CT often obscures pathology.

**TABLE 13.4. Maneuvers to Differentiate Central and Peripheral Vertigo**

MANEUVER	FINDINGS
<b>MAY INDICATE A CENTRAL CAUSE OF VERTIGO</b>	
<b>Alternate cover test (test of skew):</b> Patient looks at the examiner's nose, covers one eye, then covers the other eye.	If the uncovered eye has a correction to 1° gaze, this indicates that the eyes are in misalignment, and is suggestive of central pathology.
<b>MAY INDICATE PERIPHERAL CAUSE OF VERTIGO</b>	
<b>Head impulse (or head thrust) test:</b> Patient fixates on the examiner's nose; examiner then rotates patient's head quickly to either side.	A "catch-up" movement of their eyes back to midline.
<b>Dix-Hallpike maneuver:</b> Patient seated on exam table with head turned 45° to affected side; examiner quickly brings patient from sitting to supine position with head hanging 30° below horizontal.	⊕ test indicates the presence of a brief latency followed by onset of torsional nystagmus that lasts <30 seconds and fatigues with repeated testing; ⊕ in approximately 50% of patients with benign paroxysmal positional vertigo.
<b>MAY INDICATE CENTRAL OR PERIPHERAL CAUSE OF VERTIGO</b>	
<b>Nystagmus:</b> Named by the direction of the fast jerk.	<b>Central cause:</b> Downbeating, vertical, or multidirectional that changes with direction of gaze. <b>Peripheral cause:</b> Unidirectional torsional or horizontal, always in the same direction, <b>fatigues over time</b> , and resolves with fixation after 5-10 seconds.



### QUESTION 1

A 70-year-old woman presents with a 2-month history of severe, paroxysmal, stabbing right lower jaw pain that lasts for only a few seconds and is precipitated by eating, chewing, or brushing her teeth or even by a cold breeze. On exam, pain is elicited with light touch on the right lower gums, teeth, and jaw. Radiographs of the face and brain MRI are normal, as is a dentist's evaluation, and ESR is normal as well. What is the diagnosis and the most appropriate management course for this patient?



### QUESTION 2

A 20-year-old woman presents with a month of daily headaches that initially worsened when she lay supine but have been continuous for the past 2 weeks. Triptans have provided no relief. She has also had intermittent blurry vision and tinnitus in both ears for the past month. Her BMI is 30. She has bilateral papilledema. Neurologic exam and MRI with contrast and MR venography are all normal. What would be the most appropriate next step in management?



### KEY FACT

Peripheral vertigo can be subjectively more severe than central vertigo but should not have any associated neurologic symptoms, such as the "**D's**" associated with posterior circulation causes: Diplopia, Dysarthria, Dysphagia, Dysmetria, visual Dysfunction, or Decreased consciousness.



### KEY FACT

Vertigo is likely due to a CNS etiology if:

- The head thrust test is normal.
- Direction-changing nystagmus on horizontal gaze is present.
- Skew deviation on alternative cover test is present.



### KEY FACT

The most common peripheral causes of vertigo are benign paroxysmal positional vertigo, Ménière disease, and acute labyrinthitis.

**A****ANSWER 1**

Trigeminal neuralgia; carbamazepine is the treatment of choice. Baclofen and other anticonvulsants can be useful as well.

**A****ANSWER 2**

Suspect idiopathic intracranial hypertension (pseudotumor cerebri), which typically affects obese young women. Several symptoms point to ↑ ICP, and normal imaging excludes a mass lesion, hydrocephalus, or venous sinus thrombosis. Perform LP to confirm ↑ CSF pressure and refer for urgent ophthalmologic evaluation and visual field monitoring. If LP confirms the diagnosis, start acetazolamide to ↓ CSF production.

**KEY FACT**

Acute labyrinthitis can be distinguished from vestibular neuritis by associated hearing loss but both can be seen after an URTI and resolve spontaneously.

**MNEMONIC**

**The risk of a patient with a TIA developing a stroke within the next few days is estimated by the ABCD-2 score:**

**A**ge ≥60: 1 point.

**B**lood pressure ≥140/90 mm Hg at initial evaluation: 1 point.

**C**linical features of TIA (unilateral weakness, 2 points; speech disturbance, 1 point).

**D**uration of symptoms (10-59 minutes, 1 point; ≥60 minutes, 2 points).

**D**iabetes mellitus: 1 point.

Consider hospitalization for score of 3 or more to expedite the workup.

**TABLE 13.5. Differentiating Features of Common Causes of Central Vertigo**

	ACOUSTIC NEUROMA (CN VIII SCHWANNOMA)	POSTERIOR CIRCULATION ISCHEMIA OR HEMORRHAGE	MIGRAINE WITH BRAINSTEM AURA
Symptoms	Unilateral hearing loss with tinnitus and vertigo	<b>Depends on location of stroke</b> <b>Ataxia, cranial nerve defects from cerebellar or brainstem strokes</b> <b>Basilar artery thrombosis:</b> vertigo, impaired consciousness, CN defects <b>VBI:</b> Vertigo caused by change in head position; <b>diplopia, dysarthria, numbness</b>	Can occur independent from headache; occipital <b>headache, visual disturbances, sensory symptoms</b> Has at least two of the following symptoms: vertigo, tinnitus, hyperacusis, diplopia, ataxia, LOC
Duration	Continuous	Varies	Varies
Exam/diagnosis	MRI	MRI, angiogram	Diagnosis of exclusion
Treatment	Surgery	Stroke treatment	See Headache section for abortive and preventative migraine management

**Management**

Causes and treatment of central and peripheral vertigo are summarized in Tables 13.5 and 13.6.

**Cerebrovascular Disease**

Approximately 85% of strokes are ischemic (due to occlusion of arterial flow), with the remaining 15% caused by hemorrhage either in or around the brain (due to rupture of cerebral arteries or veins). Hypertension is the single most important risk factor for ischemic stroke.

- Stroke: Neurological deficits that last >24 hours with underlying brain infarction.
- Transient ischemic attack (TIA): Neurological deficits that last <24 hours and absent of infarction on neuroimaging. Use the “ABCD” Score to risk stratify—a score of 0-2 predicts less than 1% risk of stroke in the next week for whom expedited outpatient workup would generally be appropriate.

**ISCHEMIC STROKE**

- Stroke affecting the **anterior circulation** (Table 13.7): Arises from the **internal carotid artery (ICA)** and includes the **ophthalmic artery, the anterior cerebral artery (ACA), and the middle cerebral artery (MCA)** (Figure 13.2).
- Stoke affecting the **posterior circulation** (see Table 13.8).

**Embolic Stroke**

Emboli most commonly arise from atherosclerotic plaques of the extracranial **ICA** or from the **heart**. Common sources of emboli include paradoxical emboli (via patent

**TABLE 13.6. Differentiating Features of Common Causes of Peripheral Vertigo**

	BENIGN PAROXYSMAL POSITIONAL VERTIGO	MÉNIÈRE DISEASE	VESTIBULAR NEURONITIS/ACUTE LABYRINTHITIS	POSTTRAUMATIC
Symptoms	Onset is a few seconds <b>following head motion;</b> nausea/vomiting Often recurs	Has four repeated, classic symptoms: Episodic vertigo, <b>sensorineural hearing loss, tinnitus, and ear fullness</b> <b>Vertigo may improve but patients may become deaf</b> Bilateral in 50% of cases	May be preceded by URTI; <b>sudden, continuous</b>	Episodic dizziness associated with headaches, hearing changes, fullness and noises in the ear; similar to Ménière disease and is sometimes called hydrops
Duration	<b>Up to 1 minute</b>	One to several hours	A few days to 1 week	A few days to 1 month
Diagnosis	⊕ <b>Dix-Hallpike</b>	<b>Clinical; MRI to rule out acoustic neuroma</b> <b>Referral to ENT</b>	Clinical	Clinical; CT if concerned about basilar skull fracture
Etiology	Dislodging of otolith into the semicircular canal	Rare; distention of the endolymphatic compartment of the inner ear	Unknown; often occurs after URTI	Post head trauma to vestibular structures
Treatment	<b>Epley maneuver</b> (canalith repositioning); <b>habituation exercises</b>	Bed rest; <b>avoid triggers (caffeine, salt, EtOH, nicotine)</b> ± <b>diuretics</b> ; symptomatic treatment with antihistamines, anticholinergics, and benzodiazepines	Symptomatic (meclizine or benzodiazepines)	Symptomatic; improves with time

foramen ovale), left ventricular thrombosis from severe heart failure, valvular disease, aortic arch atherosclerosis, and atrial fibrillation.

**Exam:** Patients with embolic stroke need aggressive investigation of the potential embolic source to determine whether specific intervention is warranted. Vascular sources of emboli as follows:

- **Posterior circulation embolic stroke:** Vertebral, basilar, and posterior cerebral arteries.
- **Amaurosis fugax: Ipsilateral ICA.**
- Anterior circulation (ACA or MCA): Ipsilateral ICA or cardiogenic emboli (Figure 13.3).
- **Diagnosis and treatment** of embolic stroke is the same as that for thrombotic stroke (see the discussion below).



#### KEY FACT

Suspect cardiac emboli in a patient with ischemic strokes involving multiple vascular distributions.



#### KEY FACT

Think brainstem lesion if there are crossed symptoms such as a cranial nerve deficit with contralateral weakness or if vertigo, dysarthria, double vision, or ataxia is present.



#### QUESTION

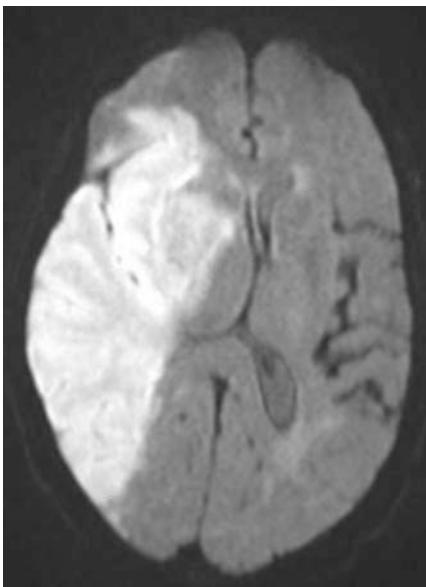
A 70-year-old man with hypertension and hyperlipidemia presented with left upper extremity weakness and numbness. He was last seen normal 10 hours ago the previous night. His BP is 170/89 mm Hg. Exam reveals left-sided neglect and hemisensory deficit, mild left central facial palsy, and left upper and lower extremity weakness. His labs and head CT are all normal. What is the most appropriate next step in this patient's management?

**TABLE 13.7. Stroke Affecting the Anterior Circulation**

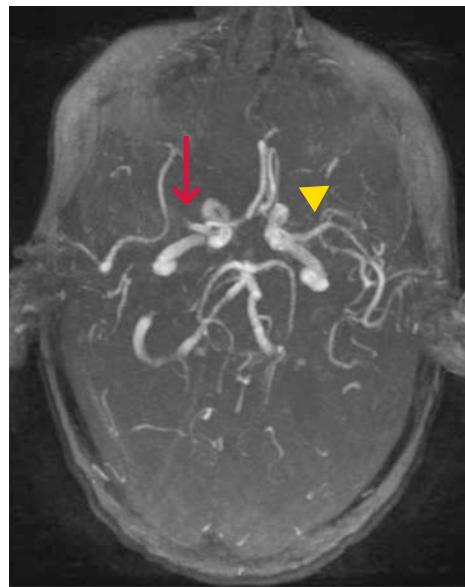
AFFECTED AREA	SIGNS/SYMPTOMS
Ophthalmic artery	Ipsilateral monocular vision loss (amaurosis fugax)
ACA	Contralateral leg weakness and sensory loss
MCA	<b>Dominant hemisphere: Aphasia;</b> contralateral face/arm weakness and sensory loss; neglect; homonymous hemianopia <b>Nondominant hemisphere:</b> Contralateral face/arm weakness and sensory loss; neglect; homonymous hemianopia



A

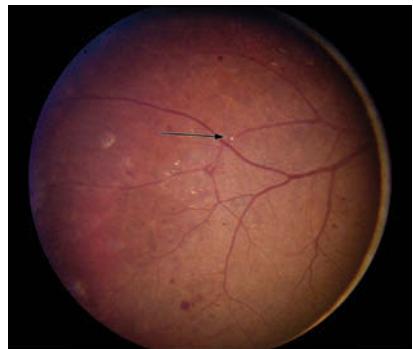


B



C

**FIGURE 13.2. Acute ischemic stroke.** Acute left hemiparesis in a 62-year-old woman. (A) Noncontrast head CT with loss of gray and white matter differentiation and asymmetrically ↓ size of the right lateral ventricle in a right MCA distribution (indicating mass effect). (B) Diffusion-weighted MRI with reduced diffusion in the same distribution, consistent with an acute infarct; **diffusion-weighted sequences are the most sensitive modality for diagnosing an acute ischemic infarct.** (C) MRA shows the cause: an abrupt occlusion of the proximal right MCA (arrow). Compare with the normal left MCA (arrowhead). (Reproduced with permission from USMLE-Rx.com.)



**FIGURE 13.3. Hollenhorst plaque lodged at a branch of the retinal arteriole.** The plaque represents cholesterol emboli that may originate in the ipsilateral ICA. This patient had a carotid bruit. (Reproduced with permission from USMLE-Rx.com.)

### Thrombotic Stroke

Occurs when a small cerebral artery gradually occludes 2° to progressive local thrombosis. The classic vessels involved are the small penetrating terminal arterioles that supply the brainstem and the deep structures of the cerebral hemispheres, including the basal ganglia, thalamus, and internal capsule. The internal capsule is of particular importance in that it contains the descending motor fibers. Occlusion of these

**TABLE 13.8. Stroke Affecting the Posterior Circulation**

AFFECTED AREA	SIGNS/SYMPOMTS
Posterior cerebral artery	Contralateral visual field deficits (homonymous hemianopia) Cortical blindness (Anton syndrome) and paresthesias may also be seen
Posterior inferior cerebellar artery	Wallenberg/lateral medullary syndrome <sup>a</sup>
Cerebellum	<b>Vertigo</b> , nystagmus, nausea, vomiting, ipsilateral incoordination
Brainstem	<b>Basilar artery:</b> Oculomotor deficits and/or ataxia with "crossed" sensory/motor deficits of the face and body; stupor, coma <b>Vertebral artery:</b> Lower cranial nerve deficits (dysphagia, dysarthria, tongue/palate deviation) and/or ataxia with crossed sensory deficits of the face and body, stupor, coma, and Wallenberg syndrome <sup>a</sup>

<sup>a</sup>Causes a constellation of vestibular symptoms (vertigo, diplopia, nystagmus, vomiting), ataxia, myoclonus, contralateral pain and temperature deficits from the body, ipsilateral pain and temperature deficits from the face, dysphagia, hoarseness, dysphonia, dysarthria, diminished gag reflex, and ipsilateral Horner syndrome.

A

### ANSWER

ASA therapy for acute right MCA ischemic stroke to prevent recurrent strokes and disability in the long term. He is not a candidate for tPA nor embolectomy because he is outside the time windows of 4½ and 6 hours for these.

small arterioles produces a discrete “lacunar” **infarct** of the small area of brain supplied by the terminal arteriole.

- **Lacunar infarct:** Can have devastating effects despite its small size. The four classic “lacunar” strokes are as follows:
  - **Pure motor hemiparesis:** Affects the internal capsule with contralateral hemiparesis.
  - **Dysarthria–clumsy hand syndrome:** Affects the pons with contralateral hand weakness and dysarthria.
  - **Ataxia hemiparesis:** Affects the internal capsule, basis pontis, and corona radiata with contralateral hemiparesis and ataxia.
  - **Pure sensory loss:** Patients have complete loss of sensation on one side of the body.
- **Other lacunar strokes:** The “named” brainstem strokes (eg, Wallenberg syndrome; see Table 13.9) are typically caused by a small vessel lacunar stroke from thrombosis.

## Diagnosis

Imaging studies are as follows:

- **Brain:** A noncontrast head CT is the initial study of choice for acute stroke, primarily to evaluate for ICH. MRI is best for characterizing the location and size of ischemic strokes.
- **Internal carotid:** Doppler ultrasound is the most reliable modality for assessing internal carotid artery stenosis. CT or MRA may also be obtained. If result shows **>70% ICA ipsilateral stenosis** in a patient with an anterior circulation embolic stroke, refer to a vascular surgeon for consideration of endarterectomy or angioplasty.
- **Heart:** Transesophageal echocardiography is superior to transthoracic echocardiography for evaluating potential cardiac sources of emboli. Consider the latter imaging test with bubble study in young stroke patients to evaluate for patent foramen ovale (PFO).
- **ECG:** The initial screening test for cardiac arrhythmias, especially AF or flutter.
- **Cardiac telemetry:** Monitoring patients on continuous cardiac telemetry for 24 to 48 hours can help detect paroxysmal AF.
- **Hypercoagulability:** Patients <50 years of age with unexplained embolic stroke should be evaluated for antiphospholipid syndrome. Other tests of hypercoagulable states (eg, antithrombin III, protein S and C deficiency, factor V Leiden mutation) are of questionable benefit.

## Management

- **Acute management of ischemic stroke** should include the following:
  - Serial neurologic exams to assess for deterioration and herniation.
  - Prevention of DVT/PE using prophylactic doses of LMWH usually started on the first day after ischemic stroke (24 hours after ischemic or hemorrhagic stroke or 24 hours post tPA administration).
  - Assessment of swallowing and measures to ↓ aspiration (eg, elevation of the head of bed; dietary modification to ↓ aspiration risk).
- Exceptions in acute management:
  - **tPA:** Only patients with acute ischemic stroke symptoms of **<3.0 hours** can receive tPA if there are no contraindications (Table 13.10).

**TABLE 13.9. Specific Brainstem Strokes**

NAME	LOCATION	SYMPTOMS
Wallenberg syndrome	Lateral medulla	Ipsilateral loss of pain and temperature on the face
		Contralateral loss of pain and temperature on the body
		Ipsilateral Horner syndrome, vertigo, slurred speech
Weber syndrome	Midbrain	Ipsilateral CN III palsy; contralateral hemiparesis



## QUESTION

A 60-year-old woman presents to the ED after awakening with vertigo, ataxia, and a headache. She has hypertension and stable angina and is on ASA, a statin, and metoprolol. BP is 168/90 mm Hg, and she has bidirectional nystagmus, gait ataxia, lethargy alternating with agitation, intractable hiccups, and dysmetria of the left upper and lower extremities. What is the most likely diagnosis?



## KEY FACT

The risk of brain herniation following an acute stroke is greatest in the first 24 to 72 hours, when cerebral edema peaks. In large MCA strokes and posterior fossa (cerebellar) strokes, neurosurgical decompression may be indicated.



## KEY FACT

In patients who survive the initial stroke, the leading causes of death are infection (UTI and aspiration pneumonia) and venous thromboembolism; thus, DVT prophylaxis is given.

**TABLE 13.10. Absolute Exclusion Criteria for tPA**

### EXAM OR HISTORY

- Head trauma or stroke within 3 months
- Suspicion of SAH
- History of intracranial hemorrhage
- Intracranial neoplasm, AVM, or aneurysm
- Active internal bleeding
- Recent intracranial or spine surgery

### LABS

- Platelets <100,000/mL
- INR >1.7
- PT >15 seconds

### IMAGING

- Hypodensity > one-third of the MCA territory on CT

**A****ANSWER**

Cerebellar infarction with classic symptoms of vertigo, ataxia, and headache along with developing signs of brainstem compression (intractable hiccups, altered mental status), indicating a need for more urgent intervention such as neurosurgical decompression.

**KEY FACT**

The most common side effect of ASA/dipyridamole is headache, which usually resolves even if the patient continues the medication.

**KEY FACT**

Do not administer tPA if patient is uncertain of time of stroke onset.

**KEY FACT**

There is no role for the closure of PFO, intracranial stenting, heparin, or anticonvulsants for the treatment of 1° or 2° stroke.

- Consider tPA if symptoms are within 3.0 to 4.5 hours' duration for patients who do not meet additional exclusion criteria of age >80 years, National Institutes of Health Stroke Scale score >25, diabetes with previous stroke, or any anticoagulant use.
- Withhold all antiplatelet/anticoagulant agents and repeat CT or MRI at 24 hours before restarting. The 1° risk of tPA treatment is ICH.
- Serial neurological exam for 24 hours post tPA with BP goal of <180/105 mm Hg.
- **Anticoagulation with IV heparin or LMWH:** Only for acute ischemic strokes due to vertebral or carotid artery dissection.
- Thrombectomy:
  - Gold standard for ischemic stroke with large vessel occlusion (eg, ICA, MCA, ACA) within 6 hours of symptom onset.
  - Consider for posterior circulation stroke (eg, PCA) within 12 hours of symptom onset.
  - Can be performed in addition to tPA.
- 2° prevention of ischemic stroke recurrence:
  - **Antiplatelet medications:** ASA is first line in the acute phase, but for 2° prevention, clopidogrel and ASA/extended-release dipyridamole are equally viable options.
  - **Statins:** All ischemic stroke patients should receive a statin to ↓ stroke recurrence.
  - **BP control:** Allow for “permissive hypertension” unless patient has BP >220/120 mm Hg, acute coronary syndrome, or aortic dissection, or thrombolytic therapy is planned.
  - **Symptomatic internal carotid stenosis:** Carotid endarterectomy or stenting within 2 weeks of the stroke/TIA if ipsilateral carotid stenosis is >70%.
  - **Warfarin:** For 3 to 6 months in a patient with paradoxical embolism or left ventricular thrombus; indefinitely in a patient with paroxysmal or chronic AF.
- **Long-term prevention of ischemic stroke recurrence: Modification of 1° risk factors:** Primarily involves smoking cessation and aggressive control of hypertension, DM, and hyperlipidemia.

**HEMORRHAGIC STROKE****Intraparenchymal Hemorrhage****Symptoms**

In contrast to ischemic stroke, intraparenchymal hemorrhage is usually associated with **headache** and **rapid deterioration in level of consciousness**.

**Diagnosis**

- The leading cause of hemorrhagic stroke is **hypertension**. Hypertensive hemorrhages classically occur in four subcortical structures—**basal ganglia, thalamus, cerebellum, and pons (part of the brainstem)** (Figure 13.4).
- Intraparenchymal hemorrhages occurring within the cortex and underlying white matter (so-called **lobar hemorrhages**) can be caused by hypertension but raise suspicion for other etiologies, such as metastatic lesions, vascular abnormalities (eg, AVMs or aneurysms), hemorrhagic conversion of an ischemic stroke, infections (especially septic emboli), cocaine use, and cerebral amyloid angiopathy.

**Management**

- Most intraparenchymal bleeds are managed with supportive care—evidence does not support urgent evacuation. A study of surgical evacuation versus medical management for patients with ICH who appeared clinically stable up to 48 hours after onset showed no difference in mortality or functional outcomes.
- **Key exception is cerebellar hemorrhage:** Swelling and herniation onto the brain-



**FIGURE 13.4. Intracerebral hemorrhage.** Noncontrast head CT shows an intraparenchymal hemorrhage and surrounding edema in the left basal ganglion in a patient with uncontrolled hypertension. (Reproduced with permission from USMLE-Rx.com.)

stem can be lethal, and thus bleeds in this location may require emergent surgical decompression.

■ Special management considerations:

- To normalize elevated BP: Target systolic BP to <160 mm Hg with use of nifedipine or labetalol.
- To normalize ICP: Mannitol, hypertonic saline, hyperventilation, and barbiturate coma.
- Intraventricular hemorrhage: Portends poor prognosis; requires immediate ventricular drainage to reduce ICP.
- Reversal of coagulopathy: Rapid reversal is achieved preferably with prothrombin complex concentrate (PCC) along with IV vitamin K as the effect of PCC alone is transient.
- Other options include fresh frozen plasma and IV vitamin K alone.
- Protamine is recommended for heparin-associated ICH.

### KEY FACT

The risk of spontaneous ICH ↑ with an INR of >4 but may occur at a lower INR, especially in elderly patients. The lack of headache and normal BP do not rule out hemorrhage.

## Extraparenchymal Bleeds

The three types of extraparenchymal ICHs are **epidural**, **subdural**, and **subarachnoid**. The most common cause of all extraparenchymal ICHs is **head trauma**. The various types of traumatic head injury are compared in Table 13.11.

### Epidural Hematoma

Typically caused by trauma to the temporal bone resulting in injury to the **middle meningeal artery**. Such hematomas can expand rapidly, as they are produced by **arterial bleeding**.

■ **Symptoms/Exam:**

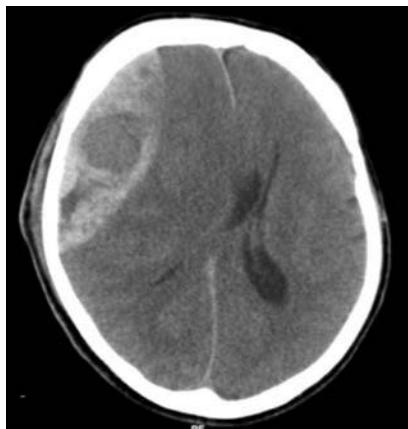
- Transient LOC followed by a “lucid period” before a rapid neurological decline is uncommon.
- Headaches.
- Ipsilateral pupillary dilation indicates uncal herniation.
- **Diagnosis:** Since the dura is tacked down to the skull at the suture lines, epidural bleeds will tamponade in a confined space and will not cross the sutures, leading to the characteristic “**lens-shaped**” **hematoma on CT scan** (Figure 13.5).
- **Management:** Symptomatic epidural hematomas must be treated with urgent neurosurgical decompression. Death can occur within hours.

### Subdural Hematoma

Subdural hematoma (Figure 13.6) is typically head trauma with injury to the cerebral bridging veins between the cortex and dura. Most often seen in **elderly patients on anticoagulation** who have **falls**. Spontaneous subdural hematomas may occur in patients with underlying coagulopathy or thrombocytopenia.

**TABLE 13.11. Various Types of Head Injury**

INJURY TYPE	PRESENTATION	CT FINDINGS	TREATMENT	COMMENTS
Concussion	LOC, headaches, dizziness, nausea, vomiting	Normal	None	Avoid athletic games/activities until asymptomatic
Contusion	LOC, headaches, dizziness, nausea, vomiting	Bruising, swelling, hematoma	None	Avoid athletic games/activities until asymptomatic
Epidural hematoma	LOC, headaches, lucid interval, rapid neurological decline	Convex layer of blood	Emergent surgical decompression	Middle meningeal artery with rapid hematoma expansion
Subdural hematoma	Gradual ↑ in confusion, LOC	Concave layer of blood	Emergent surgical decompression	Bridging cerebral vein injury; seen in elderly patients or alcoholics

**FIGURE 13.5. Epidural hematoma.**

(Source: Wilson MH, et al. Emergency burr holes: "How to do it." *Scand J Trauma Resusc Emerg Med*. 2012;20:24.)

A

**ANSWER 1**

Conventional angiography, as the patient has an intracerebral (intraparenchymal) hemorrhage with an extensive subarachnoid (extraparenchymal) hemorrhage, which is the hallmark of a ruptured AVM but can occur with ruptured MCA aneurysms as well. Angiography not only establishes the diagnosis but helps plan treatment via endovascular coiling or the surgical clipping approach, ideally within 72 hours of symptoms.

A

**ANSWER 2**

Cerebral amyloid angiopathy. Despite the name, systemic amyloidosis is absent in patients with this diagnosis.

**KEY FACT**

Within the first 72 hours, up to 10% of SAHs are not seen on CT, underscoring the importance of LP following imaging if the diagnosis is suspected. After 72 hours, the rate of  $\ominus$  CT scans  $\uparrow$  substantially.

**KEY FACT**

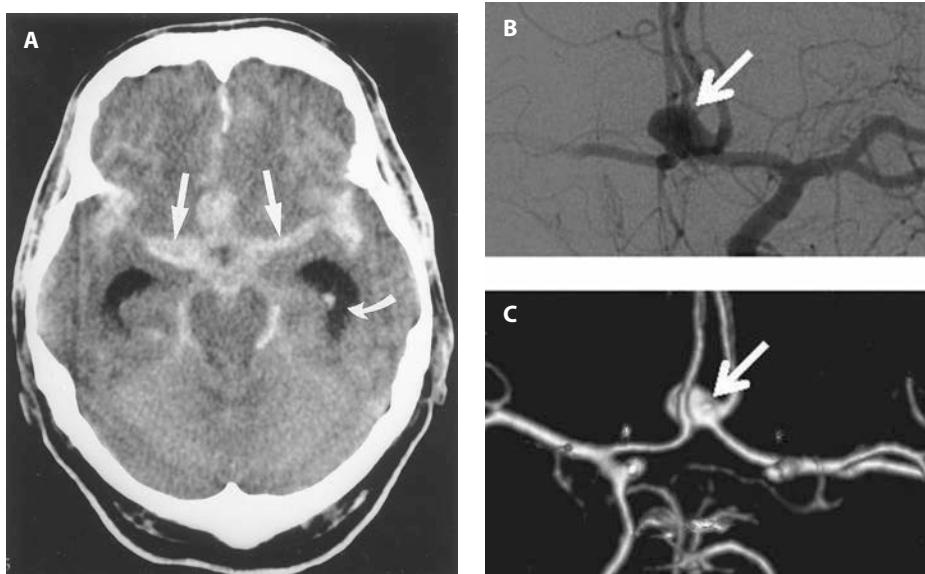
Subarachnoid hemorrhages should raise suspicion for an underlying AVM or brain aneurysm.

**FIGURE 13.6. Bilateral subdural hematoma.** Noncontrast CT scan of the head with an acute right frontal subdural hematoma and an old left subdural hematoma. Note the classic crescent shape. (Reproduced with permission from USMLE-Rx.com.)

- **Symptoms/Exam:** Indolent decline in mental status as hematoma expand under venous pressure. May not have focal neurologic deficits.
- **Diagnosis:** Head CT reveals hematoma layering along the outer surface of the cerebral cortex (see Figure 13.6). Must be in the differential of any elderly patient with dementia.
- **Management:** As with epidural hematomas, symptomatic subdural hematomas require neurosurgical decompression.

**Subarachnoid Hemorrhage**

The most common cause of nontraumatic SAH is a **ruptured intracranial aneurysm** (Figure 13.7).

**FIGURE 13.7. Subarachnoid hemorrhage.** Noncontrast CT (A) showing SAH filling the basilar cisterns and sylvian fissures (straight arrows). The curved arrow shows the dilated temporal horns of the lateral ventricles/hydrocephalus. Coned-down images from a catheter angiogram (B and C) show a saccular aneurysm arising from the anterior communicating artery (arrow). (Image A reproduced with permission from Tintinalli JE, et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th ed. New York: McGraw-Hill, 2004, Fig. 237-4. Images B and C reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery*, 13th ed. New York: McGraw-Hill, 2010, Fig. 36-6.)

- Symptoms:** Patients experience abrupt-onset severe headache (“the worst headache of my life,” or “thunderclap” headache) that is often associated with nausea and vomiting. There may also be a ↓ level of consciousness, neck stiffness, and focal neurologic deficits.
- Diagnosis:** Head CT is the initial imaging study of choice (see Figure 13.7). If CT is normal, perform an LP to look for **xanthochromia**. Patients with a confirmed SAH should then have conventional **cerebral angiography** to identify potential underlying aneurysm.
- Management:** The first priority in managing aneurysmal SAH is to secure the aneurysm as soon as possible, as the risk of **rebleeding** is significant within the first 48 hours. Currently, aneurysms are treated with either **endovascular coiling** or **neurosurgical clipping**.
- In addition to rebleeding, complications include:
  - Vasospasm** of the cerebral vessels after clipping or coiling is performed: **Nimodipine**, which ↓ complications from vasospasm, is given to all patients with SAH and can be started on the first day and continued for 3 weeks. Vasospasm is also treated with “**triple-H therapy**” (Hypertension, Hypervolemia, and Hemodilution)—IV fluids and/or vasopressors to augment blood flow in areas of vasospasm. Transcranial Doppler is frequently used to identify sub-clinical vasospasm.
  - Obstructive hydrocephalus and hyponatremia from **cerebral salt wasting**.

## Coma Exam

**Coma** refers to a condition in which patients are unresponsive, show no purposeful movement, and do not open their eyes to painful stimuli. It requires the impairment of either **both cerebral hemispheres** or the reticular activating system of the **brainstem**. It is generally caused by one of four processes (Table 13.12).

Approach to the comatose patient:

- Evaluate brainstem function: Check cranial nerves (ie, pupillary response to light; extraocular movements of the eyes to either turning the head side to side [“doll’s

TABLE 13.12. Causes of Coma

PROCESS	EXAMPLES	FOCAL SYMPTOMS	MENINGISMUS	BRAINSTEM REFLEXES
<b>Structural</b>	Mass effect with herniation, stroke, SAH	Yes	Yes (SAH)	Abnormal due to mass effect
<b>Electrical</b>	Seizures	No, usually (but may have Todd's paralysis)	No	Normal
<b>Metabolic</b>	Anoxic brain injury, hepatic encephalopathy, severe electrolyte disturbances	No	No	Normal
<b>Infection</b>	Meningitis, meningoencephalitis	No	Yes	Normal

### KEY FACT

Screening for aneurysms among first-degree relatives of patients with SAH is not recommended.

### KEY FACT

Treatment of incidentally discovered unruptured aneurysms remains controversial. Incidental unruptured aneurysms <7 mm can be followed by MRI, but those with larger aneurysms should consider surgery.

### MNEMONIC

**RSVP for complications of SAH:**

**R**ebleed  
**S**eizures or salt wasting  
**V**asospasm  
**P**ressure ( $\uparrow$  ICP due to obstructive hydrocephalus)

### KEY FACT

Mental status deterioration after SAH can indicate hydrocephalus and warrants immediate CT scan with shunt placement, if hydrocephalus is present.

### KEY FACT

In a comatose patient, the presence of any brainstem reflex—eg, “doll’s eyes” or corneal reflexes—means that brainstem function is still intact.

### KEY FACT

In a hospitalized patient with unexplained coma despite an extensive evaluation, consider subclinical status epilepticus and obtain an EEG.

**KEY FACT**

The triad of brain death includes coma, absence of brainstem reflexes, and apnea. Perform an apnea test in a comatose patient suspected of having brain death.

**KEY FACT**

Some states require that an episode of loss of awareness be reported to government authorities, either to the department of health or to the DMV.

**KEY FACT**

Juvenile myoclonic epilepsy is a common idiopathic generalized seizure that presents with morning myoclonus (eg, tremors or jitteriness) or tonic-clonic seizure.

eyes”] or placing cold water in one ear) as well as corneal reflexes, gag reflex, cough reflex, and spontaneous respirations.

- **Look for abnormal posturing** (Figure 13.8): Indicates large ↑ in ICP and/or impending herniation from severe brain injury.
- Differentiate coma from other states of impaired consciousness (Table 13.13).

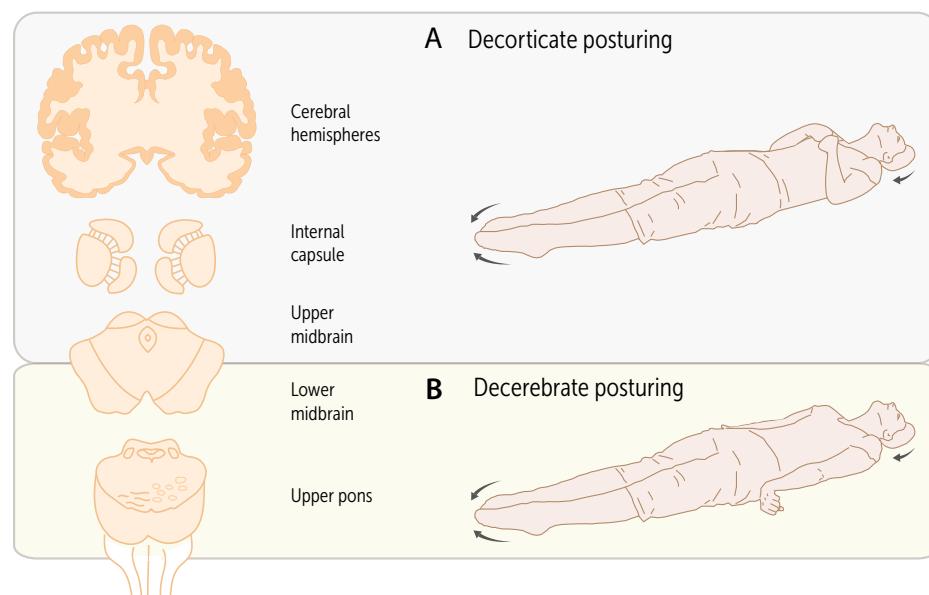
## Seizures

A **seizure** is a paroxysmal neurologic event caused by abnormal, synchronous discharges from populations of cortical neurons. Symptoms can vary widely and can include overt convulsions, subtle alterations of consciousness (eg, staring spells), or simple sensations (eg, odd smells or sounds). **Epilepsy** is a condition in which patients have **unprovoked recurrent seizures**. The key step in diagnosis and treatment is to determine whether the initial seizure activity is **generalized** or **focal** in onset.

### 1° GENERALIZED SEIZURES

Originate with abrupt-onset, simultaneous, synchronized discharges of neurons throughout both cerebral hemispheres. Selected subtypes are as follows:

- **Tonic-clonic (grand mal):** Associated with metabolic derangements (eg, hyponatremia, alcohol withdrawal, medications, CNS infections). Presents with extremities stiffness followed by rhythmic jerks, urinary incontinence, tongue biting, and postictal confusion.



**FIGURE 13.8. Decorticate and Decerebrate postures.** (A) Decorticate posturing (**injury above the red nucleus**). Damage to the upper midbrain, internal capsule, and cerebral hemispheres may cause **decorticate** posturing in which the upper limbs are flexed, the lower limbs are extended with the toes pointed slightly inward, and the head is extended. The prognosis is poor in both, although upper pontine damage carries a poorer prognosis than upper midbrain damage. (B) **Decerebrate posturing (injury to the brainstem below the red nucleus)**. Damage to the lower midbrain and upper pons causes **decerebrate** posturing in which the lower extremities are extended with the toes pointed inward and the upper extremities are extended with the fingers flexed and the forearms pronated. The neck and head are extended. (Reproduced with permission from USMLE-Rx.com.)

**TABLE 13.13.** Differentiating Coma From Other States of Impaired Consciousness

STATE	SELF-AWARENESS	MOTOR FUNCTION	BRAINSTEM REFLEXES	RESPIRATORY DRIVE	COMMENTS
Coma	No	No purposeful movements	Intact	Intact	Can fully recover or evolve into a persistent vegetative state
Persistent vegetative state	No	No purposeful movements	Intact	Intact	Becomes permanent 3 months after nontraumatic cause or 1 month after traumatic cause
Locked-in syndrome	Yes	Quadriplegia Eye movement is preserved	Intact	Intact	Infarction of the pontine Recovery is unlikely
Brain death	No	Absence of all motor movement	None	None	Order brain death exam (which includes apnea test)

- Myoclonic:** Associated with **uremia** and **anoxia** and is characterized by sudden, brief contraction of one or several muscles.
- Atonic:** Characterized by the abrupt loss of all muscle tone associated with a brief LOC that resemble syncope. Primarily seen with inherited forms of childhood epilepsy.
- Absence seizures (petit mal):** Characteristically causes sudden staring with impaired consciousness that usually last for 5 to 10 seconds and not associated with a postictal confusion.

### Symptoms/Exam

Although symptoms can vary, most generalized seizures are associated with a period of postictal confusion and lethargy generally lasting <2 to 5 minutes.

### Diagnosis

- Labs:** Routine evaluation includes a basic metabolic panel, liver chemistry panel, ECG, urine toxicology, alcohol level, and antiepileptic level in patients already on antiepileptic drugs (AEDs).
- LP:** Should be considered when an infection or inflammation is a concern.
- Imaging:** Brain MRI to investigate for structural abnormalities, particularly in the temporal lobes.
- EEG:** Obtained prior to and during a seizure may show symmetric and synchronous generalized epileptiform discharges at the onset.

### Management

- First-line treatment for generalized seizures is “broad-spectrum” anticonvulsant: **valproic acid**, topiramate, levetiracetam, zonisamide, or lamotrigine.
- Long-term treatment with anticonvulsant is an individualized decision.
- For the two unique types of generalized epilepsy: **Juvenile myoclonic epilepsy** is best treated with **valproic acid**, and **absence epilepsy** is classically treated with **ethosuximide**.
- Surgery evaluation is reserved for patients with treatment failure after ≥2 anticonvulsants.



### KEY FACT

Pseudoseizures vary in presentation but can present with moaning, crying, and arrhythmic shaking of the body for >10 minutes without LOC and with a normal EEG. Video or ambulatory EEG is the gold standard for diagnosis. Psychiatry should be consulted, as anxiety is often a major contributing factor. About 30% of patients have a history of epilepsy.



### KEY FACT

Phenytoin and carbamazepine are **not** first-line agents for 1° generalized seizures and may exacerbate seizures in generalized epilepsy. Both also ↓ warfarin levels. These agents may be helpful when 2° generalized tonic-clonic seizures are suspected (eg, from a mass lesion in the brain).



### QUESTION

A 20-year-old college student is brought to the ED from a party because he is febrile, hypertensive, tachycardic, and combative. He then has a generalized tonic-clonic seizure for about 2 minutes. His labs and head CT are normal. What is the most likely cause of his seizure, and what would be the most appropriate therapy?

**KEY FACT**

Many anticonvulsants are associated with early osteoporosis, so early screening and prevention are key.

**KEY FACT**

Patients of Asian heritage should be tested for the **HLA-B\*1502 allele** since there is an ↑ risk of hypersensitivity reaction with carbamazepine, lamotrigine, oxcarbazepine, and phenytoin with this genotype.

**KEY FACT**

If a patient taking phenytoin or carbamazepine develops transaminitis and rash (and possibly acute kidney failure and eosinophilia), suspect anticonvulsant hypersensitivity syndrome and discontinue the medication immediately.

**KEY FACT**

Lamotrigine, followed by levetiracetam, are relatively low in teratogenicity and thus are good options for pregnant women.

**Complications**

Table 13.14 outlines the side effects associated with common anticonvulsants used for seizure treatment. Other medication-related complications are as follows:

- **Anticonvulsants** (phenytoin and carbamazepine) can ↓ efficacy of OCPs and warfarin. Alternative birth control methods are recommended.
- **Anticonvulsants are teratogenic** with ↑ risk of neural tube defects. Treatment with single anticonvulsants and folate supplement are recommended for pregnant women.

**FOCAL (PARTIAL) SEIZURES**

Much more common than 1° generalized seizures, focal seizures originate from a small, discrete focal lesion within the brain that gives rise to abnormal synchronized neuronal discharges. This activity may then spread to involve other areas of the brain. Subtypes are as follows:

- **Simple focal seizures:** Focal seizures in which **no alteration of consciousness** is noted. Initial symptoms (aura) depend on the location of the seizure focus and can be thought of in three different patterns:
  - Motor: One-sided jerking or head turning.
  - Sensory (eg occipital cortex): Sensation of strange smell or sounds, visual disturbance, tingling.
  - Autonomic (eg, temporal lobe): Epigastric sensation, facial flushing, déjà vu, sensation of fear.
- **Complex focal seizures:** Begin with **stereotypical warning or aura** that progresses to **impairment of consciousness, behavioral arrest, and automatisms** (eg, lip smacking, chewing, pulling at clothes) that results in **postictal confusion**.
- **Complex focal seizures with 2° generalization:**
  - Patients with prolonged complex focal seizures can progress to 2° generalized seizures that manifest as tonic-clonic activities.
  - **Temporal lobe epilepsy:** The most common cause of simple and complex focal seizures is **temporal lobe pathology**, most commonly due to abnormalities of the **hippocampus**. Hippocampal sclerosis/calcification is seen on imaging. The classic auras of odd smells, sounds, or tastes are associated with temporal lobe epilepsy.

**Diagnosis**

Given that focal seizures arise from focal lesions, brain imaging studies are typically abnormal; EEG often shows localized (ie, asymmetric) epileptiform activity. HSV encephalitis should be considered in patients with new-onset temporal lobe seizures.

**TABLE 13.14. Classic Anticonvulsant Side Effects**

DRUG	SIDE EFFECTS
Phenytoin	Gum hyperplasia, ataxia, confusion, peripheral neuropathy, lymphoproliferative disorder, <b>Stevens-Johnson syndrome (SJS), severe hypersensitivity syndrome</b>
Carbamazepine	Hyponatremia, lymphopenia, <b>aplastic anemia, SJS, severe hypersensitivity syndrome</b> ; induces its own metabolism, the initial dose can then become ineffective
Valproate	Tremor, drowsiness, weight gain, hirsutism, <b>thrombocytopenia, liver failure</b>

**ANSWER**

Cocaine intoxication causing a sympathetic surge (tachycardia, hypertension, hyperthermia, mydriasis, agitation, and psychosis). The patient should receive sedation with lorazepam IV or IM to control agitation (↓ heart rate, BP, and temperature). Drug-induced seizures are usually self-limited and do not respond well to phenytoin, while haloperidol lowers the seizure threshold and should not be used for agitation in this patient.

## Management

- Anticonvulsants such as **phenytoin, carbamazepine, and lamotrigine** are the best treatment option. Other agents include lacosamide, valproic acid, zonisamide, levetiracetam, oxcarbazepine, and topiramate. In elderly patients, **gabapentin, lamotrigine, levetiracetam, and carbamazepine** are equally effective at controlling partial-onset seizures, but levetiracetam and lamotrigine are better tolerated.
- **Surgical resection** of the causative lesion (eg, temporal lobectomy) in refractory cases (three trials of anticonvulsants) and can produce striking results, with up to 50% to 75% of patients becoming seizure free.

## STATUS EPILEPTICUS

Ongoing or recurrent seizure activity lasting >5 minutes is considered a medical emergency and is treated as status epilepticus. Seizure activity lasting >5 minutes is unlikely to remit spontaneously and carries the risk of permanent neuronal injury.

Management requires concurrent resuscitation efforts and urgent pharmacotherapy.

- Stabilization (Airway, Breathing, and Circulation, neurology exam).
- Time seizure from onset, monitor vital signs.
- Assess oxygenation.
- Finger stick blood glucose: If <60 mg/dL, then for adults administer IV thiamine; for children, administer IV dextrose.
- ECG monitoring.
- Labs: Electrolytes, hematology, toxicology screen and anticonvulsant drug levels (if appropriate).
- Pharmacotherapy:
  - A **benzodiazepine** is first line: IV lorazepam, IM midazolam, or IV diazepam. Other options if initial therapies are not available include IV phenobarbital, rectal diazepam, and intranasal midazolam.
  - If seizures persist: IV fosphenytoin, IV valproic acid, or IV levetiracetam is an acceptable second therapy option. If none of these are available, IV pentobarbital may be used if not already given.

## Movement Disorders

### HYPOKINETIC DISORDERS

#### Parkinson Disease

Parkinson disease is an idiopathic progressive neurodegenerative disorder affecting the dopaminergic neurons of the substantia nigra (Figure 13.9). Average age of onset is 60 years; the male-to-female ratio is 1.5:1.

#### Symptoms/Exam

- The **cardinal features** are **resting tremor** (“pill rolling”), **bradykinesia**, “cogwheel” **rigidity**, and **postural instability** (see the “**TRAP**” mnemonic).
- Symptoms typically begin **asymmetrically**, usually in one extremity. Gait and balance problems are typically not present early on. Dementia develops late in the course in 30% to 40% of patients.

#### Differential

- Parkinson-plus syndromes present with parkinsonian features as well as with additional symptoms (see below).

### KEY FACT

A patient with a generalized tonic-clonic seizure who is subsequently noted to have a postictal left hemiparesis—aka postictal **Todd's paralysis**—likely had a focal-onset seizure that began in the right hemisphere and secondarily generalized.

### KEY FACT

In a patient who reports recurring bursts of anxiety, abdominal discomfort, odd smells, sounds, or tastes, suspect temporal lobe epilepsy and consider evaluating for HSV encephalitis.

### KEY FACT

The treatment of choice for status epilepticus is IV lorazepam. For patients with prior status epilepticus, lorazepam administered by rectal gel may be helpful and can be administered by family members.

### QUESTION 1

A 20-year-old woman with epilepsy asks if she can discontinue her carbamazepine. Her first generalized tonic-clonic seizure occurred at age 10 and was preceded by a complex focal seizure, with an EEG showing focal slowing in the right temporal lobe. Initial treatment with phenytoin was discontinued after 2 months because she felt fatigued. Carbamazepine was then started, but she continued to have complex focal seizures until the dose was ↑. She has now been seizure free for 1 year. Her physical exam and brain MRI are normal. What is the most appropriate treatment option?

### QUESTION 2

A 75-year-old woman presents with a left upper extremity tremor of 2 years’ duration. She is left handed. The tremor occurs when she is walking and at rest. She says she drops things, her handwriting has become smaller, and she needs help dressing. On exam, she has hypophonic speech, ↓ facial expression, slowness, rigidity, and ↓ arm swinging on the left side, but with normal balance. What is the most appropriate course of management?

**KEY FACT**

Parkinsonism with **early dementia and hallucination** is typical of dementia with Lewy bodies and not classic Parkinson disease.

**MNEMONIC**

**Parkinson features: Requires two of the four symptoms—**

**TRAP**

Tremor  
Rigidity  
Akinesia  
Postural instability

**KEY FACT**

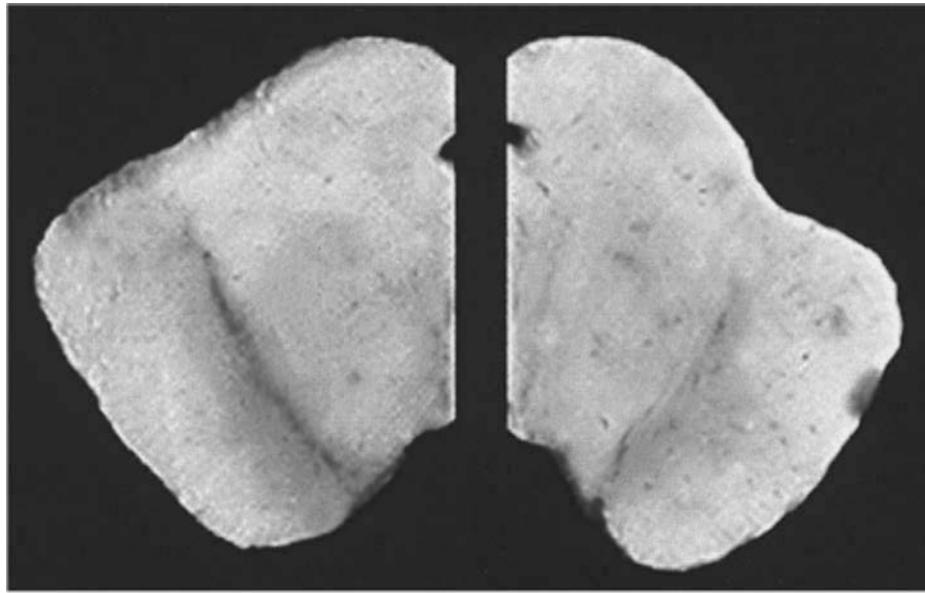
In Parkinson patients <70 years of age, dopamine agonists (pramipexole or ropinirole) are first-line treatments.

**A****ANSWER 1**

Continue carbamazepine at the current dose. Epileptic patients who are most likely to remain seizure free after medication withdrawal are those with no structural brain lesion, normal EEGs, a sustained seizure-free period (2-5 years), and no abnormalities on neurologic exam.

**A****ANSWER 2**

For patients >70 years with Parkinson disease manifested by typical features of tremor, rigidity, masked facies, bradykinesia, hypophonic speech, and small handwriting, carbidopa/levodopa is first-line treatment. COMT inhibitors and dopamine agonists (pramipexole or ropinirole) are second-line treatments in this age group.



**FIGURE 13.9. Parkinson disease.** Midbrain sections of a normal (left) and a Parkinson disease brain (right). Note the depigmentation in the substantia nigra in the ventral midbrain. (Source: Mazzio EA, et al. The biochemical and cellular basis for nutraceutical strategies to attenuate neurodegeneration in Parkinson's disease. *Int J Mol Sci.* 2011;12(1):506-569.)

- Other causes of parkinsonism include cerebrovascular disease, recurrent head trauma (eg, boxing), toxin exposure (including illicit drugs such as MPTP and heavy metals such as manganese), and antidopaminergic medications (eg, traditional anti-psychotics, metoclopramide).

**Diagnosis**

The diagnosis of idiopathic Parkinson disease relies on the history and physical combined with response to levodopa. Young patients as well as those with atypical features should undergo further workup (eg, imaging studies, toxin screens).

**Management**

Physical therapy is encouraged in all patients. The various pharmacologic treatments are discussed below. Surgical treatment options primarily include deep brain stimulation of the globus pallidus interna nucleus or subthalamic nucleus of the basal ganglia after failure of medical therapy.

**Levodopa/carbidopa:**

- The gold standard for symptomatic treatment, and first-line treatment in patients >70 years with new-onset Parkinson disease and functional impairment.
- Extensive use is associated with dyskinesia and “wearing off” phenomenon.
- A second-line agent for patients <70 years and when unresponsive to dopamine agonists.

**Dopamine agonists:**

- Pramipexole, pergolide, bromocriptine, or ropinirole can be used as initial monotherapy in patients <70 years.
- Slightly less effective than levodopa, but like COMT inhibitors, they are useful adjuncts for maintaining steady dopamine levels.
- Can cause psychosis and impulse problems (eg, hypersexuality, gambling).
- Should be avoided in patients >70 years or with dementia.

**COMT inhibitors:** Inhibition of this enzyme ↑ endogenous dopamine levels. Entacapone, tolcapone, and nitecapone are useful adjuncts as “levodopa extenders” to prevent the “wearing off phenomenon” of levodopa/carbidopa. Can be hepatotoxic.

- MAO-B inhibitors:** Selegiline and rasagiline are examples, but they have a weak symptomatic effect and are generally added to levodopa to diminish motor fluctuations, or can be used as first line for mild symptoms. Can cause sleep disturbance.
- Anticholinergics:** Trihexyphenidyl, biperiden, and benztropine. Useful for tremor and rigidity in early stages or as an adjunct to levodopa in patients <65 years. Can worsen psychosis.
- Amantadine:** First-line therapy in the elderly patient with mild tremor, bradykinesia, dyskinesia, rigidity, and fatigue. Can worsen psychosis.
- TCAs:** Can be used for nighttime sedation and associated depression.

### Parkinson-Plus Syndromes

A number of neurodegenerative diseases produce parkinsonian features along with a variety of other symptoms, including cognitive decline and cerebellar abnormalities (Table 13.15). In general, Parkinson-plus syndromes respond poorly if at all to levodopa. A Parkinson-plus syndrome should thus be considered in **any patient who presents with parkinsonism associated with cerebellar or cognitive symptoms**, especially when the parkinsonian features do not respond to levodopa therapy.

### HYPERKINETIC DISORDERS

#### Huntington Disease

An **autosomal dominant** disorder characterized by progressive **chorea**, **dementia**, and **psychiatric** symptoms. Huntington disease is a neurodegenerative disorder that particularly affects the caudate nucleus of the basal ganglia and is caused by a polyglutamine (**CAG**) **trinucleotide repeat expansion** in the Huntington gene on **chromosome 4**. This repeat can expand with successive generations, leading to the phenomenon of **anticipation**—earlier age of onset and more severe symptoms in successive generations.

#### Diagnosis

- The clinical presentation combined with a strong family history suggests the disease.
- CT/MRI show marked **atrophy of the caudate nucleus** and exclude other structural abnormalities (Figure 13.10).
- Genetic testing now provides definitive evidence of the trinucleotide (CAG) repeat expansion.

TABLE 13.15. Clinical Features of Parkinson-Plus Syndromes

SYNDROME	KEY FEATURES
Dementia with Lewy bodies	Cognitive decline; visual hallucinations; marked daily fluctuations in mental status due to cholinergic deficiency
Progressive supranuclear palsy	Cognitive decline; extraocular abnormalities, especially vertical gaze; prominent rigidity of the entire body, leading to frequent falls
Corticobasal degeneration	Cognitive decline; “alien limb” phenomenon; limb apraxia (inability to perform learned motor tasks such as brushing teeth or saluting)
Multiple-system atrophy	Encompasses a group of Parkinson-plus syndromes; autonomic dysfunction, especially <b>orthostatic hypotension</b> , may occur early; ataxia is common in the cerebellar form

#### KEY FACT

Combining selegiline with TCAs or SSRIs can potentially lead to serotonin syndrome.

#### KEY FACT

Treat Lewy body dementia with cholinergic medications (donepezil, galantamine, or rivastigmine) to alleviate the characteristic inattention, hallucinations, agitation, and fluctuating encephalopathy. Neuroleptics (eg, haloperidol and quetiapine) should be avoided, as they can cause severe parkinsonism and neuroleptic malignant syndrome in these patients.

#### KEY FACT

Huntington disease may manifest earlier in successive generations within families—the so-called anticipation phenomenon—as a result of expansion of the trinucleotide CAG repeats.

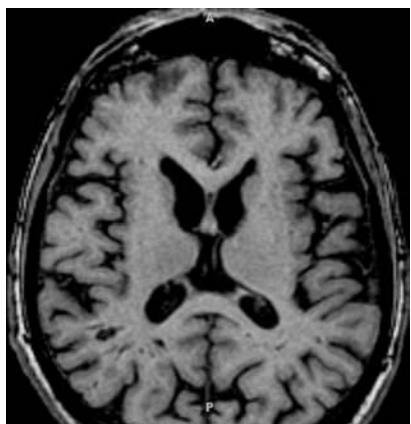
#### KEY FACT

Genetic counseling is indicated for children of patients with Huntington disease. For interested family members, testing for CAG repeats provides definitive evidence of Huntington.



#### QUESTION

A 70-year-old man complains of light-headedness, two episodes of fainting, imbalance, and frequent falls over the past 2 years. He also has urinary incontinence, constipation, and impotence. On exam, BP is 120/80 mm Hg and pulse is 70/min while lying down, and 85/55 mm Hg with no change in pulse while standing up. He has impaired gait, balance, and fine motor movements bilaterally along with mild rigidity. DTRs are brisk bilaterally, and extensor plantar response is present bilaterally. What is the most likely diagnosis?



**FIGURE 13.10. Cerebral and caudate nucleus atrophy in Huntington disease.**

MRI revealing atrophy of the caudate nuclei with right greater than left resulting in dilation of the frontal horns of the lateral ventricle. (Reproduced with permission from USMLE-Rx.com.)

### Management

- No treatment is currently available for the underlying disease process.
- Chorea can be treated symptomatically with neuroleptics (eg, haloperidol), dopamine-depleting agents (eg, reserpine, tetrabenazine), and GABAergic agents (eg, clonazepam).

### WILSON DISEASE

An **autosomal recessive** disorder characterized by progressive neuropsychiatric symptoms and liver dysfunction. Wilson disease is due to copper deposition most prominently occurs in the liver and basal ganglia (specifically the lentiform nuclei) of the brain.

- **Symptoms/Exam:** Suspect in an adolescent or young adult with liver dysfunction and neuropsychiatric illness, who may have a  $\oplus$  family history (autosomal recessive). Patients have:
  - Prominent extrapyramidal symptoms (tremor, dystonia, rigidity, bradykinesia) and cerebellar symptoms (ataxia, incoordination, slurred speech); common psychiatric symptoms include depression, psychosis, and personality changes.
  - **Kayser-Fleischer rings** on slit lamp evaluation.
- **Diagnosis:** Gold standard is liver biopsy, which reveals excess copper deposition. Also supported by:
  - Laboratory evidence of low serum copper and ceruloplasmin and high urinary copper.
  - On brain MRI, look for the “Panda Sign” (high T2 signal in the midbrain, red nuclei, basal ganglia, and substantia nigra).
- **Management:** First-line treatment is **penicillamine**, a copper-chelating agent, although side effects are common. For instance, a **myasthenia gravis syndrome** with titers of anti-ACh receptor antibodies can be induced by penicillamine therapy. Other treatment options include trientine and oral zinc.

### Essential Tremor

An idiopathic postural and action tremor that typically affects the **hands and head**. Tremor onset may occur early between 35 and 45 years of age. Family history is often strongly  $\oplus$ .

- **Symptoms/Exam:**
  - In contrast to Parkinson, essential tremor comes out with activity in the outstretched arm position and is slightly faster in frequency.
  - **Striking improvement** in tremor with **alcohol** ingestion and markedly worse with physical/emotional stress, caffeine, and steroids.
- **Diagnosis:** Based on clinical features.
- **Management:** The classic treatments are  **$\beta$ -blockers** (eg, **propranolol**) and **primidone**. Benzodiazepines and gabapentin have also been used when first-line treatments fail.



### ANSWER

Multiple-system atrophy (formerly known as Shy-Drager syndrome), which is characterized by orthostatic hypotension, neurogenic bladder, constipation, and impotence with gait-predominant parkinsonism and corticospinal tract signs.

### Tourette Syndrome

A disorder characterized by **brief involuntary actions (motor and vocal tics)** and psychiatric disturbances. Onset typically occurs in adolescents <18 years, with a **male-to-female ratio of 5:1**.

- **Symptoms/Exam:**
  - **Motor tics** can be simple (eg, eye twitching, blinking, shoulder shrugging) or complex (eg, mimicking another's actions, or **echopraxia**).

- Vocal tics can be simple sounds (eg, barking) or single words; classic vocal tics include speaking obscenities (**coprolalia**) and mimicking another's speech (**echolalia**), although neither is common. Tics are often exacerbated by physical or emotional stress.
- Associated neuropsychiatric disorders include **OCD** and **ADHD**.
- **Management:** Neuroleptics (eg, haloperidol, risperidone), **pimozide**, **clonidine**, and **benzodiazepines** (eg, clonazepam, diazepam) are indicated when tics cause occupation or social disturbances. Mild cases can be managed by reassurance, cognitive behavioral therapy, and treatment of psychiatric comorbidities.

## Dystonia

Dystonia is characterized by painful **twisting/writhing movements** and/or **abnormal tonic postures** of the head or extremities. Etiologies include inherited/genetic, neurodegenerative disorders (eg, Huntington, Wilson, Parkinson), rheumatologic disease (eg, SLE, antiphospholipid syndrome), metabolic conditions (eg, thyroid disease), and toxin exposure/medication use (eg, **neuroleptics**, OCPs).

- **Symptoms/Exam:** Can be focal or generalized. Focal dystonias most commonly include those that involve the musculature of the neck (**torticollis**), eyes (**blepharospasm**), and hands ("writer's cramp").
- **Management:** Treat **focal** dystonia with **selective injection of botulinum toxin** every 3 to 6 months for abnormal posture and associated pain. Other 1° treatments include trihexyphenidyl, clonazepam, or baclofen. For **generalized** dystonia, stop the offending medication and treat with **anticholinergics** such as benzotropine or diphenhydramine acutely. Deep brain stimulation may be effective for refractory cases.

## Restless Leg Syndrome

Uncomfortable paresthesia of the legs that is relieved by leg movement and worsens at night upon going to bed is known as restless leg syndrome. Generally idiopathic, but also seen in patients with a wide variety of chronic illnesses (eg, Parkinson, **iron deficiency anemia**, **uremia**, diabetes, COPD, thyroid disease, connective tissue diseases, neuropathies) and as a side effect of drugs (eg, caffeine, SSRI, lithium, calcium channel blockers).

- **Symptoms/Exam:**
  - Paresthesia ("crawling" or "creeping" sensation) is most severe when the legs are **at rest** or when the patient is falling asleep, but is **relieved by continued leg movement**.
  - Patients may also have periodic limb movements of sleep (PLMS)—frequent stereotypical leg movements.
- **Management:**
  - Before initiating treatment, it is essential to **check serum iron studies**. Oral iron therapy can alleviate symptoms and is recommended if serum ferritin levels are <45 ng/mL.
  - First-line medications are **dopaminergic medications** administered before bedtime (eg, **pramipexole**, **ropinirole**, or **rotigotine patch**). Other useful agents include levodopa, carbamazepine, **benzodiazepines**, **narcotics**, and **gabapentin**.

### KEY FACT

In a patient with hand tremors that are most prominent when the arms are extended and improve with alcohol (and worsen with stress and caffeine), suspect essential tremor. The family history is usually  $\oplus$ , and head tremors may also occur. Treat with  $\beta$ -blockers first.

### KEY FACT

There is an  $\uparrow$  incidence of OCD and ADHD among patients with Tourette's.

### KEY FACT

Neuroleptics such as haloperidol can cause an acute dystonic reaction. Treat with anticholinergics.

### KEY FACT

In patients with restless leg syndrome, always check a serum ferritin level to assess for iron deficiency, a common reversible etiology.

### QUESTION

A 30-year-old man presents with constant involuntary movements of his hands for the past year along with personality change of 3 years' duration. He has been forgetting things and making mistakes at work. He had an episode of depression in his 20s, and his father had a history of substance abuse, having left the family when the patient was a child. On exam, the patient is noted to have brief, brisk, irregular, and unpredictable involuntary movements fleeting from one body part to another. What is the most likely diagnosis?

## Multiple Sclerosis

### KEY FACT

MS is a **clinical** diagnosis. The diagnosis is likely if patients report two or more clinically distinct episodes of typical neurologic symptoms.

### KEY FACT

Internuclear ophthalmoplegia in a young woman is highly suggestive of MS.

### KEY FACT

Consider MS in a young patient presenting with any of the following:

- Subacute loss of vision.
- Double vision when looking to one side.
- Electrical sensation running down the spine when the neck is flexed.
- Subacute spinal cord symptoms (eg, paresthesia and bowel/bladder dysfunction).
- Worsening of neurologic symptoms with heat or exercise.



### ANSWER

Huntington disease with characteristic dancing-like chorea. The patient's age, chronicity, and associated cognitive and psychiatric changes suggest this diagnosis.

Multiple sclerosis (MS) is an autoimmune inflammatory disease affecting the myelin of the CNS. It is characterized by focal demyelinating plaques that occur at different times and locations within the CNS ("separated in space and time"). Typically affects the optic nerves, corpus callosum, periventricular white matter, brainstem, and spinal cord. Generally seen in **younger women**. Incidence ↑ with latitude of birth and is twice as high in patients of Northern European descent as in those of African descent.

### Symptoms

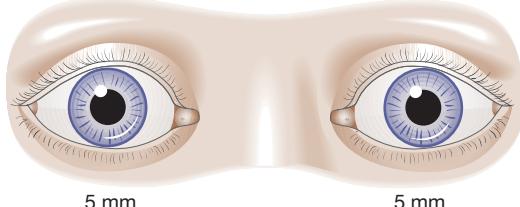
- In addition to focal abnormalities, patients often suffer from chronic **fatigue**.
- Symptoms may be **exacerbated by heat and exercise** (the Uhthoff phenomenon); old deficits may also be worsened by underlying illness, especially infections such as UTIs or URTIs.

### Exam

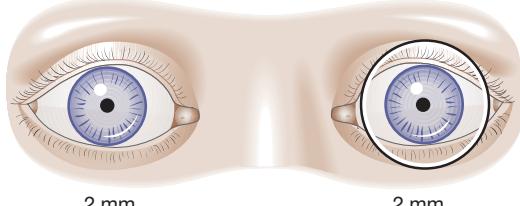
Classic lesions and exam findings include the following:

- **Optic neuritis:** Presents as unilateral subacute vision loss associated with pain with eye movement. Exam shows pallor of the optic nerve (may be normal in the acute setting), ↓ visual acuity, difficulty with color discrimination, and a **relative afferent pupillary defect** (also known as Marcus Gunn pupil; see Figure 13.11).
- **Internuclear ophthalmoplegia:** Demyelination of the medial longitudinal fasciculus that results in diplopia due to disconjugated lateral gaze with impaired adduction of the affected eye.

#### Diffuse illumination

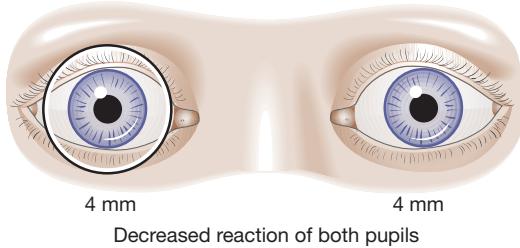


#### Light on normal eye



Normal reaction of both pupils

#### Light on eye with afferent defect



Decreased reaction of both pupils

**FIGURE 13.11. Afferent pupillary defect (Marcus Gunn pupil).** (Reproduced with permission from Riordan-Eva P, Whitcher JP. *Vaughn & Asbury's General Ophthalmology*, 17th ed. New York: McGraw-Hill, 2008, Fig. 14-32.)

- **Spinal cord:** Transverse myelitis symptoms (**paresthesia**, sensory level, bowel/bladder dysfunction, **UMN signs**) are common.
- **Lhermitte sign** (electrical radiation down the spine elicited by neck flexion) is a classic finding and is likely related to dorsal column involvement.

### Diagnosis

- **Clinical criteria:** MS is clinically heterogeneous. CSF is not needed for diagnosis but imaging is. Per the McDonald criteria, a diagnosis can be made with a combination of clinical history, physical exam findings, and evidence of lesions on imaging.
- **MRI:** Abnormalities are seen in >90% of patients (Figure 13.12). Most have multiple punctate/ovoid lesions involving the periventricular white matter (“Dawson’s finger” lesions extending from the ventricles at right angles), **corpus callosum**, brainstem, and spinal cord.
- **CSF:** Typical findings include pleocytosis (up to 50 WBCs/mm<sup>3</sup>), ↑ protein, ≥2 oligoclonal bands, and ↑ CSF IgG index.

### Management

- Acute flares: High-dose IV glucocorticoids (Solu-Medrol 1 g IV QD × 3-5 days) are typically used to treat acute attacks, but do not slow disease progression.
- **Disease-modifying therapies for relapsing-remitting MS:** Choice of therapy is rapidly evolving, taking into account aggressiveness of disease, side effects, and patient preference.
  - For aggressive forms of MS, natalizumab (if patient tests ⊖ for JC virus) or ocrelizumab.
  - For less aggressive disease, options include injectable interferons (Avonex, Betaseron) or glatiramer acetate (Copaxone)—known as the “ABC drugs.” If the patient is opposed to injections, options include oral dimethyl fumarate, fingolimod, and teriflunomide.
    - These drugs have been shown to ↓ the frequency and severity of relapses in patients with relapsing-remitting MS. Table 13.16 outlines the administration of the injectable ABC drugs and delineates their potential side effects. Table 13.17 covers the mechanisms and side effects of the newer agents.
- **Disease-modifying therapy for primary-progressive MS:** Ocrelizumab is a recombinant humanized anti-CD20 antibody that targets B-cells and is the only therapy shown to reduce the risk of disability in this form of MS.
- **Specific symptoms** are targeted with appropriate medications:
  - Hyperreflexic bladder: Oxybutynin, tolterodine.
  - Fatigue: Amantadine (first line), modafinil.



### KEY FACT

MRI with and without contrast is the imaging modality of choice for MS.



### KEY FACT

CSF testing is not required for diagnosis if the McDonald criteria have been met.



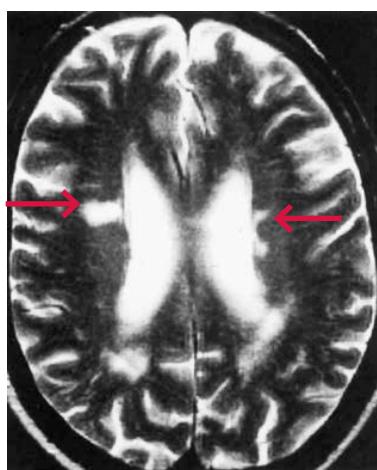
### KEY FACT

Vitamin D supplement is recommended for all MS patients as it has shown to reduce the number of MRI lesions.

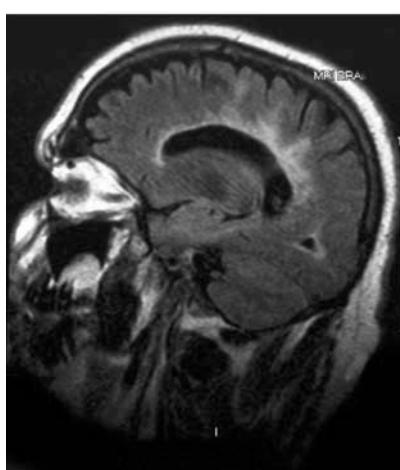


### QUESTION

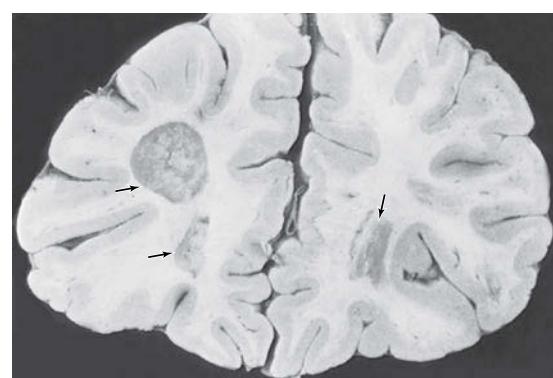
A 30-year-old woman comes to the clinic complaining of diplopia on lateral gaze in either direction that has worsened over the past week. Exam reveals paresis of the adducting eye with nystagmus of the abducting eye on horizontal gaze in either direction. MRI shows a hyperintense lesion on T2-weighted images within the pons as well as five hyperintense lesions in the cerebral white matter adjacent to the lateral ventricles. What is the diagnosis, and what long-term treatment should be considered?



**A**



**B**



**C**

**FIGURE 13.12. Multiple sclerosis.** T2-weighted MRI (A) and sagittal FLAIR image (B) show multiple MS plaques (arrows) in the periventricular matter oriented radially from the corpus callosum (“Dawson’s fingers”). (C) Areas of demyelination of the white matter (arrows) in the frontal lobe of a 54-year-old man with multiple sclerosis. (Images A and B reproduced with permission from Ropper AH, Samuels MA. *Adams & Victor’s Principles of Neurology*, 9th ed. New York: McGraw-Hill, 2009, Fig. 36-1. Image C reproduced with permission from Waxman SG. *Clinical Neuroanatomy*, 26th ed. New York: McGraw-Hill, 2010, Fig. 25-9.)

**KEY FACT**

Corticosteroids help produce faster recovery in acute flares of MS but have no impact on overall disease progression or long-term disability.

**KEY FACT**

Most patients with optic neuritis have good recovery within 6 months with or without treatment. The decision to use corticosteroids depends on patient preference, the severity of the visual deficit, the health of the other eye, and vocational requirements.

**A****ANSWER**

Bilateral internuclear ophthalmoplegia is classic for MS. With no prior history of neurologic problems, this is a clinically isolated presentation of demyelination. Disease-modifying therapy will ↓ the incidence of additional attacks in patients with monosymptomatic demyelination (including optic neuritis and myelopathy) who have multiple "silent" demyelinating lesions on brain MRI.

**MNEMONIC*****The 5 D's of myasthenia gravis:***

**D**iplopia  
**D**ysarthria  
**D**ysphagia  
**D**yspnea (respiratory muscle involvement)  
**D**escending weakness

**TABLE 13.16. Administration and Side Effects of "ABC Drugs"**

DRUG	ADMINISTRATION	SIDE EFFECTS
Interferon-β1a ( <b>Avonex</b> )	Weekly IM	Flulike symptoms, depression
Interferon-β1b ( <b>Betaseron</b> )	QOD SQ	Flulike symptoms
Glatiramer acetate ( <b>Copaxone</b> )	Daily SQ	Flushing, chest tightness

- Paroxysmal symptoms (eg, tonic spasms): Carbamazepine.
- Spasticity: Baclofen, diazepam, tizanidine.
- Limb tremor: Botulinum toxin.
- Psuedobulbar affect: Dextromethorphan-quinidine.
- Impaired mobility: Dalfampridine.

**Complications**

Interferon-β is associated with an ↑ risk of spontaneous abortions and low birth weight. Women taking immunomodulatory treatment for MS should use effective contraception or, if they want to become pregnant, should stop therapy several months before attempting to conceive.

**Neuromuscular Junction Disorders****MYASTHENIA GRAVIS**

Myasthenia gravis (MG) is an **autoimmune** disorder that is usually caused by autoantibodies to the nicotinic ACh receptor (nAChR), resulting in impaired transmission at the neuromuscular junction. Occurs in **young women** (ages 20-30 years) and **older men** (ages 50-70 years). Associated with other autoimmune diseases, particularly **thyroid** disorders. May be precipitated by aminoglycosides, procainamide, β-blockers, stress, and infection.

**TABLE 13.17. Selected Multiple Sclerosis Treatments**

MEDICATION	MECHANISM OF ACTION	SIDE EFFECT PROFILE
Natalizumab (injection)	Monoclonal antibody against adhesion molecule on activated T cell that prevents migration to the CNS; highly effective in reducing relapse	Risk of <b>progressive multifocal leukoencephalopathy (PML)</b> due to JC virus
Ocrelizumab (injection)	Monoclonal antibody against CD20+ cells	Infusion reactions ↑ in breast cancer
Alemtuzumab (injection)	Anti CD52 monoclonal antibodies that cause lysis of lymphocytes	Varicella vaccination is recommended before treatment Risk of autoimmune disease
Fingolimod (oral)	Sequesters activated lymphocytes in lymph nodes	Contraindicated in patients with complete heart block and requires cardiac monitoring with administration
Teriflunomide (oral)	Inhibits pyrimidine synthesis of rapidly dividing cells	May cause peripheral neuropathy
Dimethyl fumarate (oral)	Protects neurons against oxidative injury and promotes remyelination	Flushing and GI symptoms PML

## Symptoms/Exam

The hallmark is **fluctuating, fatigable weakness** classically affecting the **eye muscles**. There are two forms:

- **Ocular:** Isolated to the extraocular and eyelid muscles, yielding double vision and ptosis—an ice pack briefly placed on the affected eye will reduce ptosis. Extraocular muscle palsies are typically seen on lateral gaze.
- **Generalized:** Bulbar weakness, respiratory dysfunction, and limb weakness—repeated strength testing reveals easy fatigability of proximal muscles with preserved DTRs and sensation.

### KEY FACT

Myasthenia gravis is often associated with other autoimmune phenomena, such as thyroid disease, anemia from pure red cell aplasia, thymic hyperplasia, and thymomas.

## Differential

- Lambert-Eaton myasthenic syndrome (see Table 13.18).
- **Drug-induced MG:** Penicillamine can cause a reversible antibody-positive MG syndrome.
- **Botulism:** Typically presents with cranial nerve palsies, including the extraocular muscles. Patients have CSF pleocytosis and often absent reflexes.

## Diagnosis

- **Anti-nAChR antibodies:** Present in >80% of generalized MG and 50% of ocular MG cases.
- **Anti-MuSK antibodies:** Present in 20% of “seronegative” MG patients.
- **Tensilon test:** Symptom improvement with tensilon (edrophonium), a short-acting AChE inhibitor, is falling out of favor as a diagnostic test.
- **EMG/NCS:** Direct testing of the muscle with EMG/NCS remains the **best test for MG**. Repetitive nerve stimulation reveals a **decremental** motor response.

### KEY FACT

The side effects of pyridostigmine include ↑ secretions and diarrhea; at high doses, weakness can occur that may mimic a myasthenic crisis.

## Management

- **Mild cases:** AChE inhibitors (eg, pyridostigmine) may be used but should be discontinued if the patient is on ventilator support, as the ↑ secretions ↑ the risk of aspiration.
- **Moderate to severe disease:** Treat with **immunomodulators** such as glucocorticoids, cytotoxic drugs (azathioprine), plasma exchange, and IVIG.

**TABLE 13.18. Myasthenia Gravis vs Lambert-Eaton Myasthenic Syndrome**

CHARACTERISTIC	MYASTHENIA GRAVIS	LAMBERT-EATON MYASTHENIC SYNDROME
Antibody target channel	nAChR	Presynaptic voltage-gated calcium channel
Associated cancer	Thymoma	Small cell lung cancer
Eye muscle involvement	Yes	<b>No</b>
Autonomic symptoms	No	Yes
Reflexes	Normal	Hypoactive
Repetitive strength testing	Rapid fatigue	Initial improvement
Repetitive nerve stimulation	Decremental response	Initial enhancement
Sensory symptoms	No	Yes
Distribution of weakness	Descending	Ascending

### QUESTION

A 60-year-old woman has had intermittent left eyelid drooping, diplopia, dysarthria, and shortness of breath for a few weeks and inability to swallow for the past 2 days. Her symptoms worsen with fatigue and improve with rest. Exam shows left ptosis, incomplete abduction of both eyes, and weakness of the tongue, lower face, neck flexors, shoulder abductors, and hip flexors. Sensation and reflexes are normal. BMI is 22; FVC of 1.6 L. What is the appropriate treatment?

- **Thymectomy:** Patients require chest imaging to evaluate for thymic abnormalities, as 70% have hyperplasia and 10% have thymomas. Thymectomy is recommended for most patients <60 years of age with generalized MG.
- **Avoid precipitating medications:** Aminoglycoside,  $\beta$ -blockers, procainamide,  $\alpha$ -interferon, quinidine, and penicillamine.

### Complications

#### Myasthenic crisis:

- Presents with weakness with impending respiratory failure.
- It may be necessary to electively intubate the patient if FVC falls below 20 mL/kg.
- Plasmapheresis or IVIG both rapidly improve respiratory function and muscle strength.
- High-dose prednisone can transiently worsen symptoms.

### KEY FACT

The hallmark of ALS is the combination of both upper and lower motor neuron signs and symptoms.

### KEY FACT

In a patient with generalized weakness, muscle or tongue fasciculations, hyperreflexia, atrophy of the hand muscles, and normal ocular muscles, consider ALS and order an EMG/NCS.

### KEY FACT

Unique features of ALS:

- Spares the ocular muscles
- Preservation of bowel and bladder function
- Normal sensory
- Absence of pain
- Cognitive impairment late in the course

### KEY FACT

In suspected ALS, LP may be necessary to exclude infections and inflammatory myelopathies (eg, West Nile virus, paraneoplastic disease), and cervical spine MRI may be necessary to exclude cervical spondylosis.



### ANSWER

This patient is having a myasthenic crisis characterized by dysphagia that requires NG feeding and/or severe respiratory muscle weakness that necessitates ventilation. Plasmapheresis or IVIG are the treatments of choice.

## Amyotrophic Lateral Sclerosis

Also known as Lou Gehrig's disease, amyotrophic lateral sclerosis (ALS) is a progressive degenerative disease characterized by both upper motor neuron (UMN) signs (arising in the motor cortex) and lower motor neuron (LMN) signs (arising in the brainstem and the anterior horn of the spinal cord). Affects men and women equally, with onset between 50 and 70 years of age. Life expectancy is 3 to 5 years, with death usually occurring due to aspiration pneumonia or respiratory failure.

### Symptoms/Exam

- Presents with dysphagia, nasal speech, "head drop" from weakness of the neck extensors, shortness of breath, "muscle twitches," muscle cramps, and progressive generalized weakness. Eye muscles are typically spared; bowel and bladder function is typically preserved.
- Frontotemporal dementia is common late in the disorder.
- **UMN signs:** Spasticity ( $\uparrow$  muscle tone), hyperreflexia,  $\oplus$  Babinski sign.
- **LMN signs:** Atrophy (especially of the tongue and muscles of the hands), fasciculations, and weakness.

### Diagnosis

- **EMG/NCS** reveal evidence of widespread LMN injury (eg, fibrillations, fasciculations) and UMN injury that does not fall in a nerve root distribution. Sensory nerve studies are normal.
- **Spinal fluid** analysis is normal.
- **Cervical spine imaging** is normal.

### Management

- **Riluzole**, a presumed glutamate antagonist, is the only FDA-approved medication for ALS. Improves survival by approximately 3 to 6 months.
- **Noninvasive positive-pressure ventilation** improves survival and should be considered if FVC falls to <50% predicted.
- **Percutaneous gastrostomy tube placement** for patients with impaired swallowing and  $\uparrow$  risk of aspiration. Adequate nutrition and weight maintenance are essential.

## Neuropathies

Table 13.19 reviews key features of common neuropathies.

### POLYNEUROPATHIES

#### Guillain-Barré Syndrome

A postinfectious autoimmune **acute demyelinating polyneuropathy**. Given the decline of polio, Guillain-Barré syndrome (GBS) is now the most common cause of acute flaccid paralysis. Look for prior GI illness caused by *Campylobacter jejuni*, as antibodies directed toward its bacterial lipopolysaccharide cross-react with peripheral nerve myelin.



#### QUESTION

A 55-year-old woman presents with a 6-month history of progressive left foot drop and slurred speech. On exam, she has weakness, fasciculations, and atrophy of the tongue, and her left foot is weak and atrophic with fasciculations. She has left ankle clonus and extensor plantar response with a normal sensory exam. What is the most likely diagnosis?

**TABLE 13.19. Key Features of Common Neuropathies**

CLINICAL PRESENTATION	COMMON CAUSES	COMMENTS
Diabetic with sensory paresthesia in a "stocking glove" distribution	DM sensory polyneuropathy	Often associated with retinopathy or nephropathy; preventable with good glycemic control
Wrist drop in an alcoholic who fell asleep while seated on a park bench	<b>Radial nerve mononeuropathy</b> from the arm hanging over the back of a bench ("Saturday night palsy")	Usually improves with time and physical therapy
Foot drop after prostatectomy or leg crossing	<b>Peroneal nerve mononeuropathy</b> from compression related to intraoperative positioning or leg positioning	Same as above
Weakness of right ankle dorsiflexion, then left hand extension, then other motor weakness	<b>Mononeuritis multiplex</b> , most commonly from <b>vasculitis</b> (eg, polyarteritis nodosa)	Biopsy of the affected nerve to confirm the diagnosis Treat aggressively with anti-inflammatory or cytotoxic agents (eg, steroids, cyclophosphamide)
Impotence, orthostasis, dry mouth, and diarrhea	Autonomic neuropathy from diabetes, amyloid, porphyria, and many others	When autonomic neuropathy is associated with parkinsonian features, think of multiple-system atrophy (does not respond as well to antiparkinsonian medications)
Bilateral lower extremity paresthesias with ascending weakness and areflexia	Demyelinating polyneuropathy: Guillain-Barré syndrome if acute; chronic inflammatory demyelinating polyneuropathy if chronic	NCS show slowed conduction due to loss of myelin; demyelination is often due to inflammation and is thus potentially reversible
Paresthesias in a patient being treated for a $\oplus$ PPD; NCS show low amplitude	Axonal neuropathy from INH	Treat with vitamin $B_6$ (pyridoxine)
Bilateral leg weakness, hyporeflexia, ↓ vibration sense, and macrocytosis	$B_{12}$ deficiency	Neurologic changes may not reverse with $B_{12}$ treatment
Fevers, altered mental status, and flaccid leg paralysis in late summer	West Nile virus, encephalomyelitis	Flaccid weakness due to LMN injury from anterior horn cell injury
A Brazilian man with areas of hypopigmented skin and loss of sensation over the distal extremity	Leprosy	Eventually results in motor neuropathy (eg, claw hand or foot drop) Dapsone, in combination with other drugs, is the mainstay of treatment

**A****ANSWER**

ALS. Muscle weakness usually begins distally and asymmetrically in the upper or lower extremities or may be limited initially to the bulbar muscles, resulting in dysarthria and dysphagia.

**KEY FACT**

Respiratory failure in GBS patients is due to diaphragmatic weakness. Remember the 20-30-40 rule for indication to intubate:

- FVC <20 mL/kg
- Maximum inspiratory pressure (force) <30 cm H<sub>2</sub>O
- Maximum expiratory pressure (force) <40 cm H<sub>2</sub>O

**KEY FACT**

**Miller-Fisher syndrome** is a variant of GBS that produces ophthalmoplegia, ataxia, and areflexia of the upper extremities first. Anti-GQ1b antibodies support the diagnosis.

**KEY FACT**

Up to two-thirds of patients with GBS report an antecedent illness 1 to 3 weeks prior to onset of weakness.

**KEY FACT**

Critical illness polyneuropathy tends to occur in patients with multiorgan failure and sepsis and is characterized by generalized or distal flaccid paralysis, depressed or absent reflexes, ventilator dependence, distal sensory loss with sparing of cranial nerve function, and normal CSF studies.

**Symptoms/Exam**

- Back pain is prominent initially, followed by gradual ascending **symmetric weakness in the legs and can lead to respiratory failure**.
- **Autonomic symptoms include life-threatening cardiac arrhythmia.**
- Cardinal features on exam are areflexia and **symmetric progressive weakness**.

**Diagnosis**

- CSF shows “albuminocytologic dissociation”—isolated elevated protein with normal WBC counts.
- NCS reveal slow conduction velocities of the proximal peripheral nerves.
- Serial PFTs with **maximum inspiratory force** and FVC to follow diaphragmatic function.

**Management**

- Standard treatment is either **IVIG** or **plasmapheresis**; steroids are **not beneficial**. Mechanical ventilation should be considered when FVC falls to <20 mL/kg. Keep patients with autonomic symptoms on **cardiac telemetry**.
- Avoid IVIG in renal insufficiency, CHF, or IgA deficiency. Avoid plasmapheresis in those with labile BPs or infection.

**Chronic Inflammatory Demyelinating Polyneuropathy**

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a symmetric demyelinating disease of peripheral nerves that is characterized by proximal and distal weakness, areflexia, and distal sensory loss.

- **Diagnosis:** Related to but distinct from **GBS**, as both share similar clinical and pathologic findings (including areflexia, weakness, ↑ CSF protein, and demyelination). CIDP, however, has **no associated antecedent illness** and evolves over **weeks to months**, often with a **relapsing and remitting course**.
- **Management:** As for GBS, CIDP typically responds to IVIG, steroids, or plasmapheresis.

**Charcot-Marie-Tooth Disease (Hereditary Sensorimotor Neuropathy)**

- Characterized by a strongly **⊕ family history**; usually autosomal dominant. The most common inherited neurologic disorder. Life expectancy is normal despite morbidity from progressive weakness.
- **Symptoms:** Begin in the first and second decades, usually with distal weakness in the legs and clumsiness. Patients have “**inverted champagne bottle**” legs; high-arched feet (pes cavus) and hammer toes; progressive atrophy and weakness of the hands and feet; distal sensory loss; and ↓ or absent reflexes.
- **Management:** No treatment is currently available. Physical therapy may be beneficial.

**Diabetic Neuropathy**

- Diabetes is the most common cause of peripheral neuropathy in the United States. Sixty percent of diabetics develop some form of neuropathy, usually associated with retinopathy and nephropathy.
- **Symptoms:** Starts with paresthesias and pain in the feet and progresses to **stocking-glove distribution** of sensory and motor deficits. Can also affect autonomic nerves.
- **Management:** Prevention depends on tight glycemic control. Neuropathic pain symptoms (burning, pain) can be treated with TCAs such as amitriptyline, SSRIs, or anticonvulsants such as gabapentin or carbamazepine.

## Metabolic/Infectious Neuropathies

- Many insidious and chronic polyneuropathies are **metabolic** in nature, with common causes being nutritional deficiencies (eg, vitamin B<sub>12</sub>), toxin exposure (eg, alcohol), and drug exposure (eg, vincristine, INH, dapsone).
- Many **infections** can also cause indolent polyneuropathies, including HIV, HSV, and HCV associated cryoglobulinemia; leprosy (Hansen disease, caused by *Mycobacterium leprae*) remains one of the most common causes of polyneuropathy worldwide.

## MONONEUROPATHIES

### Carpal Tunnel Syndrome

- Caused by compression of the **median nerve** at the flexor retinaculum of the wrist. Risk factors include repetitive hand-finger activities such as typing.
- Symptoms/Exam:** Classic features include sensory loss over palmar surface of first three digits and weakness of thumb opposition. Exam findings include the following:
  - Atrophy of the thenar eminence.**
  - Phalen sign:** Hyperflexion of the wrists leading to ↑ paresthesias.
  - Tinel sign:** Tapping over the median nerve at the level of the wrist eliciting electrical sensations along the thumb and index finger.
- Diagnosis:** May be confirmed with nerve conduction studies (NCS) showing median nerve abnormalities at the wrist.
- Management:** Options include immobilization with wrist splints, NSAIDs, local steroid injections, and surgical release at the wrist.

### Radial Nerve Palsy

Typically results from acute injury to the nerve in the spiral groove of the humerus, most commonly by **fracture of the humerus** or direct compression of the nerve ("Saturday night palsy").

- Symptoms/Exam:** The most prominent symptom is "wrist drop"; weakness of elbow extension (triceps) is also common.
- Diagnosis:** May be confirmed with NCS to identify the exact location and extent of the injury.
- Management:** Mainly supportive. **Wrist splints** may temporarily restore function.

### Ulnar Neuropathy

- An overuse injury commonly **caused by repetitive elbow flexion** leading to trauma or compression at the elbow, particularly near the medial epicondyle. Common among thin women.
- Symptoms/Exam:** Typical features include paresthesia of the **fourth and fifth fingers** and weakness of the muscles that spread the fingers apart; in its most chronic form, resembles a "claw hand."
- Management:** **Splinting the elbow** at night is first-line treatment and is most helpful in conjunction with NSAIDs if there is pain. Surgical release or transposition of the nerve near the elbow is often tried but is not always beneficial.

### Peroneal Nerve Compression

- Symptoms:** Compression of the **peroneal nerve** near the fibular head produces a "foot drop" 2° to weakness of foot dorsiflexors, as well as paresthesia along the lateral aspect of the lower leg. Compression can be 2° to frequent leg crossing, trauma, or local masses (eg, cysts).
- Management:** Involves identifying the risk factors for compression, initiating physical therapy, and using an ankle-foot orthosis; surgery is occasionally needed when a local mass is identified as the etiology of compression.

### KEY FACT

Patients with carpal tunnel syndrome often have ↑ symptoms at night that are relieved by shaking or wringing of the hands.

### QUESTION 1

A 30-year-old man presents with numbness and tingling in both feet that has progressed over several days to gait instability, hand weakness, diplopia, and dyspnea. The symptoms started about a week after a viral illness. On exam, he cannot walk and has proximal and distal weakness in the upper and lower extremities bilaterally, areflexia, and marked vibratory and position sense loss in the toes and fingers. What is the most likely diagnosis and the most appropriate treatment?

### QUESTION 2

A 30-year-old woman presents with 2 months of progressive, symmetrical proximal and distal weakness. HIV infection was diagnosed 4 weeks earlier and combination therapy with efavirenz, zidovudine, and lamivudine was started. On exam, she has diffuse extremity weakness, areflexia, and ↓ vibratory sensation in the distal upper and lower extremities. What is the most likely diagnosis?

### QUESTION 3

A 50-year-old man with 60-pack-year smoking history presents with rapid cognitive decline over the past 2 months. He loses his way in familiar places, is unable to drive, and neglects housework/finances. He has had numerous episodes of unresponsive staring with lip smacking followed by brief periods of confusion. On exam, he is disheveled and confused; MMSE is 23/30 (missing points on orientation and recall). MRI shows symmetric areas of abnormal T2 signal bilaterally in the hippocampus (medial temporal lobes) with minimal enhancement with gadolinium and no mass effect. What is the most likely diagnosis?

**KEY FACT**

If a patient presents with a facial droop, look for upper facial weakness. If the upper face is also weak, the lesion is peripheral (eg, Bell palsy)—and there is no need to order brain imaging. If the upper face is normal, the lesion is central (eg, stroke).

**A****ANSWER 1**

Guillain-Barré syndrome is characterized by proximal and distal weakness, distal sensory loss, autonomic symptoms, cranial nerve involvement, and respiratory failure. Confirm with LP. Treatment is with IVIG or plasmapheresis.

**A****ANSWER 2**

CIDP presents similarly to GBS but symptoms (characterized by proximal and distal weakness, areflexia, distal sensory loss) progress for at least **8 weeks**. In contrast, toxic neuropathies may manifest acutely but are generally axonal; distal sensory loss and weakness with loss of the Achilles tendon reflexes are present but not diffuse areflexia.

**A****ANSWER 3**

Paraneoplastic limbic encephalitis. HSV infection is unlikely because of the subacute behavioral problems. Limbic encephalitis is most commonly associated with small cell lung cancer (in older smokers) and ovarian teratoma (in younger women). The former is associated with the anti-Hu antibody; the latter with anti-NMDA antibody.

**Bell Palsy**

An acute-onset, unilateral paralysis of CN VII (the facial nerve). Although a clear cause generally cannot be identified in most cases, infections (eg, HSV, VZV, HIV, Lyme) and infiltrative (sarcoidosis) are possible etiologies.

■ **Symptoms/Exam:**

- **The upper and lower halves of one side of the face are affected**, resulting in inability to fully close the eye or move the mouth on that side (Figure 13.13). By contrast, facial weakness from a central cause (eg, a stroke) typically spares the upper half of the face, producing unilateral lower facial weakness.
- May also present with loss of taste, salivation, lacrimation, and hyperacusis.
- **Ramsay Hunt syndrome** presents with unilateral facial paralysis associated with herpetic blisters in the external auditory canal.

■ **Management:**

- Treat idiopathic Bell palsy with **prednisone if within 72 hours of onset**.
- Eye protection (artificial tears; use of an eye patch at night) is crucial for preventing corneal abrasions.

**Paraneoplastic and Autoimmune Encephalitides**

Antibody-mediated encephalitides are rare syndromes caused by underlying paraneoplastic disorders or by autoimmune attack of CNS antigens. Both are treated with immunosuppressive therapies (steroids, IVIg, PLEX, rituximab). Paraneoplastic causes also require treatment of the underlying cancer.

Neurologic paraneoplastic syndromes may be due to antibodies that cross-react with specific neuronal populations (Table 13.20).



**FIGURE 13.13. Prototypic Bell palsy.** (A) A 28-year-old female with acute-onset left facial paralysis involving the entire left face. She was treated with oral steroids. (B) The same patient following a full recovery 2 months after symptom onset. (Reproduced with permission from Lalwani AS.)

*Current Diagnosis & Treatment in Otolaryngology—Head & Neck Surgery, 2nd ed. New York: McGraw-Hill, 2008, Fig. 68-1.*

**TABLE 13.20. Key Features of Neurologic Paraneoplastic Syndromes**

SYNDROME	KEY FEATURES	UNDERLYING CANCER	ASSOCIATED ANTIBODY
Lambert-Eaton myasthenic syndrome	Fluctuating muscle weakness that spares the eyes and improves on repetitive muscle testing; autonomic symptoms are common, and reflexes are ↓	<b>Small cell lung cancer</b>	Anti-voltage-gated calcium channel
Subacute cerebellar degeneration	Middle-aged women with subacute onset of slurred speech, ataxia, and limb incoordination	Ovarian or breast cancer	Anti-Yo (Purkinje cells)
Limbic encephalitis	Subacute behavioral problems, memory difficulties, and focal-onset seizures (Figure 13.14) Resembles HSV encephalitis, but HSV is more acute in onset	Small cell lung cancer <b>Ovarian teratoma</b>	Anti-Hu <b>Anti-NMDA</b>
Sensory neuronopathy	Slowly progressive sensory loss that first affects the lower extremities Exam shows areflexia and incoordination related to loss of proprioception	Small cell lung cancer	Anti-Hu
Opsoclonus-myoclonus	<b>Opsoclonus:</b> Involuntary, erratic, rapid jerking of the eyes in either the horizontal or the vertical direction <b>Myoclonus:</b> Brief, jerklike contractions	Breast cancer or neuroblastoma (children)	Anti-Ri

**FIGURE 13.14. Limbic encephalitis.** MRI FLAIR sequence shows symmetric ↑ signal in the mesial temporal lobes. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 97-2.)**KEY FACT**

Paraneoplastic encephalitis may be the first manifestation of cancer. Unlike autoimmune encephalitis, paraneoplastic encephalitis responds poorly to treatment unless the underlying tumor can be successfully managed.

## NOTES

## CHAPTER 14

# Oncology

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## Cancer Treatment

### CHEMOTHERAPEUTIC AGENTS

#### Patterns of Toxicity

Table 14.1 outlines common and serious toxicities of various chemotherapeutic agents. All chemotherapies can cause bone marrow suppression and nausea/vomiting.

#### Targeted Therapies

Novel agents have a specific molecular target and often have fewer and less severe side effects than conventional chemotherapy. Modalities include hormonal therapy, cytokines, monoclonal antibodies, and small molecules that target enzymes. Monoclonal antibodies are often combined with standard chemotherapeutic regimens. Table 14.2 outlines common targeted therapies and their indications.

TABLE 14.1. Toxicities of Common Chemotherapeutic Agents

DRUG	SIDE EFFECTS	MONITORING REQUIRED
Alkylators (cyclophosphamide, ifosfamide)	<b>Hemorrhagic cystitis</b> , neurotoxicity (ifosfamide), severe nausea/vomiting, male sterility	UA to monitor for hematuria; <b>mesna</b> to bind to toxic metabolite
Anthracyclines (doxorubicin, epirubicin, idarubicin, mitoxantrone)	Dose-dependent <b>cardiac toxicity</b> (CHF), nausea/vomiting, stomatitis, bone marrow suppression	Baseline echocardiogram and echocardiogram after a specified amount of chemotherapy (eg, 300 mg/m <sup>2</sup> for doxorubicin)
Bleomycin	<b>Pulmonary fibrosis</b>	Baseline PFTs
Cytarabine	Neurotoxicity, rash	Cerebellar exam prior to each dose; steroids if rash is severe
5-fluorouracil (5-FU) and capecitabine	<b>Hand-foot syndrome</b> (painful erythema and desquamation of skin on the palms and soles), diarrhea	No special monitoring
Gemcitabine	<b>Rare interstitial fibrosis</b>	No special monitoring
Irinotecan	Diarrhea	
Methotrexate	Renal failure, hepatic enzyme elevation, stomatitis	Check for effusions before administration (clearance is slowed if they are present, ↑ the risk of renal failure) LFT monitoring is required
Platinums (carboplatin, cisplatin)	<b>Neuropathy</b> , ototoxicity, renal failure, potassium and magnesium wasting, severe nausea/vomiting (cisplatin)	Monitor renal function Conduct an audiologic exam at baseline (cisplatin only) if the patient has any hearing complaints
Taxanes (docetaxel, paclitaxel)	Allergic reactions, fluid retention, <b>neuropathy</b>	<b>Premedicate with steroids</b>
Vinca alkaloids (vinblastine, vincristine)	<b>Neuropathy</b> (including motor neuropathy) with <b>severe constipation</b>	Determine if the patient has had a bowel movement within 48 hours of a dose

TABLE 14.2. Common Targeted Therapies and Their Uses

DRUG	APPLICATION	SIDE EFFECTS
<b>HORMONAL AGENTS</b>		
GnRH agonists (goserelin, leuprolide)	Androgen deprivation for prostate cancer	<b>Osteoporosis, hot flashes, anemia, weight gain</b>
Tamoxifen	Adjuvant therapy for breast cancer	As above, but <b>without osteoporosis</b> ; also ↑ risk of <b>uterine cancer</b>
Aromatase inhibitors (anastrozole, letrozole, exemestane)	Adjuvant therapy for breast cancer	As above, <b>with osteoporosis</b>
<b>TYROSINE KINASE INHIBITORS</b>		
Erlotinib (EGFR inhibitor)	Non–small cell lung cancer (NSCLC)	<b>Acneiform rash</b> ; rare pulmonary fibrosis
Imatinib (BCR-ABL tyrosine kinase inhibitor)	CML, gastrointestinal stromal tumor (GIST)	Edema, transaminitis
Sorafenib (VEGF inhibitor)	Renal cell and hepatocellular carcinoma	<b>Diarrhea, rash, hand-foot syndrome, hypertension</b>
Sunitinib (VEGF inhibitor)	Renal cell carcinoma, GIST	<b>Diarrhea, rash, hypothyroidism</b>
Pazopanib (VEGF inhibitor)	Renal cell carcinoma	<b>Hypertension, hepatotoxicity</b>
<b>CYTOKINES</b>		
Interferon	CML, melanoma, renal cell carcinoma	<b>Depression</b> with suicidal ideation; <b>bone marrow suppression</b>
Interleukin-2	Renal cell carcinoma, melanoma	<b>Hypotension, renal failure, edema</b>
<b>MONOCLONAL ANTIBODIES</b>		
Alemtuzumab (anti-CD52 antibody)	CLL	Bone marrow suppression, CMV reactivation
Bevacizumab (VEGF inhibitor)	Metastatic colorectal cancer, NSCLC	<b>Bleeding, hypertension, proteinuria</b>
Cetuximab (EGFR inhibitor)	Head and neck cancer, metastatic colorectal cancer	<b>Acneiform rash</b>
Ipilimumab (anti-CTLA4)	Melanoma	<b>Immune-related enterocolitis</b>
Rituximab (anti-CD20 antibody)	B-cell lymphomas	<b>Allergic reactions, HBV reactivation</b>
Trastuzumab (HER2/neu antibody)	Breast cancer with HER2/neu overexpression	<b>Cardiac toxicity (CHF)</b>
Vemurafenib (BRAF inhibition)	Melanoma	<b>Arthralgias, rash, photosensitivity</b>

## PRINCIPLES OF ONCOLOGY

### Combination Regimens

- Allow for maximum cell kill with less toxicity (lower doses of individual agents).
- Prevent cross-resistance (different drugs lead to different mechanisms of resistance).
- Synergistic effects between drugs with non-overlapping toxicities.

### Response to Therapy

- **Complete response:** Disappearance of all evidence of disease for at least 4 weeks.
- **Partial response:** Reduction by at least 30% of the sum of the largest diameter of all measurable lesions with no new disease appearing, maintained for at least 4 weeks.
- **Progressive disease:** Growth of existing disease by 20% of the sum of the largest diameter of all measurable lesions, or new lesions during treatment.

### Chemotherapy Resistance

Include upregulation of downstream enzymes and anti-apoptotic proteins as well as **MDR1**, the multidrug resistance gene which encodes a pump that removes toxins (chemo) from cancer cells.

### Adjuvant and Neoadjuvant Chemotherapy

- **Adjuvant chemotherapy:** Chemotherapy given after surgery to ↓ the risk of recurrence.
- **Neoadjuvant chemotherapy:** Chemotherapy given before surgery to make resection easier and to ↓ recurrence.

## RADIATION THERAPY

### Mechanism of Action

- Radiation induces ionization in biological tissues that damages DNA (cancer cells are less capable of repair than normal cells).
- Acute side effects largely limited to irradiated area and largely from associated edema. Chronic side effects occur months to years after treatment and mostly due to fibrosis (Table 14.3).

TABLE 14.3. Acute and Chronic Side Effects of Radiation Treatment

	ACUTE	CHRONIC
CNS	Fatigue, lethargy, nausea/vomiting, cerebral edema	Necrosis, memory loss, personality changes, optic neuropathy, paralysis (2/2 spinal cord irradiation, rare)
GI	Nausea, vomiting, diarrhea, dysphagia, mouth sores, abdominal pain	Chronic dysphagia, malabsorption, proctitis, strictures
Hematologic	Bone marrow suppression	Leukemia
Cardiovascular	Pericarditis (rare)	CAD
Pulmonary	Radiation pneumonitis	Fibrosis
Skin/musculoskeletal	Desquamation, alopecia	Skin cancer Osteonecrosis (classically of the jaw); risk ↑ with dental work

## Methods of Administration

- **External beam radiation therapy:** The most commonly used modality. Toxicities can be minimized via:
  - **Conformal radiation therapy:** Shaping the radiation beam to precisely fit the tumor outline.
  - **Intensity-modulated radiation therapy:** Changing the intensity of the radiation beam.
- **Brachytherapy (implants):** The radiation source (in the form of seeds) is implanted within the tumor. Most often used in the treatment of **prostate cancer**.
- **Stereotactic radiosurgery:** A three-dimensional technique that delivers high-dose radiation to a very small volume. Used primarily for treating small 1° tumors and metastatic cancer.

### SURGICAL ONCOLOGY

- Surgery may be employed to **diagnose** (biopsy) or to **treat**. May be **curative** or **palliative**.
- **Resection** is predicated on the ability to achieve ⊖ margins, usually with at least 1 cm of normal tissue if possible (or more in special circumstances).
- **Debulking**, or removal of tumor without obtaining ⊖ margins, plays a role in diseases such as **ovarian cancer**.
- Direct manipulation of tumor is avoided where possible to prevent local recurrence.

## Oncologic Emergencies

### SUPERIOR VENA CAVA SYNDROME

Compression of the superior vena cava (SVC) by tumor or thrombosis of the SVC.

- **Symptoms:** Include facial edema or erythema, shortness of breath, orthopnea, hoarseness, headaches due to ↑ ICP, and arm or neck swelling. Onset may be insidious reflecting ↑ occlusion of the SVC.
- **Exam:** Reveals edema of the face, tongue, neck, and arms; dilation of upper body veins; and plethora (Figure 14.1).
- **Diagnosis:** CT of the chest and neck or CXR. CT most useful for evaluating cause, level, and degree of obstruction. **Lack of lower-extremity edema distinguishes SVC syndrome from right-sided heart failure.**
- **Management:** Includes temporizing measures such as corticosteroids and diuretics. After a tissue diagnosis is made, radiotherapy and prompt initiation of chemotherapy are required. Thrombolytics, anticoagulation, or stenting can be performed for thrombosis.
- **Complications:** Laryngeal and cerebral edema is life-threatening.

### SPINAL CORD COMPRESSION

Affects 1% to 5% of patients with metastatic cancer. Diagnostic and treatment delays are associated with paralysis and loss of bladder and bowel control.

#### Symptoms

- **Early:** Presents with pain localized to the spine or radicular pain due to nerve root compression. Pain is exacerbated with movement, coughing, lying down, sneezing, or Valsalva/straining. **Pain generally precedes functional loss by weeks to months.**
- **Late:** Muscle weakness, sensory loss/sensory level, urinary retention, constipation, sphincter dysfunction, paralysis, and autonomic dysfunction.



**FIGURE 14.1. Plethora of the neck and shoulders in superior vena cava syndrome.** Skin displays a purplish hue that blanches after compression. (Source: Shaikh I, et al. Thrombogenic catheter-associated superior vena cava syndrome. *Case Rep Emerg Med*. 2013;2013:793054.)

#### KEY FACT

Cancer and thrombosis cause most cases of SVC syndrome; NSCLC, small cell lung cancer, and non-Hodgkin lymphoma account for most cases (95%) of malignancy-related SVC syndrome.

#### KEY FACT

Spinal cord compression should be considered in any patient with bilateral motor and sensory dysfunction in the extremities in the absence of any signs or symptoms of brain or brainstem dysfunction.

**KEY FACT**

Vertebral metastases are most frequently found in the thoracic spine (60% of cases), followed by the lumbosacral (30%) and cervical spine (10%).

**KEY FACT**

Back pain is the cardinal symptom of spinal cord compression. Thus, for a patient with a history of cancer who has new onset back pain, suspect vertebral metastases until proven otherwise. MRI is the imaging study of choice.

**Exam**

- **Findings** include tenderness over the affected area of the spine, focal neurologic findings, UMN signs, abnormal plantar responses, sensory loss, and ↓ rectal tone.
- **Cauda equina syndrome** refers to compression of the cauda equina (below L1), but the physiology and treatment are the same as those for cord compression.

**Diagnosis**

- Plain films are not helpful in ruling out cord compression.
- **MRI** is the gold standard for diagnosis (Figure 14.2). Gadolinium enhances the ability to visualize epidural metastases without bony involvement.
- If MRI is unavailable/contraindicated, myelography, CT, or CT myelography can confirm the diagnosis.

**Management**

- Preservation of neurologic function depends on **rapid** assessment and diagnosis.
- If patients can walk at diagnosis, they will likely preserve their function with appropriate treatment.
- Early steroid administration ↓ swelling and pressure on the cord. Administer high-dose bolus dexamethasone 10 mg followed by 4 to 10 mg q 6 h.
- Definitive treatment options include immediate surgical decompression, radiation therapy (for radiation-sensitive malignancies), or, rarely, chemotherapy. **Consult neurosurgery, radiation oncology, and medical oncology early.**

**TUMOR LYYSIS SYNDROME**

Rapid release of intracellular contents due to massive lysis of cancer cells resulting in life-threatening metabolic consequences. **Most commonly found in rapidly pro-**



**FIGURE 14.2. Spinal cord compression caused by peripheral primitive neuroectodermal tumor.** Precontrast MRI shows an irregular mass around the compressed sixth cervical vertebra that is iso-intense on T1-weighted image (A) and iso-intense on T2-weighted image (B). Contrast MRI shows the mass with significant enhancement (C). (Source: Tan Y, et al. Peripheral primitive neuroectodermal tumor: dynamic CT, MRI and clinicopathological characteristics—analysis of 36 cases and review of the literature. *Oncotarget*. 2014;5(24):12968-12977.)

gressing acute leukemias and aggressive lymphomas (such as Burkitt lymphoma). It is especially common after initial doses of chemotherapy but can also occur spontaneously. Rarely seen in solid tumors.

### Diagnosis

- Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia (the excess phosphate binds calcium).
- A markedly ↑ LDH points to a risk of tumor lysis.
- May lead to oliguric renal failure.

### Management

- Prevention:
  - Identify patients at risk for tumor lysis syndrome before starting chemotherapy based on type of cancer (ie, Burkitt lymphoma high risk, most solid tumors low risk).
  - Aggressive IV hydration prior to initiation of chemotherapy ↓ risk.
  - Urine is often alkalinized with sodium bicarbonate infusion, although supportive evidence for this common practice is lacking.
  - Prophylactic allopurinol given before chemotherapy can ↓ the level of hyperuricemia (monitor for changes in CrCl and adjust the dose if necessary).
- Treatment:
  - Focus on aggressive hydration and allopurinol.
  - Closely monitor serum laboratory values, including potassium, uric acid, calcium, phosphorus, and Cr (q 4 h initially; then as clinically indicated).
  - Consider **rasburicase**, an expensive enzyme that metabolizes uric acid into allantoin, in cases of severe tumor lysis (generally considered when uric acid levels are >10 mg/dL). Rasburicase may be given prophylactically for cancers that are especially high risk of TLS (ie, Burkitt lymphoma).

## NEUTROPENIC FEVER

Neutropenic fever is either a single oral temp ≥38.3°C (101°F) or 38°C (100.4°F) for more than an hour. Patients with ANC <500/µL for >7 days are at high risk for infection. Etiologies are as follows:

- **Bacteria** (gram-negative bacilli, gram-positive cocci): Coagulase-negative staphylococci (*Staphylococcus epidermidis*) are now the **most common** causes of bacteremia, but gram-negative organisms (eg, *Pseudomonas aeruginosa*) are typically associated with the **most severe** infections.
- **Fungal infections:** More common in patients on broad-spectrum antibacterial therapy, corticosteroids, or in those with prolonged neutropenia such as following allogeneic bone marrow transplant. Most common pathogens are *Candida* and *Aspergillus*.
- **Viruses:** Viral infections occurring during neutropenia include the herpesviruses (CMV, HSV, VZV, EBV) and respiratory viruses (RSV, influenza A and B, parainfluenza, rhinovirus, adenovirus).

### Exam

**Thorough physical examination** is directed at uncovering potential sources of infection and should focus on venous access sites and examination of the oropharynx, lungs, abdomen, and skin.

### Diagnosis

- Obtain two sets of blood cultures, a urine culture, a culture of any catheter or catheter drainage, and a CXR.
- Additional evaluation is dictated by signs and symptoms (ie, LFTs and/or RUQ ultrasound for suspected biliary disease).



### MNEMONIC

**Tumors that commonly metastasize to bone—**

**BLT with Mayo, Mustard, and Kosher Pickle**

Breast

Lung

Thyroid

Multiple Myeloma

Kidney (renal cell)

Prostate



### KEY FACT

Calcium is **low** in tumor lysis syndrome because excess phosphate binds calcium. Potassium, uric acid, phosphorus, and LDH are ↑.



### KEY FACT

IV fluids and allopurinol given prior to the initiation of chemotherapy are critical to preventing tumor lysis syndrome.



### KEY FACT

Gram-negative bacilli and gram-positive cocci account for most cases of neutropenic fever. In the 25% of neutropenic fever patients with + blood cultures, coagulase-negative staphylococci are the most commonly isolated organisms.

### Management

- Prevention is ideal. Neutropenic patients should be placed in “protective” isolation.
- **Empiric antibiotic therapy:** Done in stepwise fashion, taking into consideration historical culture data (if any), and local resistance patterns (ie, extended spectrum  $\beta$ -lactamase-producing organisms).
- **First step:** For high-risk patients, monotherapy with antipseudomonal  $\beta$ -lactam (cefepime, ceftazidime, piperacillin-tazobactam, meropenem, or imipenem).
- **Vancomycin:** Generally not part of first-line empiric therapy. Used only under the following conditions and should be discontinued after 2 to 3 days if no evidence of gram-positive infection:
  - Suspected central line infection.
  - Blood cultures with gram-positive cocci.
  - Pneumonia.
  - Skin or soft-tissue infections.
  - Hemodynamic instability or other signs of severe sepsis.
- **Second step:** For patients with persistent fevers >4 to 7 days and no source identified, add empiric antifungal (voriconazole or caspofungin).
- **G-CSF/GM-CSF:** Has not been shown to reduce mortality and is costly. Reserve this for patients with prior neutropenic fever or severe neutropenic infections.
- **Duration of treatment:** If source identified, treat for standard duration for that infection (ie, 14 days for gram-negative bacteremia). If no source identified, continue until ANC  $\geq 500/\mu\text{L}$  and patient is afebrile for 48 hours.

### KEY FACT

In patients with neutropenic fever, vancomycin is not used **empirically** as first-line therapy **unless** hypotensive/ septic without a known source; has a blood culture showing gram-positive cocci; suspected central line infection; pneumonia; skin or soft tissue infection.

### KEY FACT

Genetic syndromes markedly  $\uparrow$  the risk of breast cancer, although they account for a minority of cases of breast cancer.

### KEY FACT

Inflammatory breast cancer is an aggressive form of breast cancer characterized by thickened skin (peau d'orange). Breast conservation (lumpectomy) is generally considered inappropriate for local control.

### KEY FACT

HER2 is overexpressed in only 10% of breast cancers and confers a poorer prognosis. Treatment should include trastuzumab ( $\pm$  other HER2-targeting agents).

## Breast Cancer

Risk of breast cancer  $\uparrow$  with age. Lifetime risk is  $\sim 10\%$ ; 75% of patients have no known risk factors. Known risk factors include:

- **Genetic syndromes:** Most patients without known genetic predisposition. Those with genetic predisposition should be screened beginning at least 10 years before the earliest-onset cancer in the family history.
  - **BRCA1:** Associated with a dramatic  $\uparrow$  risk of breast cancer (56%-85% lifetime risk), ovarian cancer (15%-45% lifetime risk), and prostate cancer (less frequent). Autosomal dominant inheritance; Ashkenazi Jews are at highest risk.
  - **BRCA2:** Associated with breast and ovarian cancer as well as with pancreatic cancer and melanoma. **BRCA1 and BRCA2 account for 50% of all inherited breast cancers.**
  - **Li-Fraumeni syndrome:** Breast cancer along with sarcomas, brain tumors, leukemia, lymphoma, and adrenal cancer.
- **Other risk factors:** Include family history of early-age breast cancer in family members, early menarche, late menopause, obesity, nulliparity or late age at first pregnancy, use of estrogen replacement therapy, and OCP use (controversial).

### Differential

Fibrocystic disease, fibroadenoma, atypical hyperplasia, abscess, adenosis, scars, mastitis. Note that no changes in screening intervals are recommended for these findings.

### Diagnosis

- Breast cysts can be evaluated with ultrasound and then aspirated.
- Breast masses require either fine-needle aspiration (FNA) or core needle biopsy, possibly followed by excisional biopsy.
- **All palpable masses require both diagnostic mammogram and ultrasound.** Simple cysts do not require aspiration (the sensitivity of mammography and ultrasound is

75% to 90%, with more false-negatives found on the denser breast tissue of younger women).

- **Algorithm:** Palpable mass → diagnostic **mammogram and breast ultrasound** → biopsy required for anything beyond a simple cyst (see also Figure 14.3).
- **Breast MRI** has higher sensitivity but much lower specificity than mammography. Currently two main uses:
  - Screening very high-risk women who elect not to have prophylactic surgery.
  - Evaluating patients with axillary lymph node metastases whose breasts are found to be normal by physical exam and mammography.

### Management

Treatment of early-stage breast cancer:

- **Ductal carcinoma in situ (DCIS):** Noninvasive malignancy confined to the breast ducts with similar risk factors as invasive breast cancer. Treatment involves excision with  $\ominus$  margins (**lumpectomy**) and **radiation therapy** to the breast, often with the addition of hormone therapy.
- **Lobular carcinoma in situ:** Associated with  $\uparrow$  risk of breast cancer arising **elsewhere in both breasts**. Treatment with tamoxifen may be considered, but close follow-up and observation are indicated.
- **Invasive ductal or lobular carcinoma:**
  - Lumpectomy followed by radiation therapy is equivalent to mastectomy in terms of overall survival, but the risk of local recurrence is lower with mastectomy. Re-excision, often followed by radiation, is indicated in patients with  $\oplus$  tumor margins that are detected after lumpectomy.
  - **Sentinel lymph node biopsy** involves injecting dye or tracer in the tumor and identifying which lymph node takes it up. The node or nodes are then excised and assessed for metastasis to determine need for additional chemotherapy.
  - Mastectomy is appropriate for large or multifocal tumors, for patients with a strong family history, or in accordance with patient preference.
- **Adjuvant therapy:** Guidelines for use are as follows:
  - In general, any patient with an **infiltrating** ductal or lobular cancer  $>1$  cm or with  $\oplus$  **lymph nodes** should receive **chemotherapy**. In hormone-positive



### KEY FACT

At the time of surgery for breast cancer, complete axillary node dissection is warranted only in sentinel node-positive or clinically node-positive tumors.



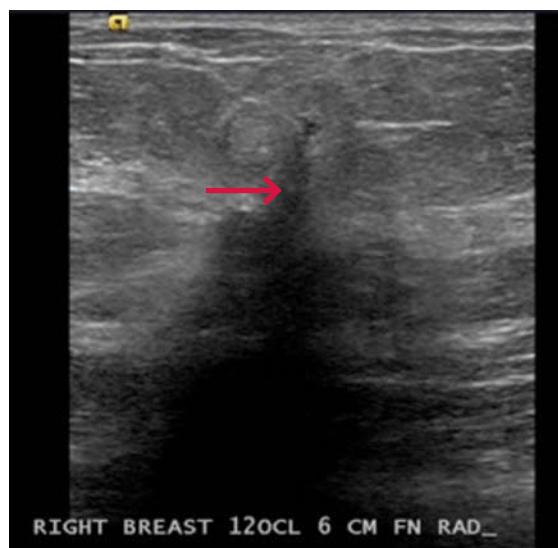
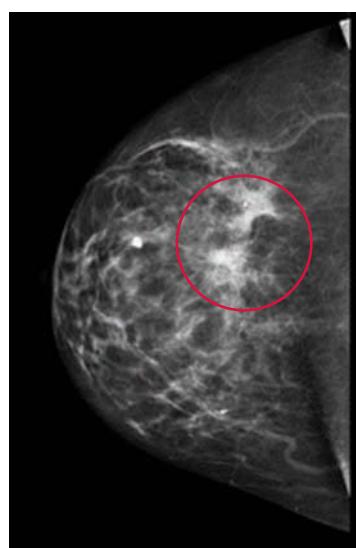
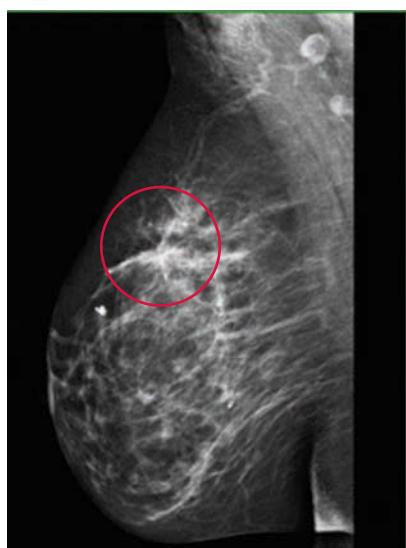
### KEY FACT

DCIS is a noninvasive malignancy that should be treated with lumpectomy and radiation therapy. Hormone therapy is added if ER/PR positive.



### QUESTION

A 55-year-old postmenopausal woman with recently diagnosed ER/PR-positive, HER2-negative breast cancer with no evidence of lymph node involvement presents for follow-up after lumpectomy of a 1° 0.2-cm tumor and radiation therapy. History includes hysterectomy 10 years ago for uterine fibroids (ovaries remain intact) and osteopenia treated with raloxifene for the past 2 years. Exam is normal. What is the most appropriate next step in management?



**A**

**B**

**C**

**FIGURE 14.3. Breast cancer.** Mediolateral oblique (A) and craniocaudal (B) views from a mammogram demonstrate a spiculated mass with a satellite mass (circle) in the central and outer upper right breast. A targeted breast ultrasound (C) in a different patient demonstrates a hypoechoic mass (arrow) that is taller than it is wide and demonstrates dense posterior acoustic shadowing. (Reproduced with permission from USMLE-Rx.com.)

**KEY FACT**

For breast cancers that are either ER- or PR-positive, hormonal therapy (with tamoxifen or aromatase inhibitors) should be used. Tamoxifen and aromatase inhibitors are effective only in patients with ER-positive and/or PR-positive tumors. Adjuvant chemotherapy for breast cancer should be given to patients with an **infiltrating** ductal or lobular cancer  $>1$  cm or with  $\oplus$  **lymph nodes**.

**A****ANSWER**

Start adjuvant therapy with an aromatase inhibitor (ie, anastrazole), which is more effective than tamoxifen in preventing breast cancer recurrence in postmenopausal women. This patient's risk of distant recurrence outside the breast over the next 10 to 15 years is almost 15%. Furthermore, since she was already on a selective estrogen receptor modulator (SERM) when her breast cancer developed, it is unlikely that tamoxifen would be of benefit.

**KEY FACT**

Tamoxifen is the only FDA-approved drug for the 1° prevention of breast cancer, resulting in 50% risk reduction in pre- and postmenopausal women who have an ↑ risk.

**KEY FACT**

Squamous cell cancers cause hypercalcemia due to the secretion of parathyroid hormone-related protein (PTHrP). Such cancers can also cavitate.

cancers, hormone therapy (tamoxifen for premenopausal, aromatase inhibitor for postmenopausal) should be added for at least 5 years. In HER2-positive disease, 1 year of trastuzumab should be given.

- Hormone therapy with **tamoxifen** or an **aromatase inhibitor** is effective **only in patients with ER- or PR-positive** breast cancers. Aromatase inhibitors are only used in postmenopausal patients.
- For ER/PR-negative tumors, **chemotherapy** is the recommended adjuvant treatment. For ER- or PR-positive tumors, chemotherapy may be needed in addition to hormonal therapy.

**Treatment of advanced (metastatic) breast cancer:****First-line treatment:**

- **Postmenopausal:** Aromatase inhibitors, which prevent the conversion of adrenal androgens into estrogens by targeting aromatase enzymes in muscle and fat, resulting in nearly complete elimination of estrogen production. Associated with hot flashes, bone density loss, and sexual dysfunction. These symptoms can be alleviated with SSRIs, calcium/vitamin D supplementation, and nonhormonal vaginal lubricants.

**Premenopausal:** Tamoxifen, a SERM.

- **Second-line nonhormonal therapy:** If disease progresses or is **hormone receptor-negative**, treat with single-agent **chemotherapy**. Active drugs include paclitaxel, docetaxel, doxorubicin, methotrexate, vinorelbine, capecitabine, and 5-FU.

**Patients with overexpression of HER2:**

- Comprise 10% of patients with breast cancer.
- Associated with a poorer prognosis.
- May respond to trastuzumab, a humanized monoclonal antibody against the HER2 receptor.

**Prevention**

See the discussion of cancer screening in the Ambulatory Medicine chapter.

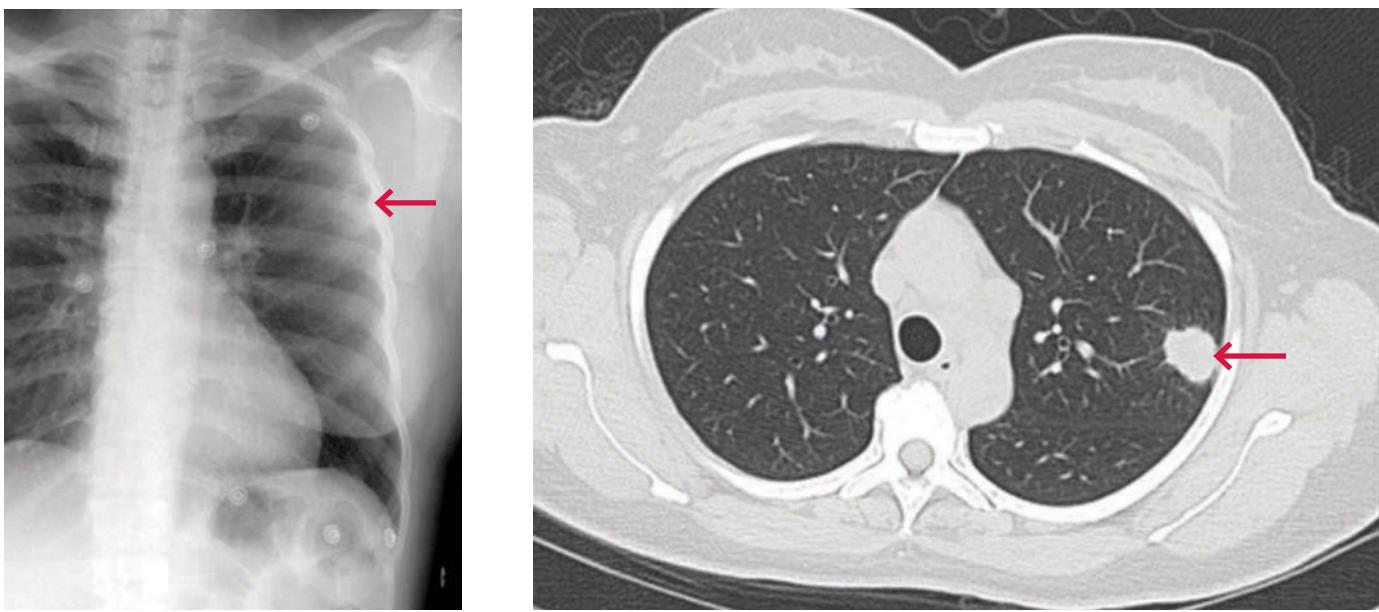
**Lung Cancer**

Smoking cessation is the best means of preventing 1° and recurrent lung cancer. Of all cases of lung cancer, 87% are related to smoking. Significantly higher risk in those with both asbestos exposure and tobacco smoke. Lung cancer presents with weight loss, cough, hemoptysis, fatigue, recurrent bronchitis, and chest pain. Classically divided into categories based on pathology: NSCLC and small cell lung cancer (SCLC).

**NON-SMALL CELL LUNG CANCER**

More common than small cell lung cancer. NSCLC is classified by histology: adenocarcinoma in situ (previously bronchoalveolar), adenocarcinoma, large cell, and squamous. **Accurate staging is key to determining the appropriate therapy.**

- **Diagnosis:** CXR, CT of the chest and abdomen (Figure 14.4); blood work, including a liver panel; possibly a PET scan.
- **Management:** Treat in accordance with stage:
  - **Stage I or II:** Consider surgical resection. Chemotherapy often added for stage II and beyond.
  - **Stage IIIA** (spread to ipsilateral hilar, peribronchial, or intrapulmonary—but not to mediastinal—lymph nodes): Potentially curable with surgery. Adjuvant

**A****B**

**FIGURE 14.4. Non-small cell lung cancer.** Lung adenocarcinoma (arrows) on frontal CXR (A) and CT (B). (Reproduced with permission from USMLE-Rx.com.)

chemotherapy may be administered after surgery. If nonsurgical candidate, **curative-intent** approach includes both chemotherapy and radiation.

- **Stage IIIB (spread to mediastinal lymph nodes):** Not surgically curative. Consider chemotherapy and radiation.
- **Stage IV (metastatic disease):** Chemotherapy has been shown to improve quality of life and modestly prolong survival compared with the best supportive care. Immunotherapy with nivolumab and pembrolizumab can be used for both SCC and adenocarcinomas after progression on chemotherapy.
- **All metastatic NSCLC should be tested for driver mutations such as ALK and EGFR.** Initial treatment depends on the presence of a driver mutation. Tyrosine kinase inhibitors are first-line therapy for NSCLC with these mutations (eg, erlotinib for EGFR  $\oplus$ ). If no driver mutation is present or NSCLC is squamous subtype, a platinum-based regimen is used (ie, cisplatin/paclitaxel).

#### SMALL CELL LUNG CANCER

Characterized by early metastasis; **surgical resection is not part of therapy**. Often associated with neuroendocrine and paraneoplastic features (Figure 14.5). Associated **paraneoplastic phenomena** include SIADH, neurologic disorders (ie, Lambert-Eaton myasthenic syndrome, cerebellar ataxia), and Cushing syndrome.

#### Diagnosis

Two stages:

- **Limited:** All the visible cancer can be encompassed by a single radiation port in the chest.
- **Extensive:** Anything that is not limited.

#### Management

- Combined chemotherapy and radiation improve outcomes in limited-stage disease, but the prognosis remains poor.
- Chemotherapy plus prophylactic whole-brain irradiation is the treatment of choice for patients with extensive-stage disease, yielding high response rates (palliation for



#### KEY FACT

NSCLC with a malignant pleural effusion is stage IV and unresectable.



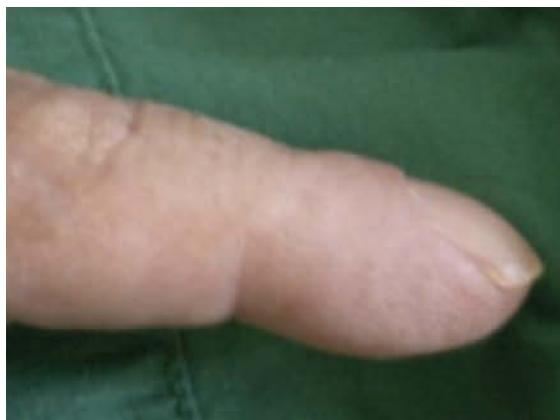
#### KEY FACT

Tyrosine kinase inhibitors are now first-line therapy for metastatic NSCLC harboring driver mutations (ie, ALK  $\oplus$   $\rightarrow$  crizotinib, EGFR  $\oplus$   $\rightarrow$  erlotinib).



#### QUESTION

A 70-year-old woman with an extensive smoking history presents with 6 months of hemoptysis, weakness, and a 50-lb weight loss. She has been bedridden for the past week. Exam is normal. Lab results show a sodium level of 128 mEq/L; CT scans show a 14-cm left hilar lymph node mass, multiple liver metastases, and three brain metastases; a bone scan shows too many metastases to count. Bronchoscopic biopsy reveals SCLC. What are the most appropriate next steps?

**A****B****C**

**FIGURE 14.5. Hypertrophic osteoarthropathy associated with small cell lung cancer.** (A) Large-sized right hand with edematous swelling. (B) Periungual erythema and clubbing. (C) X-ray of the femur showing extensive characteristic periosteal bone apposition. (Source: Kanen BLJ, et al. Hypertrophic osteoarthropathy as the cause of a super scan of the bone in a patient with prostate cancer: a case report. *J Med Case Reports*. 2008;2:104.)

#### KEY FACT

Almost any paraneoplastic syndrome may be seen with SCLC. The exception is hypercalcemia due to PTHrP secretion, which is due to SCC.

#### KEY FACT

SCLC metastasizes early and has a unique staging system: "limited" (ie, all the cancer encompassed by a single radiation port) versus "extensive" (everything else). Chemotherapy and prophylactic cranial irradiation should be considered for SCLC.

**A**

#### ANSWER

Chemotherapy and whole brain radiation therapy. Most patients with SCLC (even those with widespread metastases) respond dramatically to chemotherapy and whole brain radiation therapy. This patient's hyponatremia is most likely caused by SIADH and will resolve following response to chemotherapy.

1-2 years is possible in 50% of cases). However, treatment is rarely curative, virtually all patients relapse.

- Patients with limited-stage disease who respond to chemotherapy have improved survival with prophylactic cranial irradiation.
- Chemotherapy drugs of choice include etoposide and cisplatin.
- Bisphosphonate therapy: Bisphosphonates pamidronate and zolendronate help ↓ skeletal pain and fractures.

#### Mesothelioma

- Arises from mesothelial surfaces of the peritoneum, pleura, pericardium, and tunica vaginalis (testes). **Asbestos** exposure ↑ the risk. Smoking and asbestos exposure are synergistic.
- Most commonly presents with dyspnea and a large unilateral pleural effusion; less commonly presents with malignant ascites.
- Poor prognosis. Tumor debulking, thoracentesis, and pleurodesis may ↓ the impact of pleural-based disease. Chemotherapy only modestly effective.

#### Thymoma

- An anterior mediastinal tumor often detected during workup for **myasthenia gravis**. Most are benign, but some progress to thymic carcinoma. Other paraneoplastic syndromes associated with thymoma include **pure red cell aplasia**.
- Resection is the most effective treatment. If spread occurs outside the mediastinum, chemotherapy and radiation may be used as well but have limited efficacy.

#### Squamous Cell Carcinoma of the Head and Neck

Many SCCs are curable. Major risk factors include tobacco (cigarettes, chewing tobacco, cigars), alcohol use, and HPV. Lesions progress as follows: leukoplakia →

erythroplakia → dysplasia → carcinoma in situ → invasive carcinoma. The highest risk of morbidity and mortality associated with head and neck cancer results from local extension rather than from metastasis.

### Symptoms/Exam

May present with a hoarse voice, globus, otalgia, a sore in the mouth or throat, a lump in the throat, numbness in the face or throat, odynophagia, dysphagia, lymphadenopathy, tinnitus, or hearing loss. Evaluate the scalp, cranial nerves, lymph nodes, and oral cavity.

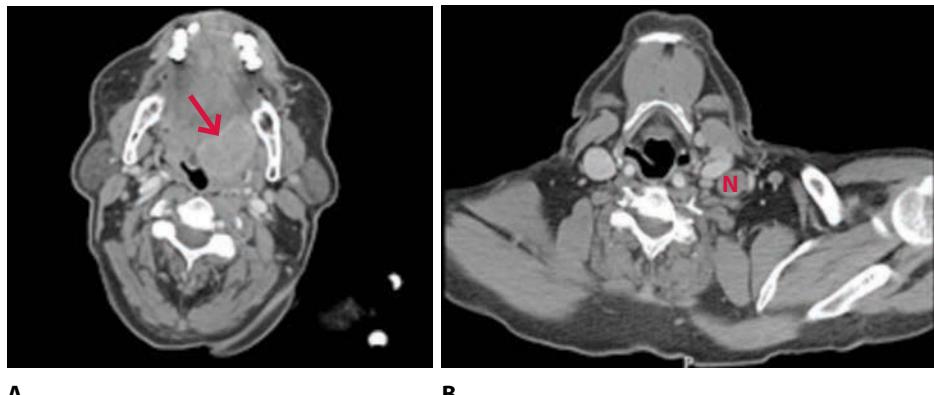
### Diagnosis

- Pan-upper endoscopy should be performed under anesthesia to evaluate the entire aerodigestive tract.
- FNA is the standard means of establishing involvement of cervical lymph nodes.
- Core needle biopsy is not done on newly diagnosed lesions owing to concerns over tumor recurrence in the needle tract.
- MRI or CT of the head and neck (Figure 14.6); CXR.

### Management

Depends on both the anatomical site (eg, the oral cavity, base of tongue, oropharynx, pharynx, hypopharynx, or larynx) and the presence of lymph node involvement. Treatment with definitive radiation therapy to the pharyngeal axis and bilateral neck, radical neck dissection, or a combination of these local modalities is typically recommended. Long-term disease-free survival is seen in about 40% to 67% of cases.

- **Early-stage tumors in the oral cavity, base of the tongue, or lips:** May be treated with radiation or surgery alone.
- **Early-stage tumors of the oropharynx:** Radiation is the preferred modality.
- **Cervical lymph node involvement:** Treat with surgery, radiation, or chemoradiation. Patients often require a PEG tube due to toxicity of radiation to mucosa. Commonly used chemotherapeutic agents include cisplatin, carboplatin, 5-FU, paclitaxel, docetaxel, methotrexate, and, recently, cetuximab.
- For some patients with laryngeal cancer, voice-sparing treatments (partial laryngectomy, chemoradiotherapy) should be considered; as many as 25% can avoid laryngectomy.



**FIGURE 14.6. Squamous cell carcinoma of the tongue base.** (A) Transaxial contrast-enhanced CT image shows a large enhancing mass at the base of the tongue (arrow). (B) Transaxial image lower in the neck shows metastatic left cervical lymph nodes, the largest of which (N) is posterior to the left internal jugular vein. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

Of patients with myasthenia gravis, 10% have thymomas.  
Of patients with thymomas, 30% have myasthenia gravis.



### QUESTION

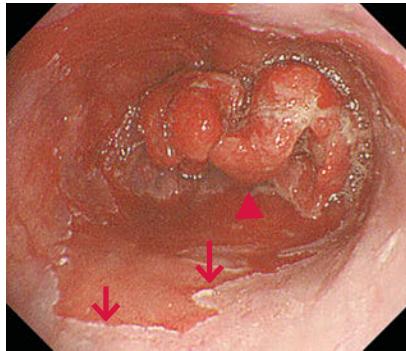
A 40-year-old man presents with a swelling in his neck of 4 months' duration. He has a 30-pack-year smoking history. On exam, he has a firm, 3-cm lymph node in the mid-cervical region. FNA of the lymph node reveals squamous cell carcinoma (SCC). What is the most appropriate next diagnostic step?

**KEY FACT**

Prior EBV infection—not smoking—is the key risk factor for nasopharyngeal cancer.

**KEY FACT**

Adenocarcinoma of the esophagus arising from Barrett esophagus is ↑ in incidence.

**FIGURE 14.7. Esophageal cancer.**

Esophageal adenocarcinoma (arrowhead) on endoscopy against a background of the pink tongues of Barrett esophagus (arrows). (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008, Fig. 285-3D.)

**FIGURE 14.8. Sister Mary Joseph nodule.**

(Reproduced with permission from USMLE-Rx.com.)

**ANSWER**

Triple endoscopy (pharynx, larynx, esophagus, trachea, and bronchi) for evaluation and treatment of likely SCC of the head and neck with an unknown 1° site. The location and pathology suggest a head and neck 1° tumor.

## Nasopharyngeal Carcinoma

- Associated with EBV infection, *not* tobacco or alcohol. **Endemic to China and parts of Africa.**
- Presents with a change in hearing, a sensation of ear stuffiness, tinnitus, nasal obstruction, and/or a mass in the neck.
- Not a surgical disease; requires chemotherapy (**cisplatin**) with concurrent **radiation**. Two-thirds of patients are cured.

## Thyroid Cancer

Refer to the Endocrinology chapter for a more detailed discussion of this topic.

## Esophageal Cancer

The 1° histologies are SCC and adenocarcinoma (↑ in incidence). Risk factors for SCC include tobacco, EtOH, HPV infection. SCC is three times more common among African Americans than among Caucasians; adenocarcinoma is more common in Caucasians. Risk factors for adenocarcinoma include obesity, GERD, EtOH, and **Barrett esophagus** (associated with a **30-fold ↑ risk**).

- Presents with dysphagia, odynophagia, weight loss, cough, and hoarseness.
- **Staging evaluation:** Evaluate with endoscopy and biopsy (Figure 14.7), chest/abdomen CT, endoscopic ultrasound, and bronchoscopy (to rule out tracheal invasion).
- **Management:**
  - **Localized esophageal cancer:** Typically treat with surgery (esophagectomy vs endoscopic resection depending on depth of tumor invasion) with neoadjuvant chemotherapy or chemoradiation (5-FU plus cisplatin and external beam radiotherapy). Postoperative chemoradiation should be considered for locally advanced cancers.
  - **Metastatic disease:** Treatment is palliative; drugs include cisplatin, paclitaxel, 5-FU, and gemcitabine. Trastuzumab added for tumors that are HER2 +.
  - PEG tubes are often required to get patients through chemoradiation (as in head and neck cancer).

## Gastric Cancer

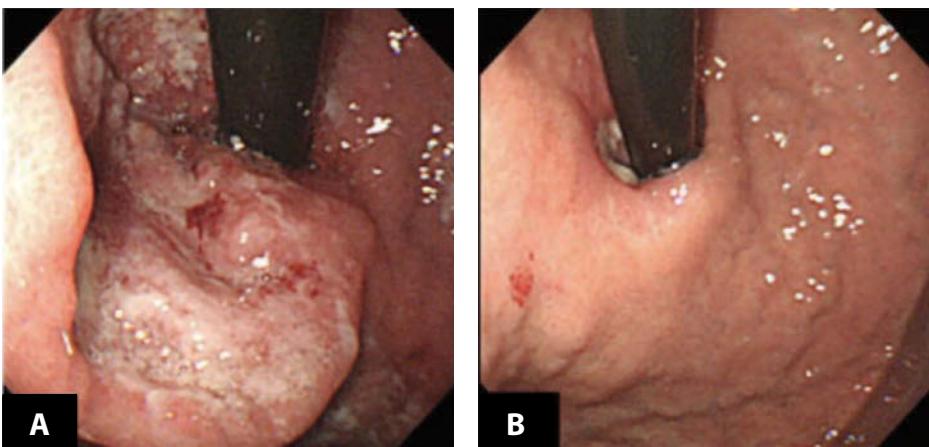
**Most commonly occurring in Asia,** gastric cancer is associated with a diet of smoked and pickled foods that is **high in nitrates** and low in vegetables. Risk factors include coal mining, nickel, rubber, and timber processing smoking. *H pylori* infection, chronic atrophic gastritis, intestinal metaplasia, and pernicious anemia.

### Symptoms/Exam

Presents with pain, anorexia, weight loss, vomiting, and GI bleeding. Left supraclavicular lymphadenopathy (Virchow node) and periumbilical lymphadenopathy (Sister Mary Joseph nodule; Figure 14.8) may also be seen.

### Diagnosis

- Endoscopy (Figure 14.9) and biopsy.
- Staging evaluation includes CT of the chest, abdomen, and pelvis as well as endoscopic ultrasound.
- Adenocarcinoma is the predominant histology.

**KEY FACT**

Left supraclavicular lymphadenopathy (Virchow node) and periumbilical nodularity (Sister Mary Joseph nodule) may represent spread from gastric cancer and other GI malignancies.

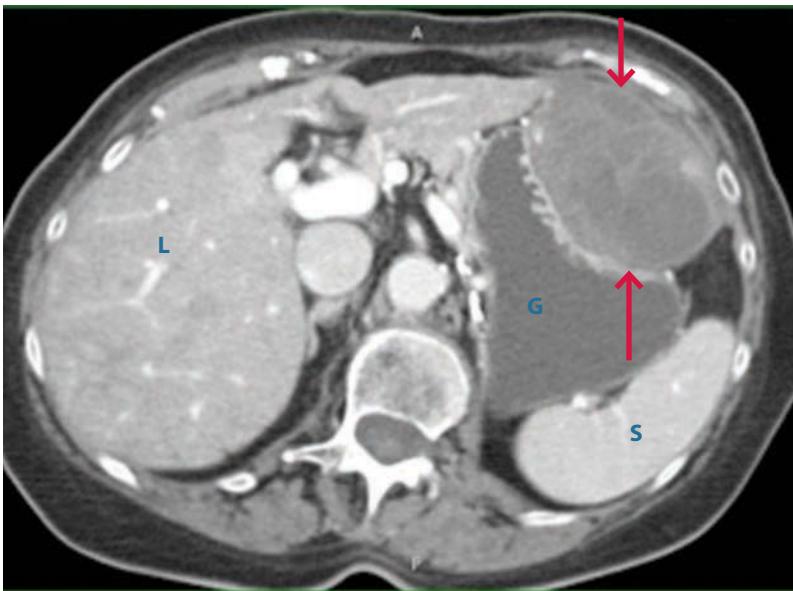
**FIGURE 14.9. Gastric cancer.** (A) Upper GI endoscopy shows Borrmann type II tumor measuring  $5.0 \times 4.0$  cm. (B) Follow-up endoscopy after first course of chemotherapy shows scar lesion and no further lesions. (Source: Matsuno Y, et al. A complete response to S-1 plus cis-diamminedichloroplatinum in advanced-stage esophageal and gastric adenocarcinoma: a case report. *World J Surg Oncol.* 2012;10:133.)

### Management

- Surgery preferred for resectable gastric cancer along with neoadjuvant and/or adjuvant chemotherapy for those with locally advanced disease. Rarely, gastric cancers may express HER2, in which case trastuzumab is given.
- Treat metastatic gastric cancer with chemotherapeutic agents such as epirubicin, cisplatin, and 5-FU.

### GASTROINTESTINAL STROMAL TUMORS

- Sarcoma of the stomach or small bowel wall, GI stromal tumors (GIST), is shown in Figure 14.10. Associated with an activating mutation in the c-kit oncogene.



**FIGURE 14.10. Gastrointestinal stromal cell tumor.** Transaxial image from a contrast-enhanced CT demonstrates a large, heterogeneously enhancing mass (arrows) arising from the anterior gastric wall, displacing the gastric lumen posteriorly. L = liver; G = gastric lumen; S = spleen. (Reproduced with permission from USMLE-Rx.com.)

**KEY FACT**

GIST tumors often express c-kit and frequently respond to treatment with imatinib. Sunitinib and dasatinib, newer tyrosine kinase inhibitors, can be used for GIST that becomes resistant to imatinib.

**KEY FACT**

Eradication of *H pylori* is the treatment of choice for MALT lymphomas.

**KEY FACT**

CA 19-9 levels are not specific for pancreatic cancer but may be a useful means of following **treatment response** in patients with pancreatic cancer.

**KEY FACT**

In pancreatic cancer, invasion into the superior mesenteric artery or vein implies unresectable disease.

**Management:**

- Localized disease treated surgically. **High-risk localized tumors** (based on size and mitotic count) treated with prolonged imatinib (tyrosine kinase inhibitor) following resection.
- **Metastatic GIST** highly resistant to standard chemotherapy. Targeted therapy with **imatinib** can lead to dramatic and prolonged responses in patients with previously intractable and incurable disease. New agents, sunitinib and dasatinib, can be used if GIST becomes resistant to imatinib.

**MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA**

Gastric mucosa-associated lymphoid tissue (MALT) is linked to *H pylori* infection; >80% of cases regress after treatment for *H pylori*.

**Pancreatic Cancer**

A highly lethal cancer with a median survival of 9 to 12 months and a **5-year survival of 3%**. **Resection only potentially curative option.** More than 50% are metastatic or unresectable at time of diagnosis. Risk factors include hereditary disease (ie, Peutz-Jeghers syndrome), tobacco exposure, chronic pancreatitis, and diabetes mellitus.

**Symptoms/Exam**

- Presents with weight loss, jaundice, pain, glucose intolerance, and a nontender palpable gallbladder (Courvoisier's sign).
- **Painless jaundice** is a sign of intrapancreatic bile duct obstruction and may allow for early detection of resectable disease.

**Diagnosis**

- The serum marker **CA 19-9** can be **useful in monitoring treatment but is not specific enough to be used for diagnosis.**
- CT of the abdomen with fine cuts through the pancreas (pancreatic protocol CT); endoscopic ultrasound; ERCP.

**Management****Resectable disease:**

- Defined as that which does not involve the major vessels or celiac axis, with no distant metastases.
- The only curative therapy is pancreaticoduodenectomy (the Whipple procedure), although long-term survival rates are poor.
- Borderline resectable disease can potentially become resectable with neoadjuvant chemotherapy.
- **Adjuvant therapy** after pancreaticoduodenectomy typically involves gemcitabine as well as concurrent chemotherapy/combined radiation therapy with 5-FU.

**Unresectable disease:**

- Improved survival with FOLFIRINOX or gemcitabine-based chemotherapy. Gemcitabine is FDA approved for the treatment of metastatic pancreatic cancer and results in improved clinical benefit and overall survival compared with 5-FU. Palliation with radiation, a biliary stent, or choledochojejunostomy.
- A nerve block to the celiac plexus may relieve pain.

## Hepatocellular Carcinoma

Risk factors for hepatocellular carcinoma (HCC) include HBV (especially vertical transmission), HCV, alcohol abuse (especially in combination with HCV), chronic hepatitis and cirrhosis, hemochromatosis,  $\alpha_1$ -antitrypsin deficiency, and aflatoxin exposure.

### Diagnosis

- High-risk patients to be considered for screening are Asian male HBV carriers >40 years, Asian female HBV carriers >50 years; all HBV carriers with cirrhosis; African and North American blacks with HBV; patients with a family history of HCC; those with high HBV DNA concentrations; all other patients with cirrhosis.
- High-risk patients should be screened with hepatic ultrasound, with or without  $\alpha$ -fetoprotein, generally in 6- to 12-month intervals, although the appropriate interval has not been established.
- AFP alone should not be used for screening unless ultrasound is unavailable, as this measure alone does not correlate with the size, stage, or prognosis of HCC. It is  $\uparrow$  only about 50% of the time in HCC.
- Markedly  $\uparrow$  AFP in concert with consistent imaging (Figure 14.11) and high-risk liver disease may obviate the need for a biopsy.

### Management

- Resection is the treatment of choice if liver function is adequate and anatomy permits. Resection with partial hepatectomy is associated with a very high risk of hepatic decompensation.



**FIGURE 14.11. Hepatocellular carcinoma.** Coronal reformation from a contrast-enhanced CT shows large left hepatic lobe HCC (arrows). St = stomach; S = spleen. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

The classic appearance of HCC on triple-phase CT of the abdomen is a lesion that is hypervascular in the arterial phase and washes out in the portal/venous phase. Biopsy is not necessary for confirmation if imaging is characteristic.



### QUESTION 1

A 70-year-old man presents with a 1-month history of light stools, dark urine, and pruritus. Exam reveals jaundice and fullness in the RUQ. Lab results: AST 99 U/L, ALT 140 U/L, alkaline phosphatase 520 U/L, and total bilirubin 16.2 mg/dL. Abdominal CT shows marked intrahepatic bile duct dilatation, dilated gallbladder, and a mass in the head of the pancreas. What is the most appropriate next step?



### QUESTION 2

A 55-year-old woman with cirrhosis from HCV presents with fatigue. Exam shows mild jaundice, spider angiomas, and mild peripheral edema. Lab results: bilirubin 3.0 mg/dL, INR 1.5, platelet count 80,000/ $\mu$ L, AST 70 U/L, ALT 60 U/L, alkaline phosphatase 120 U/L, normal hematocrit, and serum  $\mu$ -fetoprotein (AFP) 450 ng/mL. Abdominal ultrasonography shows a coarse liver, mild ascites, and a 2.5-cm hyperechoic hepatic mass that was absent on previous imaging. CT of the liver shows vascular enhancement of the mass. What is the most appropriate next step?

**KEY FACT**

Resection should be considered for patients with a solitary HCC confined to the liver that shows no radiographic evidence of invasion of the hepatic vasculature, no evidence of portal hypertension, and well-preserved hepatic function (Child-Pugh class A).

**KEY FACT**

HNPCC has few polyps, but FAP has thousands of polyps; thus, treatment for FAP is colectomy.

**KEY FACT**

Treatment of stage III (node-positive) colon cancer includes adjuvant chemotherapy, which ↓ recurrence and ↑ survival.

**A****ANSWER 1**

Endoscopic retrograde cholangiopancreatography (ERCP) for evaluation of new-onset obstructive jaundice, which in an elderly patient is most often due to pancreatic or biliary tract cancer. ERCP can also be used to obtain biopsy specimens and for therapy with stent deployment.

- Patients with cirrhosis may be offered transplantation for single tumors <5 cm or three tumors <3 cm each.
- Chemoembolization, intratumoral ethanol injection, cryotherapy, and radiofrequency ablation are all options for unresectable lesions.
- There is no standard chemotherapy with proven efficacy. The multikinase inhibitor **sorafenib** has been shown to prolong survival in patients with good hepatic function.
- See the Gastroenterology and Hepatology chapter for further details on cirrhosis and liver transplantation.

**Colorectal Cancer**

Seventy-five percent of colorectal cancer cases occur in those with no risk factors (eg, family history, obesity, smoking, diets high in animal fat, genetic syndromes, IBD, acromegaly). Genetic syndromes include:

- **Hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome):** Characterized by few polyps (nonpolyposis); associated with endometrial, gastric, renal, ovarian, and skin cancer and with the mismatch repair genes MLH1/2 and MSH1/2.
- **Familial adenomatous polyposis (FAP):** Characterized by thousands of polyps; treatment of choice is colectomy. Associated with a mutation in the APC gene.
- **Li-Fraumeni syndrome:** Associated with the p53 mutation.
- **Peutz-Jeghers syndrome:** Autosomal dominant disorder with hyperpigmented macules on lips. ↑ risk of colorectal, stomach, small intestine, and pancreatic cancers.

**Symptoms/Exam**

Presentation is highly variable. May be asymptomatic or present with symptoms ranging from abdominal pain to colonic obstruction, lower GI bleeding, changes in bowel habits, anorexia, fever, or weight loss.

**Diagnosis**

Diagnosed by a mass detected by digital rectal exam (DRE), fecal occult blood test, or during sigmoidoscopy or colonoscopy; confirmed by colonoscopy and biopsy (Figure 14.12).

**Management**

- **Treat in accordance with stage:**
  - **Stage I:** Partial colectomy; no further therapy.

**A****ANSWER 2**

A new hepatic mass with vascular enhancement in a patient with HCV cirrhosis and ↑ AFP is virtually diagnostic of HCC, and biopsy is unnecessary. Patients with advanced liver disease and HCC should usually be evaluated for liver transplantation.

**A****B**

**FIGURE 14.12. Colon cancer.** (A) Colonoscopy examinations show an ulcerated tumor in the ascending colon. (B) CT scan with contrast media reveals mucosal thickness in the ascending colon without lymph node involvement or metastatic tumors. (Source: Iwamuro M, et al. Serum anti-p53 antibody as a tumour marker for colorectal cancer screening. *Ecancermedicalscience*. 2015;9:560.)

- **Stage II:** Partial colectomy. Adjuvant therapy is controversial. Consider adjuvant chemotherapy for certain high-risk features (eg, high-grade disease, obstruction, perforation, very large tumors).
- **Stage III:** Partial colectomy. These cancers with lymph node involvement all merit adjuvant chemotherapy as this ↓ recurrence and ↑ survival. The standard is 5-FU or 5-FU/leucovorin/oxaliplatin (FOLFOX).
- **Stage IV:** Palliative colectomy or colon diversion to prevent obstruction. Chemotherapy for metastatic disease is generally palliative. Regimens include FOLFOX or FOLFIRI with addition of cetuximab if KRAS wild type status. The exception is stage IV disease due to one or more resectable hepatic metastases, which may still be curable with resection (the liver is generally the first site of metastasis). In this case, surgery should be aggressively pursued.
- **Chemotherapeutic agents:** Two medications are the mainstay of chemotherapy for colon cancer:
  - **5-FU:** Converted to F-dUMP; inhibits thymidine production and interferes with DNA synthesis.
  - **Leucovorin (folinic acid):** Stabilizes the bond between F-dUMP and thymidylate synthetase, enhancing the efficacy of 5-FU.
  - Other drugs include irinotecan, oxaliplatin, cetuximab, and bevacizumab.
- **Rectal cancer:** Owing to the anatomy of the rectum (and the desire to preserve the rectal sphincter if possible), surgical approaches have less room for adequate margins. Therefore, **radiation therapy is often given either before or after surgery** in addition to or in combination with chemotherapy.

### Prevention

See the discussion of cancer screening in the Ambulatory Medicine chapter.

## Prostate Cancer

The most common non-skin cancer in men. A  $\oplus$  family history and African American ethnicity are both risk factors for prostate cancer.

### Symptoms/Exam

No symptoms typically in early-stage disease. May have lower urinary tract symptoms due to coexisting benign prostatic hyperplasia. Hematuria unusual presenting feature. **Asymmetric induration or nodules** on DRE concerning for prostate cancer.

### Diagnosis

- **Prostate biopsy:** Indicated in men with nodule on DRE or PSA  $>4$  ng/mL, and should be considered if PSA  $<4$  ng/mL but rapidly rising.
- **Gleason score:** Involves microscopic evaluation of grade; tumors are graded from 2 to 10, with 2 being almost benign and 10 being highly aggressive. Has a prognostic impact on outcomes in almost every stage of prostate cancer.

### Management

- **Localized disease:** Four major options are available for the treatment of **localized prostate cancer**:
  - **Active surveillance:** For those with significant comorbidities, elderly patients, or those with low-risk disease (PSA  $<10$  ng/mL, T1, and Gleason score  $\leq 6$ ). Patients with recently diagnosed prostate cancer and a PSA of  $<10$  ng/mL have a low incidence of bony metastasis.
  - **External beam radiation therapy:** For patients at risk for extraprostatic spread or contraindications to surgery.

### KEY FACT

The liver is the most frequent site of metastasis in colon cancer, whereas rectal cancers may spread through paravertebral venous and lymphatic channels directly to the lungs without liver involvement.

### KEY FACT

Colon cancer with one or more resectable liver metastases can still be curable with surgery. This is one of the few metastatic cancers that can be cured.

### KEY FACT

Most men die with their prostate cancer, not from it.

### QUESTION 1

A 55-year-old man presents for follow-up after resection of stage II colon cancer. He received no adjuvant therapy. Exam is normal. Lab results show ↑ CEA (50 ng/mL), which was normal 1 year ago. CT of the chest and abdomen shows multiple pulmonary nodules  $<1$  cm and five hepatic lesions of 3 to 8 cm. Biopsy of a liver lesion reveals adenocarcinoma consistent with the 1° tumor. What is the most appropriate next step?

### QUESTION 2

A 70-year-old man presents with acute onset of back pain 10 years after he underwent external beam radiation therapy for prostate cancer. He takes leuproreotide, initiated 5 years ago for a rising PSA without evidence of metastases. Lab results include normal Hb, PSA  $<0.4$  ng/mL, and testosterone 16 ng/mL; x-rays of spine show a T6 acute fracture. Bone scan reveals intense radioisotope uptake at T6. What disease process led to the fracture?

**KEY FACT**

The decision to screen for prostate cancer should include a thorough discussion with the patient about risks (false-positives, uncertain efficacy in reducing death from prostate cancer, posttreatment complications such as urinary incontinence or proctitis) and benefits (earlier diagnosis and treatment may improve survival). Testing in men >age 75 years is not recommended.

**KEY FACT**

The key to treating metastatic prostate cancer is androgen deprivation. Options include bilateral orchectomy, GnRH agonists (goserelin, leuprolide), and antiandrogens such as flutamide. Side effects include osteoporosis, hot flashes, gynecomastia, anemia, impotence, loss of libido, and weight gain.

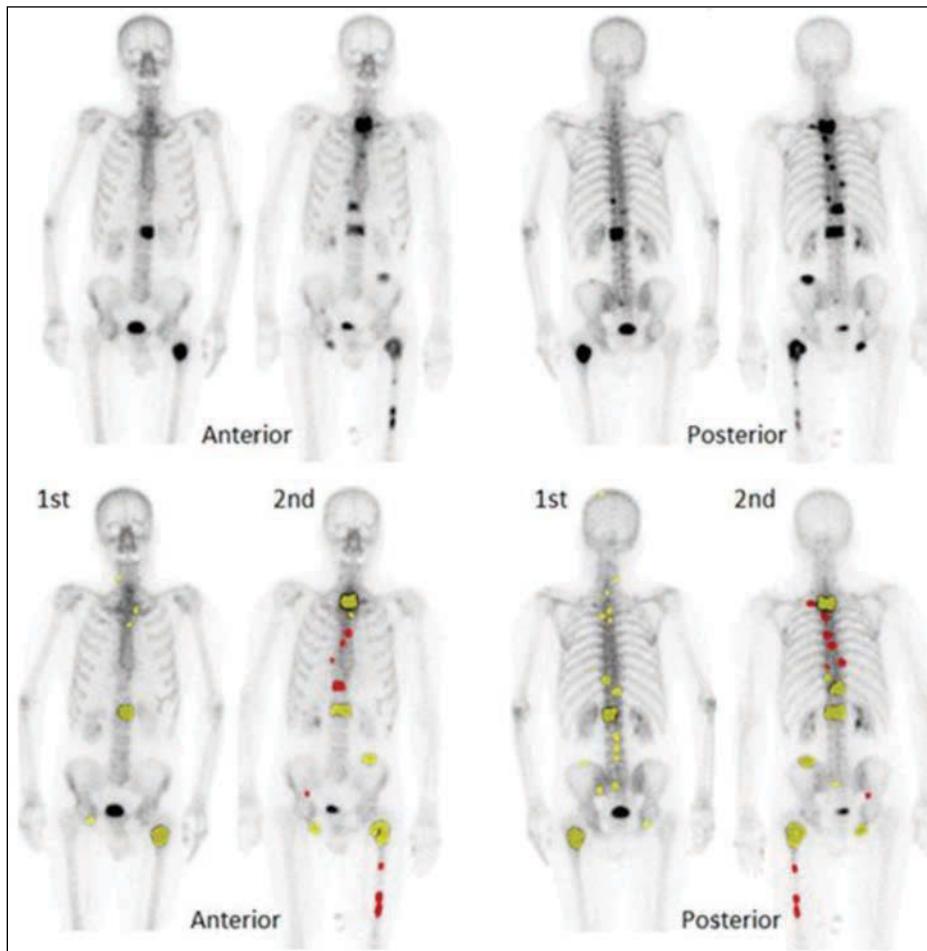
**A****ANSWER 1**

Patients with colon cancer and unresectable liver metastases require systemic treatment with chemotherapy. Hepatic resection of metastatic colon cancer is indicated only for isolated metastatic disease.

**A****ANSWER 2**

Osteoporosis. Bone scans are  $\oplus$  in regions of osteoblastic activity, which may represent either prostate cancer metastasis or osteoporotic fracture. In patients with prostate cancer, GnRH agonists such as leuprolide can cause bone loss by  $\downarrow$  serum testosterone.

- **Brachytherapy:** Implantation of radioactive seeds in the prostate gland.
- **Radical prostatectomy:** For patients with long life expectancy and high likelihood that the cancer is confined to the prostate.
- **Advanced disease** (ie, recurrence after local therapies or metastatic disease; Figure 14.13) is treated as follows:
  - **Castration-sensitive prostate cancer:** Androgen deprivation is the most effective. Treatments include:
    - Bilateral orchectomy.
    - GnRH agonists (leuprolide, goserelin) suppress testosterone secretion by inhibiting FSH/LH release from the pituitary.
    - Oral antiandrogens are less proven but have fewer side effects. Generally used only in combination with GnRH agonists.
  - **Castration-resistant metastatic prostate cancer:**
    - Treatment options include newer antiandrogens (enzalutamide and abiraterone), systemic chemotherapy (docetaxel plus prednisone), and non-chemotherapy (radium and immunotherapy).
    - All patients with advanced prostate cancer and bone metastases recommended to receive either bisphosphonate or denosumab to  $\downarrow$  osteoporosis and fracture risk.



**FIGURE 14.13. Bone metastases in prostate cancer.** Bone scans from a patient with progress of metastatic disease. Anterior and posterior views from the first (1st) and second (2nd) scans without (above) and with (below) marks showing lesions detected by the automated method. Red marks indicate new lesions and yellow marks indicate old lesions. (Source: Kaboteh R, et al. Progression of bone metastases in patients with prostate cancer—automated detection of new lesions and calculation of bone scan index. *EJNMMI Res.* 2013;3:64.)

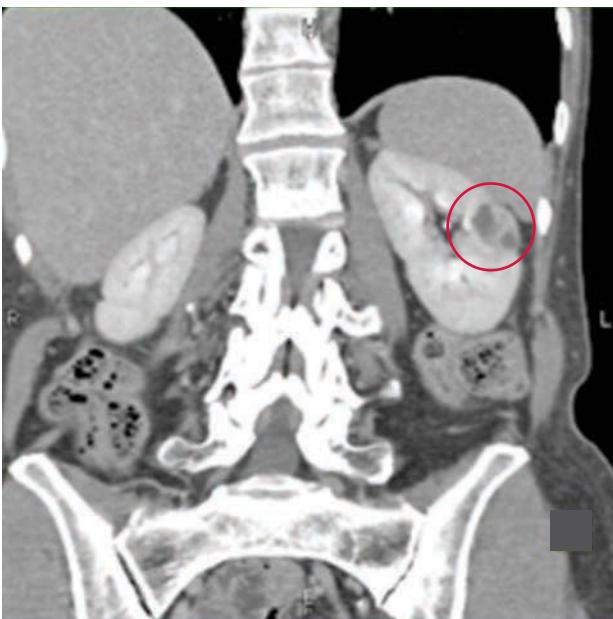
## Prevention

- Finasteride shown to ↓ incidence of prostate cancer, but no improvement in prostate cancer mortality. It has a possible association with higher-grade tumors.
- For further details, see the discussion of cancer screening in the Ambulatory Medicine chapter.

## Kidney Cancer

About 85% of kidney cancers are renal cell carcinoma (RCC). Risk factors include obesity, smoking, and von Hippel–Lindau syndrome (associated with retinal angiomas, CNS hemangioblastomas, and kidney cancer).

- **Symptoms/Exam:** ~ 10% present with classic triad (flank pain, hematuria, palpable mass) suggesting advanced local disease. May also present with left-sided varicocele (due to left gondal vein draining into left renal vein).
- **Diagnosis:** RCC must be ruled out in patients with unexplained hematuria. CT typically performed (Figure 14.14).
  - Associated with numerous paraneoplastic phenomena including fever, erythropoietin production, PTHrp, insulin, and glucagon.
  - Presumptive diagnosis based on radiologic appearance. Tissue diagnosis typically done at time of nephrectomy/partial nephrectomy. Needle biopsy rarely done, carries small risk of seeding track with tumor cells.
- **Management:**
  - **Localized disease:** Partial or complete nephrectomy.
  - **Metastatic disease:**
    - First-line treatments are the VEGF/MTOR drugs sunitinib, pazopanib, axitinib, sorafenib, everolimus). IL-2 rarely used due to its toxicity, but may be used in young people. Nivolumab, a new immunotherapy agent, approved for pretreated patients.
    - Debulking nephrectomy or radical nephrectomy may be indicated for metastatic disease if the kidney tumor itself represents the bulk of the cancer.



**FIGURE 14.14. Renal cell carcinoma.** (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

For castration-sensitive disease, **androgen deprivation with** GnRH agonists + oral antiandrogens = “combined” androgen blockade.

### KEY FACT

In patients with suspicious kidney masses seen on imaging, biopsy should **not** be done given the risk of seeding the tumor. These patients should be referred to a urologist to discuss surgical resection.



### QUESTION 1

A 25-year-old man presents with an enlarged, painless right testicular mass. Lab results:  $\beta$ -hCG 30 mU/mL, AFP 40 ng/mL, and normal LDH. Scrotal ultrasound reveals a solid, hypoechoic, 5-cm right testicular mass. Radical orchiectomy confirms the tumor is as yolk sac carcinoma with choriocytic elements. A week later,  $\beta$ -hCG is 1.8 mU/mL, and AFP is 16.3 ng/mL. What is the most appropriate next step?



### QUESTION 2

A 30-year-old man presents with ↑ abdominal girth, intermittent midabdominal pain radiating to the back, and a 15-lb weight loss over the past 4 months. Exam reveals fullness in the mid-abdomen without tenderness and normal descended testes. CT scan of the abdomen shows 8-cm retroperitoneal mass, found to be a poorly differentiated carcinoma via needle biopsy. Lab results:  $\beta$ -hCG 212 mU/mL and AFP 478 ng/mL. Testicular ultrasound is normal. What is the most appropriate next step?

## Testicular Cancer

### KEY FACT

An undescended testicle is a major risk factor for testicular cancer in both testes, even after orchidectomy.

### KEY FACT

↑ AFP in testicular cancer signifies nonseminoma.

A

### ANSWER 1

Check AFP again 14 days after surgery to evaluate the patient's prognosis, as the half-life of AFP is ~ 1 week, whereas that of  $\beta$ -hCG is ~ 24 hours. This patient has stage I nonseminomatous testicular cancer confined to the testis and probably has already been cured by the initial surgery.

A

### ANSWER 2

Young male patients with poorly differentiated midline carcinomas containing germ cell cancer markers are likely to have extragonadal germ cell cancer and may respond to cisplatin-based chemotherapy.

The most common solid cancer in men aged 15 to 35 years; a second peak occurs >60 years of age. An **undescended testicle** is a **major risk factor** in BOTH testes. Other risk factors include prior testicular cancer, Klinefelter syndrome (47 XXY), and a  $\oplus$  family history. The 5-year survival rate for all patients with germ cell tumors is roughly 95%.

### Symptoms/Exam

- Typically presents with nodule or painless lump on one testicle. May also present with pain or discomfort.
- Testicular pain does **not** indicate a benign etiology.
- Up to 10% present with symptoms due to metastatic disease (eg, cough from pulmonary metastasis, bone pain).

### Diagnosis

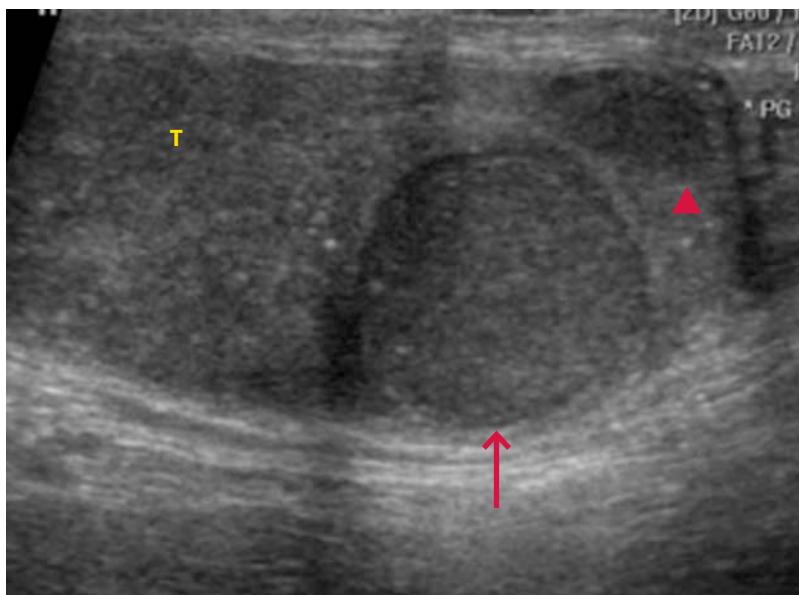
- Any solid, firm testicular mass is **malignant until proven otherwise**. Evaluate with testicular ultrasound to identify a mass (Figure 14.15).
- Tissue diagnosis made via radical inguinal orchietomy. Needle biopsy contraindicated. Also check serum AFP,  $\beta$ -hCG, and LDH.
- Two major pathologic classifications important for choosing treatment: seminoma versus nonseminoma (Table 14.4).
- Following tissue diagnosis, obtain chest/abdomen/pelvis imaging to evaluate for metastatic disease. **Retroperitoneal lymph nodes** typically first involved, **not** inguinal nodes, given testicular descent.

### Management

The treatment of germ cell cancers is determined by prognostic features and stage:

#### ■ Early-stage seminoma:

- Orchietomy usually curative when disease limited to testicle.
- Radiotherapy or platinum-based chemotherapy if evidence of retroperitoneal metastasis on imaging.



**FIGURE 14.15. Seminoma.** Longitudinal ultrasound image of the testicle (T) showing a homogeneous intratesticular mass (arrow) and an additional, smaller focus of tumor (arrowhead). (Reproduced with permission from USMLE-Rx.com.)

**TABLE 14.4. Seminoma vs Nonseminomatous Germ Cell Tumors**

	SEMINOMA	NONSEMINOMA
AFP levels	Never ↑	May be ↑
β-hCG	May be ↑ (~ 20%)	May be ↑
Treatment of early stage disease	Orchiectomy usually curative if limited to testicle	May need retroperitoneal lymph node dissection and chemotherapy in addition to orchiectomy
Treatment of advanced stage disease	Combination chemotherapy	Combination chemotherapy
Prognosis	Generally excellent	Generally not as good as seminoma

- Early-stage nonseminoma:** Radical inguinal orchiectomy ± retroperitoneal lymph node dissection ± single cycle platinum-based chemotherapy (dependent on tumor features). Abdominal radiation is inappropriate in nonseminomatous testicular cancer.
- Advanced seminoma or nonseminoma:** All patients receive chemotherapy (eg, bleomycin, etoposide, cisplatin). High cure rates (>85%). Brain metastases can be treated with whole brain radiation therapy and combination chemotherapy.
- Prognostic features:** Poor-risk features for nonseminomas include high tumor marker levels, nonpulmonary metastases, and mediastinal 1° site. Seminomas have overall good prognosis unless patients have metastasis outside the lungs and lymph nodes.
- Monitoring:** Nonseminomas typically surveilled using tumor markers. Seminomas typically monitored with exam and imaging. Intensive follow-up is essential, as even relapsed patients have high rates of cure.

### Complications

- Perform sperm banking prior to chemotherapy in all men wishing to preserve fertility.
- Potential sequelae of treatment include hypogonadism, pulmonary injury (2/2 bleomycin), and metabolic syndrome.

## Bladder Cancer

Risk factors for bladder cancer include cigarette **smoking**, ↑ age, Caucasian race, analgesic abuse (phenacetin, not available in United States), chronic urinary tract inflammation, infection with *Schistosoma haematobium*, amiline dye, and occupational exposures (eg, painters, printers, hairdressers, and machinists).

### Symptoms/Exam

Presents with **painless hematuria**, difficulty voiding, renal failure, and bladder irritation/pain.

### Diagnosis

- Cystoscopy and biopsy, cytology, CT of the abdomen and pelvis, CXR, and bone scan if alkaline phosphatase is ↑.
- Transitional cell carcinoma most common in United States, SCC rare, but more frequent in schistosomiasis-endemic regions.

### Management

- Superficial bladder cancer** (no penetration into muscle): Treat with excision. Add intravesicular BCG or intravesicular chemotherapy for moderate or high-risk disease.

### KEY FACT

In patients who have metastatic testicular cancer at the time of diagnosis, in addition to starting chemotherapy, the affected testicle must be removed, because chemotherapy does not penetrate well into the testicles.

### KEY FACT

Bladder cancer is most often transitional cell carcinoma. The exception is bladder cancer due to schistosomiasis, which is SCC.

### KEY FACT

Gross hematuria in a patient >40 years should prompt workup for bladder cancer.

### QUESTION

A 55-year-old woman presents with a 4-month history of fatigue, dyspnea, and back pain 10 years after diagnosis of stage IIB ovarian cancer. Exam reveals dullness to percussion, diminished breath sounds at posterior lung bases, bulging flanks, and abdominal distention. Lab results: alkaline phosphatase 120 U/L, ALT 90 U/L, AST 80 U/L, total bilirubin 3.0 mg/dL, CA-125 200 U/mL, and CA 15-3 350 U/mL. Mammogram shows microcalcifications and poorly defined mass in her right breast. Chest/abdomen/pelvis CT scans show pleural effusions with pleural studding, ascites, several space-occupying hepatic lesions, and mixed lytic/sclerotic lesions in several vertebral bodies. What is the most likely diagnosis?

- **Muscle-invasive bladder cancer:** Neoadjuvant platinum-based chemotherapy plus radical cystectomy.
- **Metastatic disease:** Gemcitabine and cisplatin are first-line chemotherapy.

## Cervical Cancer

Risk factors include sexual activity at an early age, multiple partners, cigarette smoking, and HIV infection. More than 99% of cervical cancer associated with HPV infection (subtypes 16, 18, 31, 33, and 35).

- **Symptoms/Exam:** The most common presenting symptoms are vaginal bleeding between menses, postcoital bleeding, and vaginal discharge.
- **Diagnosis:** Biopsy will demonstrate malignancy—squamous cell in the majority, about 25% adenocarcinoma.
- **Management:** Options for early-stage disease include radiation therapy, cone excisional biopsy, and simple or radical hysterectomy. Treat locally advanced disease with combined chemotherapy and radiation therapy.
- **Prevention:** See the discussion of cancer screening in the Ambulatory Medicine chapter.

## Endometrial Cancer

The most common genital tract malignancy in women, occurring primarily in postmenopausal women. Risk factors include unopposed estrogen (either endogenous or exogenous), obesity (due to ↑ aromatization of androgens to estrogens), HNPCC and high levels of animal fat in diet. Childbearing ↓ the risk; tamoxifen is associated with an ↑ risk.

- **Symptoms/Exam:** Presents with postmenopausal vaginal bleeding.
- **Diagnosis:** Suggested by transvaginal ultrasound, and confirmed by biopsy obtained during endometrial sampling or dilation and curettage.
- **Management:** Treatment of choice is radical hysterectomy, bilateral salpingo-oophorectomy, and lymph node sampling, with adjuvant radiation therapy for selected patients. Progestins and paclitaxel/doxorubicin/cisplatin play a role in treating metastatic disease.

## Ovarian Cancer

Risk of ovarian cancer ↓ by multiparity, OCP use, breast-feeding, and tubal ligation. BRCA1, BRCA2, and HNPCC are genetic risk factors; family history strongest risk factor.

### Symptoms/Exam

- Typically advanced stage at diagnosis as few symptoms in early stage.
- ↑ abdominal girth, early satiety, rectal pressure, and urinary frequency are found in advanced disease.

### Diagnosis

- Ultrasound of ovary shows solid mass and may see ascites.
- Confirmed by biopsy of mass or cytology of ascites.

### Management

- Favorable early stage (confined to ovary only, and not high grade or clear cell): Surgery only (TAHBSO).
- Unfavorable early stage (ovary ruptured, or + peritoneal washings, or clear cell or high grade): Surgery plus adjuvant chemotherapy.

### KEY FACT

For early-stage cervical cancer, treatment options include radiation therapy, cone excisional biopsy, and simple or radical hysterectomy.

### KEY FACT

Risk factors for endometrial cancer include unopposed estrogen, tamoxifen, obesity, HNPCC, and a diet high in animal fats.

### KEY FACT

Postmenopausal bleeding always requires further evaluation to rule out endometrial cancer.

### KEY FACT

CA-125 is ↑ in 50% to 90% of women with ovarian cancer but is not specific for ovarian cancer. May be helpful in monitoring treatment response. CA-125 screening not shown to be effective.

A

### ANSWER

Despite the history of ovarian cancer with poor prognosis, this presentation is more consistent with metastatic breast cancer. Ovarian cancer rarely metastasizes to bone, liver, or breast. Tumor markers CA-125 (ovarian cancer) and CA 15-3 (breast cancer) may be ↑ in both cancers.

### KEY FACT

For stage III ovarian cancer, **intraperitoneal** chemotherapy associated with improved survival.

- Improved survival seen following optimal surgical debulking (remaining tumor mass <1 cm).
- Stage III disease: Can improve survival with intraperitoneal chemotherapy.

## Sarcoma

- Sarcomas are a heterogeneous group of cancers of mesenchymal tissue that include osteosarcoma, chondrosarcoma, Ewing sarcoma, leiomyosarcoma, and other soft tissue sarcomas.
- Often present with swelling and pain of an extremity.
- Sarcomas typically metastasize hematogenously; the most common site is the lung.
- MRI often more effective for imaging sarcomas than CT.
- Limb-salvaging procedures should be attempted when possible.

## Anal Cancer

The most common histological types are squamous cell and cloacogenic (transitional cell), which behave similarly.

- Present with bleeding, pain, or mass sensation in anal canal.
- Lymph node drainage dependent on anatomic location. Tumors located below dentate line, drain to inguinal lymph nodes. Tumors above dentate line drain to paravertebral and perirectal nodes.
- Treatment of very small tumors is surgical removal. Larger tumors or with lymph node involvement require chemoradiotherapy (mitomycin C).
- Screen with anal Pap smear in high-risk patients.

## Primary Brain Tumors

Characterized by a bimodal age distribution; affect pediatric patients and those >20 years of age (the peak is between 75 and 85 years). Subtypes are as follows:

- **Gliomas:** Most common; range from low to high grade (glioblastoma multiforme). Most gliomas in adults are high grade and incurable.
- **Meningiomas:** Benign tumors that cause morbidity by mass effect. Most common in peri- and postmenopausal women.

### Symptoms/Exam

Present with symptoms secondary to ↑ ICP (headache, nausea, vomiting), or neurologic deficits, seizures, and strokelike phenomena are also seen.

### Diagnosis

- MRI (Figure 14.16) followed by biopsy or surgical resection.
- Meningiomas extraaxial with homogenous enhancement on imaging.

### Management

- Meningioma: Radiographic and clinical observation is usually appropriate for small ( $\leq 3$  cm), asymptomatic meningiomas. Surgery is appropriate for symptomatic lesions.
- Gliomas:
  - Surgery is the definitive therapy for brain tumors.
  - Radiation may be considered for unresectable, recurrent, atypical, or anaplastic disease. Stereotactic or gamma-knife radiotherapy may be used for small tumors in locations where resection is difficult.
  - Resection and radiation therapy are indicated for most high-grade gliomas.

### KEY FACT

Paget disease is a risk factor for osteosarcoma.

### KEY FACT

**Ewing sarcoma** affects children and adolescents, classically arising in the diaphysis. Highly sensitive to combination chemotherapy; 5-year survival rates are high.

### KEY FACT

HIV and genital warts due to HPV are independent and additive risk factors for anal cancer.

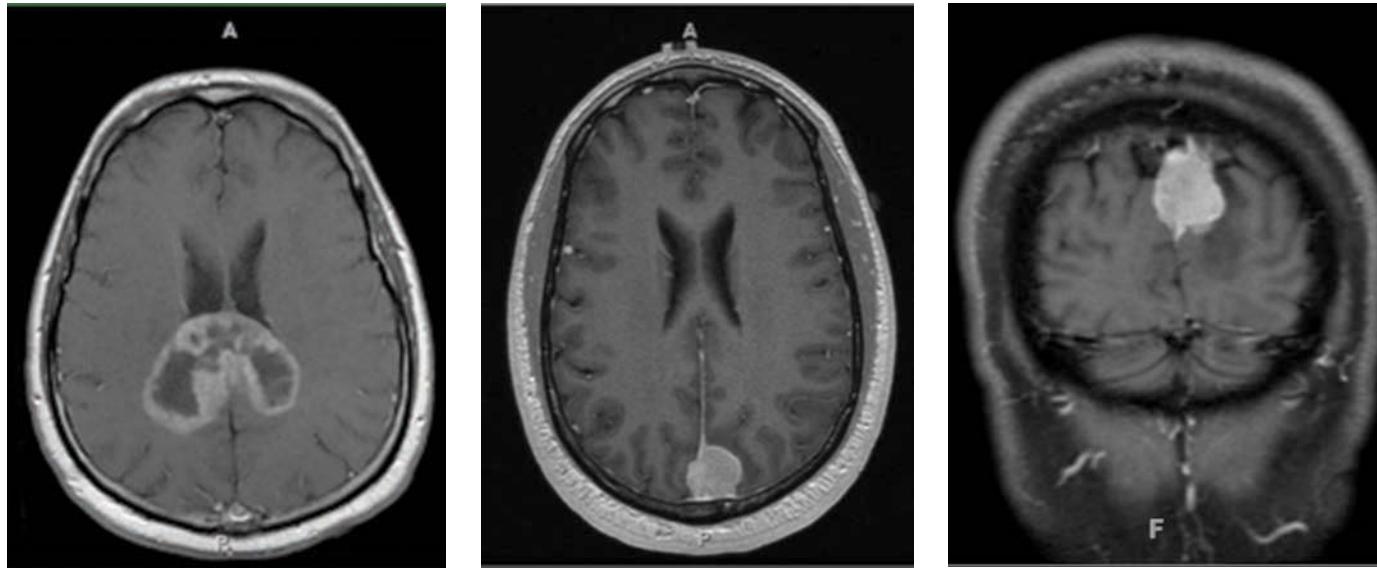
### KEY FACT

Consider metastases to the leptomeninges (carcinomatous meningitis) as a cause of neurologic deficits or altered mental status in patients with advanced cancer. Leptomeningeal metastases are most common in breast cancer, signify a poor prognosis, and respond poorly to intrathecal chemotherapy.



### QUESTION

A 35-year-old woman is evaluated for generalized tonic-clonic seizures that last 5 minutes. Exam and lab results are unremarkable. Head CT scan without contrast shows an area of low attenuation with mass effect in the left frontal lobe. Brain MRI with contrast shows a 4-cm area of ↑ T2 signal in the left frontal lobe. A T1-weighted image with gadolinium shows ring enhancement with some central necrosis. Biopsy reveals a grade 4 astrocytoma (glioblastoma multiforme). What are the most important determinants of prognosis?

**A****B****C**

**FIGURE 14.16. Primary intracranial neoplasms.** (A) Transaxial contrast-enhanced MRI showing a centrally necrotic, enhancing intra-axial mass crossing the corpus callosum, in this case a glioblastoma multiforme. (B) Axial T1-weighted and (C) coronal T1-weighted MRI images show a well-circumscribed, homogeneously enhancing mass within the left aspect of the sagittal sinus with edema of the adjacent brain parenchyma within the left occipital lobe. Note, the “dural tail” sign most often seen adjacent to a meningioma. (Reproduced with permission from USMLE-Rx.com.)

- Chemotherapy reserved for unresectable, progressive tumors that fail to respond or recur after radiation therapy. *Exception: oligodendrogiomas are highly chemosensitive* (associated with chromosome 1p and 19q loss). Oligodendroglial tumors carry a more favorable prognosis than astrocytomas, with a median survival of 10 to 15 years. Other features indicative of better prognosis are age <40 years, good performance status, and ↑ extent of surgical resection.
- Chemotherapeutic agents for 1° brain tumors include temozolomide, bevacizumab, and combination PCV (procarbazine, CCNU, vincristine).



### MNEMONIC

**Tumors that commonly metastasize to brain—**  
“Lots of Bad Stuff Kills Glia”

Lung  
Breast  
Skin (melanoma)  
Kidney (renal cell carcinoma)  
Gastrointestinal (colon)



### ANSWER

Cell type and tumor grade are the most important determinants of survival in glioma. Grade 4 carries the worst prognosis, with a median survival of only 9 to 12 months.

### BRAIN METASTASES

Occur in 15% of patients with solid tumors, most commonly lung and breast cancer. In general, metastases portend a poor prognosis (Figure 14.17).

- **Symptoms/Exam:** Leptomeningeal spread may present as a cranial neuropathy or as spinal polyradiculopathy. Occasionally present with encephalopathy due to seizures, diffuse brain infiltration, or communicating hydrocephalus from obstruction of arachnoid granulations.
- **Management:**
  - Solitary brain metastasis in accessible locations: Resection followed by whole brain radiotherapy to prevent new metastases.
  - Solitary or few metastases: Stereotactic radiosurgery.
  - Multiple brain metastases: Whole brain radiotherapy.
  - Prophylactic antiepileptic medication is not indicated.

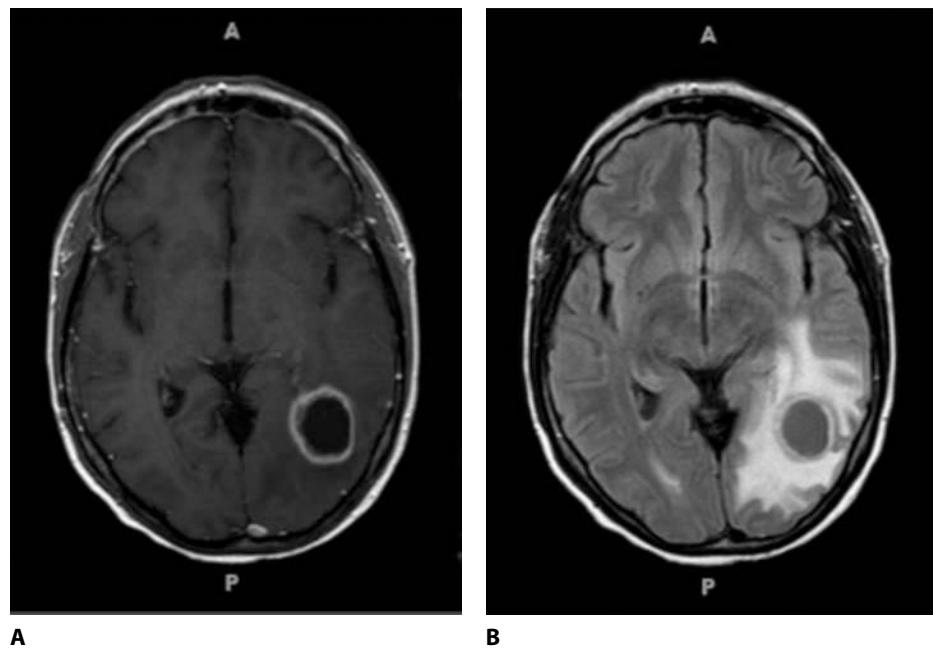


### KEY FACT

Brain metastases usually respond poorly to systemic chemotherapy due to poor penetration of chemotherapy through the blood-brain barrier.

### Carcinoma of an Unknown 1° Site

Comprise 2% of all cancer diagnoses in which a biopsy of a lymph node or other tissue reveals a cancer diagnosis but basic evaluation with history, exam, labs, and imaging (including CT scan of chest, abdomen, and pelvis) fails to point to a 1° site.



**A**                    **B**

**FIGURE 14.17. Lung cancer metastasis to brain.** (A) Post-contrast axial T1-weighted MRI shows contrast-enhancing lesion with central necrosis at the gray-white junction. (B) Axial T2-weighted MRI shows brain edema surrounding brain metastasis. Patient was a 60-year-old woman with seizures and history of adenocarcinoma of the lung. (Reproduced with permission from USMLE-Rx.com.)

#### KEY FACT

Women with adenocarcinoma of the axillary lymph nodes without clinically or radiologically detected breast abnormalities should be treated for stage II breast cancer with radiation and chemotherapy.

### Diagnosis

- Evaluation of the biopsy with immunohistochemical stains or electron microscopy may help determine 1° malignancy.
- If unclear from pathologic examination where 1° tumor is, next step is to focus on age- and gender-specific cancers:
  - Mammography and breast examination in women; testicular examination, DRE, and PSA testing in men.
  - Colonoscopy in all patients >50 years.
  - $\beta$ -hCG and AFP in all patients (for germ cell tumor). Other tumor markers (eg, CEA, CA-125, CA 19-9, CA 15-3) are too nonspecific to aid in diagnosis.
  - PET scan controversial but may be useful.

### Management

Some special scenarios are as follows:

- **Women with axillary lymph nodes containing adenocarcinoma:** Should be treated like breast cancer—ie, with mastectomy and axillary lymph node dissection, and consider adjuvant therapy.
- **Cervical lymph nodes and SCC:** Treat like SCC of the head and neck following thorough ENT evaluation.
- **Inguinal lymph nodes and SCC:** Evaluate anus and penis in men, vagina, uterus, cervix, vulva, and anus in women.
- **Young men with poorly differentiated carcinoma and a mediastinal or retroperitoneal mass:** Treat as germ cell tumors; evaluate for occult testicular cancer.
- **Men with bone metastasis:** Evaluate with PSA testing for prostate cancer.
- **Women with peritoneal carcinomatosis:** Treat for ovarian cancer.
- **Chemotherapy regimen for patients not falling into the above categories:** Etoposide and a platinum (cisplatin or carboplatin). The addition of paclitaxel may improve response and survival.

## NOTES

# CHAPTER 15

# Psychiatry

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## Psychiatry Pearls

- All psychiatric illnesses can be divided into four major categories: psychosis, anxiety, mood, and other (Figure 15.1). As with other illnesses, symptoms suggest categories that can then be further clarified. See Table 15.1 for case presentations of the common psychiatric disorders.

### Diagnosis

- In general, there are no objective laboratory tests for psychiatric diagnostic clarification, so a careful **history** is essential.
- Some psychiatric syndromes are diagnoses of exclusion; therefore, likely medical etiologies must be ruled out before such diagnoses can be made. **Functional impairment** is required for many psychiatric disorders.

### Management

- Pharmacologic treatment: Follows from the diagnosis or  $1^{\circ}$  symptoms (see Figure 15.1). Psychotic disorders are treated with antipsychotics. Anxiety disorders are treated with anxiolytic agents. Mood disorders are treated with antidepressants or mood stabilizers, depending on unipolarity or bipolarity.
- Some psychiatric **syndromes** have symptoms from two major disease categories (eg, schizoaffective disorder, which has both psychotic and mood disorder symptoms). For these syndromes, treatment generally involves medication with  $>1$  category, targeting each symptom separately.
- The choice of medication in each class should be based on several factors:
  - Proven efficacy for the illness being treated.
  - Patient demographics (which may include age, gender, and/or race, depending on medication).
  - Availability of generic formulation (for patients with limited ability to pay).
  - The likely adverse effect profile and tolerability to the patient.
  - Patient preference (to maximize patient adherence).
  - Drug-drug interactions with other medications.
- The choice of benzodiazepine should be based on the nature of the anxiety symptom being treated (Figure 15.2).

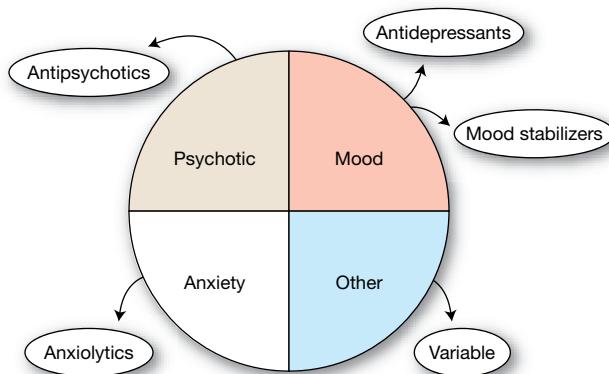
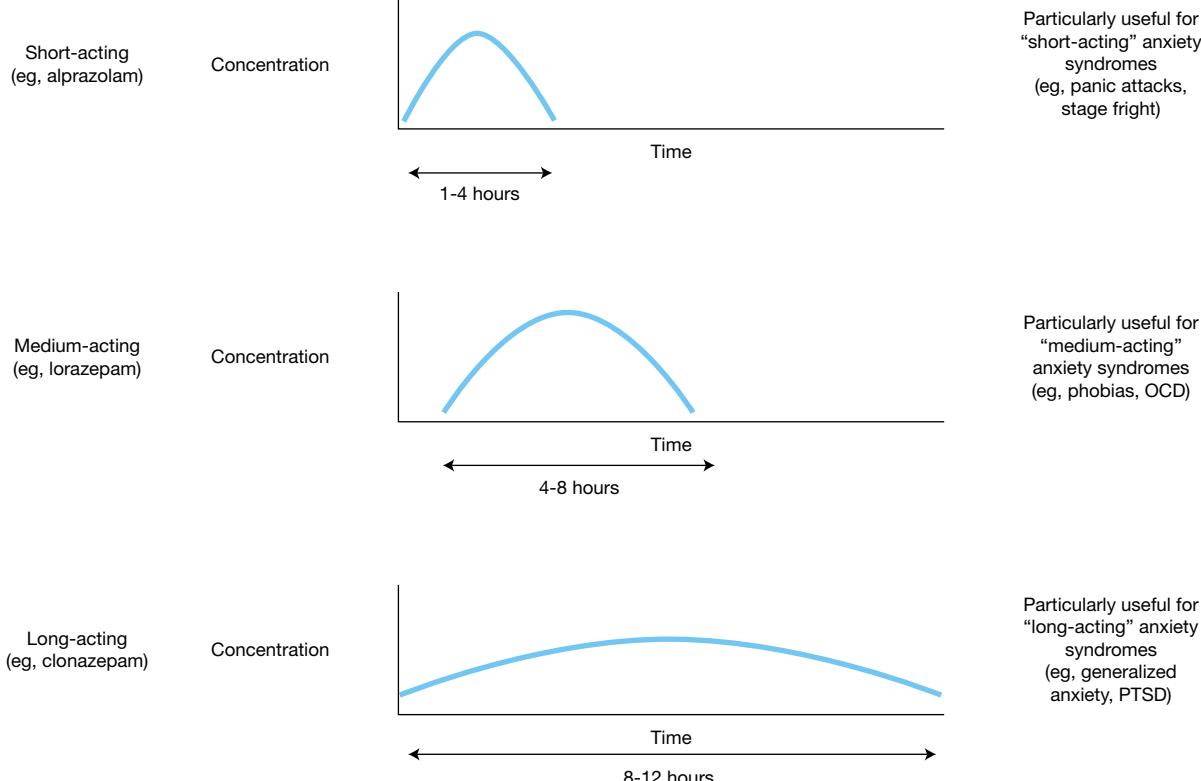


FIGURE 15.1. Pharmacologic management of psychiatric illness.

**TABLE 15.1.** Classic Case Presentations of Common Psychiatric Disorders

MAJOR DEPRESSIVE EPISODE	GENERALIZED ANXIETY DISORDER	BIPOLAR DISORDER	SCHIZOPHRENIA
<ul style="list-style-type: none"> <li>■ A 36-year-old woman with mild psychomotor retardation and dark circles under her eyes complains of excessive fatigue, as well as waking up in the middle of the night and being unable to fall back asleep.</li> <li>■ She also has difficulty concentrating on child care, guilt about being a “bad mother,” and lack of pleasure in activities she once enjoyed.</li> <li>■ Her symptoms began 3 months ago and have gradually worsened to the point at which she can no longer perform her normal work and child care duties.</li> </ul>	<ul style="list-style-type: none"> <li>■ A 42-year-old man with mild psychomotor agitation complains that for the past 6 months “my nerves have been shot.”</li> <li>■ He mentions that he worries “all the time and over everything” and can’t fall asleep, adding that he often “snaps at his wife.”</li> <li>■ The patient also has chronic neck and shoulder tension as well as mild daily headaches that are relieved by acetaminophen.</li> </ul>	<ul style="list-style-type: none"> <li>■ A 25-year-old woman being treated for depression presents wearing heavy makeup and a revealing red dress “because my husband told me I have to; he says my personality has changed. He just can’t handle my womanhood.”</li> <li>■ The woman, previously demure, describes the artwork in your office as “unusually sensual; I might have to test your kissing ability some day.” She speaks very quickly and becomes angry and louder whenever interrupted.</li> <li>■ Her anger dissipates within seconds and is replaced by feelings of joy. She leaves after only a few questions but gives you a \$100 “tip,” stating “I’ll be rich soon now that I’ve started my consulting business.” She sings on her way out.</li> </ul>	<ul style="list-style-type: none"> <li>■ A 19-year-old disheveled man is brought to your office by his parents, who state that their son “just got kicked out of college for harassing the dean.”</li> <li>■ On interview, the man seldom speaks unless asked a question and rarely makes eye contact except to ask you if his eyes look okay, “because I see colors too brightly now.” Occasionally he seems to talk to himself, stating, “Yeah, yeah, I know, but I like the doctor.”</li> <li>■ When asked what happened at college, the man states that “no one there can handle the truth—the truth of the elders of the dean and his spies.”</li> </ul>

**FIGURE 15.2.** Length of action of benzodiazepines.

## Anxiety Disorders

### PANIC DISORDER

Panic disorder consists of at least **two** untriggered panic attacks, with impaired function due to **fear of having another**.



### MNEMONIC

#### **Symptoms of a panic attack—PANICS**

- P**alpitation
- A**bdominal distress
- N**umbness/**N**ausea
- I**ntense fear of death/going crazy/losing control
- C**hoking/**C**hills/**C**hest pain
- S**weating/**S**haking/**S**hortness of breath

### KEY FACT

Panic disorder can occur **with or without agoraphobia** (fear of open spaces or of being alone in a crowd or leaving the home).

### Symptoms

- Panic attacks must develop abruptly and peak within 10 minutes. While variable in duration, they do not typically last longer 20 minutes (longer episodes are likely exacerbation of generalized anxiety). They must also include **at least four of the symptoms outlined in the PANICS mnemonic**. A panic attack may be triggered or may occur spontaneously.
- For a diagnosis of panic *disorder*, panic attacks are recurrent, and patient worries about recurrent attack between episodes.

### Differential

- **Endocrine:** Hypoglycemia, hypothyroidism, hyperthyroidism, hyperparathyroidism, pheochromocytoma.
- **Neurologic:** Seizure disorders, vestibular dysfunction, neoplasms, TIAs.
- **Pharmacologic:** Acute intoxication or withdrawal, medication-induced symptoms.
- **Cardiovascular:** Arrhythmias, MI, angina, mitral valve prolapse.
- **Pulmonary:** COPD, asthma exacerbation, pulmonary embolus.
- **Psychiatric:**
  - **Generalized anxiety disorder:** Patients typically have more chronic baseline anxiety and multidomain worries.
  - **Obsessive-compulsive disorder (OCD):** Patients generally have recurrent repetitive thoughts (obsessions) and mannerisms (compulsions).
  - **Posttraumatic stress disorder (PTSD):** Patients have a history of a traumatic event, recurrent nightmares or intrusive memories, and no history of panic attacks.

### Diagnosis

Rule out all likely medical etiologies (eg, ECG, electrolyte panel, TSH, CXR). Note that a medical diagnosis may **coexist**.

### Management

- **Behavioral:** Cognitive behavioral therapy (CBT).
- **Medication:** Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are first line; benzodiazepines only if severe and cannot wait for SSRI/SNRIs to take effect (if prescribed, providing a prescription for only five to be carried in case of emergency can be effective in reducing onset of further attacks).

### GENERALIZED ANXIETY DISORDER

Generalized anxiety disorder is defined as uncontrollable worry about a **broad range of topics** (eg, work/school, relationships, health) over time (ie, more days than not for at least **6 months**).

### Symptoms

Patients have poor control over their anxiety and at least **three** of the following: restlessness, poor concentration, irritability, easy fatigue, muscle tension, and difficulty sleeping. Symptoms **must cause functional impairment** (ie, they must interfere with social or occupational functioning).



### KEY FACT

Generalized anxiety disorder is characterized by anxiety in many different situations (eg, at work, during mealtimes, in social situations, while falling asleep). The episodes of anxiety are typically less intense but much longer lasting than with panic disorder.

## Differential

- **Endocrine:** Hypoglycemia, hyperthyroidism, carcinoid syndrome, pheochromocytoma.
- **Substance abuse:** Amphetamines, cocaine, caffeine, nicotine, alcohol.
- **Cardiovascular:** Arrhythmias.
- **Psychiatric:**
  - **PTSD:** Patients must have a history of a traumatic event and recurrent nightmares or intrusive thoughts.
  - **Major depressive disorder:** Patients usually have depressed mood and other physical symptoms.
  - **OCD:** Patients typically have recurrent repetitive thoughts (obsessions) and mannerisms (compulsions), and anxiety is only around the obsessions.

## Diagnosis

Rule out all likely medical etiologies (TSH, glucose, ECG, other tests if suggested by history and examination).

## Management

- **Behavioral:** CBT, individual and group therapies.
- **Medication:** SSRIs; can use **long-acting** benzodiazepine anxiolytic agents (eg, clonazepam) while waiting for SSRI to take effect.

## Complications

Often leads to **depression** if left untreated. May be seen with comorbid panic disorder.

### SPECIFIC PHOBIAS

Fear of specific items, situations, or activities is termed *specific phobias*.

- **Symptoms:** Presents with excessive or unreasonable fear of a particular trigger; patients realize that their response is excessive. Must also cause **functional impairment** (ie, must interfere with social or occupational functioning).
- **Differential:**
  - **Panic disorder:** Panic attacks can be untriggered.
  - **PTSD:** Patients avoid things that are reminiscent of a witnessed or experienced traumatic event.
  - **Generalized anxiety disorder:** Patients have chronic baseline anxiety and worry about many things, not just when they are exposed to a trigger.
- **Management:**
  - **Behavioral:** Exposure-response prevention therapy (exposes the patient to the stressor and prevents their usual fleeing response; desensitizes the patient to the stressor).
  - **Medication:**  $\beta$ -blockers; short-acting benzodiazepines (eg, alprazolam).

### OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder is defined as obsessions and compulsions causing significant impairment that are recognized by the patient as excessive or unreasonable.

## Symptoms

- **Obsessions:** Recurrent or persistent thoughts that **cause anxiety** (eg, germs, contamination, safety).
- **Compulsions:** Behaviors or rituals that temporarily **relieve anxiety** (eg, washing, checking).

### KEY FACT

Specific phobias are the most common anxiety disorder.



### QUESTION 1

A 23-year-old woman presents to the ED for palpitations, dyspnea, chest heaviness, and muscle soreness that began several hours earlier while she was at home watching television. She had several similar episodes in the past year, two of which required ED visits with  $\ominus$  workups (including a normal TSH). She describes recent fatigue, poor sleep, difficulty concentrating, and irritability. She has been increasingly worried about her job, the environment, her relationship with her husband, and the safety of her child. In the ED, she is normotensive; heart rate, 92 bpm. ECG is unremarkable, as is laboratory work, including urine toxicology test. What intervention is most likely to help this patient?



### QUESTION 2

A 29-year-old physician returns from an overseas deployment in which he was working in a war zone. He is now spending most of his time at home and has noted poor concentration as well as occasional nightmares that wake him from sleep. He wants to return to work but does not feel that he can go back to the hospital because of his experience overseas. What treatments would be best for him?

**KEY FACT**

Obsessions cause ↑ anxiety that is temporarily relieved by compulsions.

- Patients must recognize that their symptoms are unreasonable and that their obsessions are their own thoughts.

**Differential**

- Delusional disorder:** Patients do not find the thoughts unreasonable.
- Schizophrenia:** Patients have psychotic symptoms (such as hallucinations) along with affective flattening, asociality, and avolition.
- Generalized anxiety disorder:** Patients have anxiety in several different areas of their lives that are generally not relieved by compulsive acts.

**Management**

- Behavioral:** Exposure-response prevention therapy; CBT (teaches patients how to diminish their cognitive distortions of the stressor and how to change their behavioral response).
- Medication:** Clomipramine, SSRIs (eg, paroxetine, sertraline, fluvoxamine). Higher doses than those used for depression or generalized anxiety are usually required.

**Complications**

Often leads to depression if left untreated.

**POSTTRAUMATIC STRESS DISORDER****A****ANSWER 1**

An SSRI and possibly psychotherapy. This patient has generalized anxiety disorder and is now having functional impairment that warrants treatment. Long-acting benzodiazepines might prove useful as well, but SSRIs are generally first-line therapy.

Posttraumatic stress disorder (PTSD) is a reaction to a traumatic event characterized by reexperiencing, avoidance, and ↑ arousal. Prevalence is up to 3%, but up to 30% of veterans are affected.

**Symptoms**

- Patients must have a perceived life-threatening trauma and all three of the following:
  - Reexperiencing (eg, flashbacks, nightmares).
  - Avoidance (places, thoughts, feelings, people related to the trauma).
  - ↑ arousal (insomnia, hyperstartle, poor concentration, anger outbursts).
- Patients must have all symptoms for a minimum of 1 month.

**A****KEY FACT**

In acute stress disorder, symptoms last <1 month. In PTSD, symptoms last >1 month.

**Differential**

- Depression:** Patients do not reexperience a traumatic event.
- Generalized anxiety disorder:** Patients have multiple domains of anxiety, not limited to anxiety focusing on issues about a past trauma.
- Adjustment disorder:** Patients have stress, anxiety, depression, or behavioral changes that are related to a specific trigger but do not have all three 1° symptoms of reexperiencing, avoidance, and ↑ arousal. Adjustment disorder fades when the situation causing it is removed or reconciled.

**A****ANSWER 2**

Treatment of PTSD involves CBT combined with an SSRI. Benzodiazepines can be used for short-term symptoms, but SSRIs and CBT will likely achieve the best long-term efficacy.

**Management**

- Behavioral:** Various forms of individual and group psychotherapy, particularly trauma-focused CBT.
- Medication:** SSRIs or SNRIs are first line. Atypical antipsychotics are second line and only used for severe cases of PTSD with flashbacks or dissociation. Can use sleep agents (eg, trazodone) for sleep, prazosin for nightmares.

**Prevention**

Some research suggests that reducing autonomic activation (with β-blockers) shortly after the trauma may ↓ the likelihood of developing PTSD.

## Complications

- Long-term use of benzodiazepines can lead to psychological dependence, so prescribe with caution/selectivity; PTSD is frequently seen with comorbid substance abuse, particularly depressants.
- Avoidance of stimuli associated with the trauma can generalize to avoidance of wide-ranging things (which become secondarily associated with the trauma in the patient's mind). This leads to a far greater ⊖ impact on the patient's life.

## Mood Disorders

### MAJOR DEPRESSIVE DISORDER

In major depressive disorder, the male-to-female ratio is 1:2. Risk is higher if there is a family history. Untreated episodes usually last ≥4 months.

#### Symptoms

Patients must have **depressed mood** or loss of interest/pleasure (**anhedonia**) and **five** of the symptoms outlined in the **SIG E CAPS** mnemonic. Symptoms must represent a **change from baseline**; cause **functional impairment** (eg, work, school, or social activities); and last at least 2 weeks continuously.

#### Differential

- Adjustment disorder:** Patients have a known stressor that causes a reaction similar to a depressive episode, but the reaction is less severe and is triggered specifically by that stressor.
- Dysthymic disorder:** Patients have “low-level depression” (ie, depression involving <5 SIG E CAPS symptoms) that lasts at least 2 years.
- Anxiety disorders:** Generalized anxiety disorder, PTSD, OCD.
- Bipolar disorder:** Patients report a history of previous or current manic symptoms in addition to depressive symptoms.
- Medical “masqueraders”:** Hypothyroidism, anemia, malignancy, Parkinson disease.
- Substance-induced mood disorder:** Illicit drugs, thiazide diuretics, digoxin, β-blockers, glucocorticoids, benzodiazepines, cimetidine, ranitidine, cyclosporine, sulfonamides, metoclopramide.

#### Diagnosis

Eliminate potential medical etiologies (eg, check TSH and CBC).

#### Management

- Behavioral:** Various forms of individual and group psychotherapies.
- Medication:** SSRIs; other classes of antidepressants (eg, SNRIs, TCAs). Medication selection should be based on symptom profile and anticipated side effect tolerability as well as on how activating or sedating the medication can be. Options include:
  - Activating:** Bupropion, fluoxetine.
  - Sedating:** Paroxetine, fluvoxamine, mirtazapine.
  - Neutral:** Sertraline, venlafaxine, citalopram.
- Electroconvulsive therapy:** Often reserved for medication-resistant depression; especially useful in the elderly.

#### Complications

- Severely depressed patients can develop psychotic symptoms (eg, auditory hallucinations, paranoid ideations, ideas of reference). These symptoms can be treated with a low dose of an antipsychotic agent.



#### MNEMONIC

**Symptoms of major depressive disorder—**

#### SIG E CAPS

- Sleep** (hypersomnia or insomnia)
- Interest** (loss of interest or pleasure in activities)
- Guilt** (feelings of worthlessness or inappropriate guilt)
- Energy** (↓)
- Concentration** (↓)
- Appetite** (↑ or ↓)
- Psychomotor agitation or retardation**
- Suicidal ideation**



#### KEY FACT

Patients complaining of early morning awakenings should be screened for major depressive disorder. It is the most common form of sleep impairment for this disorder and less commonly seen in other mood disorders or anxiety disorders.



#### KEY FACT

Psychotherapy and antidepressants together are more effective for depression than either treatment alone.



#### KEY FACT

If a patient has not responded at all after 8 to 12 weeks of an SSRI given for depression, switch to another medication either of the same class or of a different class.

**KEY FACT**

Watch for **serotonin syndrome** for all patients on SSRIs. Symptoms include tachycardia, hypertension, fever, hyperthermia, myoclonus, muscle rigidity, convulsions, coma.

**KEY FACT**

Consider augmentation therapy if a patient has achieved only a partial response after maximal treatment with one SSRI for depression. Use a second drug from a different class (eg, bupropion, venlafaxine, mirtazapine).

**MNEMONIC****Risk factors for suicide—****SAD PERSONS**

**S**ex (male)  
**A**ge (elderly or adolescent)  
**D**epression  
**P**revious attempt  
**E**thanol abuse  
**R**ational thought loss  
**S**ickness  
**O**rganized plan  
**N**o spouse  
**S**ocial support lacking

**MNEMONIC****Symptoms of manic episodes—**

**DIG FAST**  
**D**istractability  
**I**nsomnia ( $\downarrow$  need for sleep)  
**G**randiosity ( $\uparrow$  self-esteem)  
**F**light of ideas (or racing thoughts)  
 $\uparrow$  **A**ctivities/psychomotor **A**gitation  
Pressured **S**peech  
**T**houghtlessness (poor judgment—eg, spending sprees, unsafe sex)

■ **Suicidality:** One of the major comorbidities of untreated depression is suicidality (see the mnemonic **SAD PERSONS**).

- Women generally make more attempts, but attempts made by men are usually more lethal.
- Clinicians must assess the degree of risk (eg, consider the number of prior attempts, degree of premeditation, lethality of method, and access to the proposed method) and **hospitalize** if necessary to ensure patient safety.

**BIPOLAR AFFECTIVE DISORDER**

Extreme mood swings between mania and depression define bipolar affective disorder. Risk is higher if there is a family history. There are two types: **type I**, which typically alternates between mania and depression, and **type II**, which alternates between depression and hypomania (ie, fewer symptoms for a shorter duration).

**Symptoms**

- The symptoms of manic episodes in bipolar affective disorder are described by the mnemonic **DIG FAST**. Manic episodes **must last at least 7 days or lead to hospitalization** to be called mania. Hypomanic episodes last between 4 and 6 days.
- See the entry on depression for symptoms of the depressive episodes of bipolar disorder; remember the mnemonic **SIG E CAPS**.

**Differential**

- **Major depressive disorder:** Patients have no history of a manic or hypomanic episodes.
- **Schizoaffective disorder:** Patients have both **psychotic symptoms** and mood symptoms. Psychotic symptoms occur in the **absence** of mood symptoms.
- **Schizophrenia:** Patients do not have mood symptoms.

**Management**

- **Acute manic episode:** Hospitalize; consider atypical antipsychotic agents (eg, haloperidol, olanzapine, risperidone).  $\uparrow$  doses of mood stabilizers (see maintenance treatment).
- **Maintenance treatment:** Give mood stabilizers. Lithium is first line but significant side effects (arrhythmias, renal failure, diabetes insipidus) and requires regular monitoring of blood level concentration. Second-line agents include anticonvulsants (valproic acid, carbamazepine, lamotrigine) or atypical antipsychotics (quetiapine, aripiprazole, olanzapine, risperidone). Titrate to the lowest effective dose to maintain mood stability.
- **Depressive episodes:** Antidepressants alone may trigger mania, so use carefully; consider individual and group psychotherapies.

**Prevention**

- $\uparrow$  the mood stabilizer dose in the presence of imminent symptoms of mania.
- Educate patients and their families to recognize the earliest signs of mania/depression (sleep changes are often the first sign), and encourage them to seek additional help early.

**Complications**

- In severe phases of mania or depression, patients can have psychotic symptoms.
- **If the condition is left untreated, many patients have progressively more rapid cycling** (more frequent and shorter-duration episodes). Of all psychiatric illness, untreated mania has among the highest rates of incarceration, injury, or death.

## Psychotic Disorders

### SCHIZOPHRENIA

Schizophrenia is diagnosed by a history of **severe and persistent** psychotic symptoms ( $\geq 1$  month) in the context of chronic impairment in function ( $>6$  months). There are several subtypes. **Age of onset is mostly in the late teens or 20s** for men and in the 20s to 30s for women; risk is higher if there is a family history.

#### Symptoms

Patients must have  $\geq 2$  of the following:

- **Delusions:** Fixed false beliefs.
- **Hallucinations:** Most often auditory, but can be visual, olfactory, gustatory, or tactile.
- **Disorganized speech or thoughts.**
- **Grossly disorganized or catatonic behavior.**
- **Negative symptoms:** Affective flattening, avolition, alogia (poverty of speech), asociality (Table 15.2).

#### Differential

- **Bipolar affective disorder:** Patients have psychotic symptoms only during extreme manic or depressive episodes.
- **Schizoaffective disorder:** Patients have psychotic symptoms **but also have prominent mood symptoms** (either depression or mania).
- **Delusional disorder:** Patients have **one** fixed false belief that is nonbizarre and that does not necessarily have a broad impact on functioning. Hallucinations are not experienced.
- **Developmental delay:** Patients do not have overtly psychotic symptoms and **have not deteriorated from a higher-functioning baseline.**
- **OCD:** Patients are aware that their obsessions (recurring repetitive thoughts) are their own thoughts.
- **Depression with psychotic features:** Patients have psychotic symptoms that occur only during depressive episodes, and the **depressive symptoms can occur without psychotic symptoms.**
- **Generalized anxiety disorder:** Patients have severe and chronic anxiety but no psychotic symptoms.
- **Substance-induced psychosis:** Especially associated with amphetamine or cocaine, both of which can cause paranoia and hallucinations. Patients have other signs/symptoms of substance use.
- **Medical “masqueraders”:** Examples include neurosyphilis, herpes encephalitis, Wilson disease, heavy metal poisoning, Wernicke-Korsakoff syndrome, dementia, and delirium.
- **Neurologic “masqueraders”:** Include complex partial seizures, temporal lobe epilepsy, and Huntington disease.

**TABLE 15.2. Positive and Negative Symptoms of Schizophrenia**

POSITIVE	NEGATIVE
Hallucinations	Blunted affect (eg, emotions not expressed)
Delusions (eg, paranoia, thought insertion, ideas of reference)	Cognitive changes
Disorganized speech (eg, rambling)	Diminished speech
Catatonic behavior	Apathy (eg, avolition, social withdrawal)

#### KEY FACT

Treating a bipolar patient with antidepressant monotherapy can lead to a manic episode.

#### KEY FACT

Type 1 bipolar affective disorder only requires the presence of a manic episode; although depressive episodes are typically seen, they are not necessary for diagnosis. Type 2 bipolar affective disorder requires the presence of a hypomanic episode and depressive episode.

#### KEY FACT

Psychotic = “break with reality”

#### MNEMONIC

##### **The 4 A's of schizophrenia:**

**A**ffective flattening  
**A**sociality  
**A**logia (paucity of speech)  
**A**uditory hallucinations

#### KEY FACT

There is often a prodromal phase of schizophrenia involving  $\ominus$  symptoms without  $\oplus$  symptoms (delusions or hallucinations).

#### KEY FACT

Auditory are the most common type of hallucinations seen in schizophrenia. If visual hallucinations are noted, carefully consider medical, medication, or substance abuse causes.

#### QUESTION

A 47-year-old man with schizophrenia presents with  $\uparrow$  “twitching” of his lips and tongue over the past several months. On exam, he is noted to have dyskinetic movements of his tongue and lips but is otherwise doing well. He has no other medical problems and takes haloperidol for his schizophrenia. What would be the most appropriate therapy for his facial movements?

### Diagnosis

Diagnose by history. Neuropsychological testing can be helpful in clarifying the diagnosis but is not typically indicated.

### Management

Choose an antipsychotic agent that minimizes both symptoms and side effect profile:

- **First-line treatment:** Atypical antipsychotics (eg, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole) are now considered first-line agents because they have fewer motor side effects than do typical antipsychotics such as haloperidol. However, atypicals are much more expensive and can lead to significant weight gain. Clozapine is one of the most effective antipsychotics, but is usually reserved for patients who have failed multiple trials of other medications; clozapine requires weekly lab WBC and ANC monitoring to prevent potentially life-threatening agranulocytosis.
- **Acute psychotic episodes:** Hospitalize; ↑ the dose of antipsychotic agent and consider the use of anxiolytic agents (eg, alprazolam, clonazepam). Group therapy sessions can provide a forum for reality checks if patients can tolerate them.
- **Maintenance treatment:** Titrate to the lowest effective dose of antipsychotic agent to maintain stability. Individual and group therapy and structured day programs provide safety, socialization skills, and reality checks.

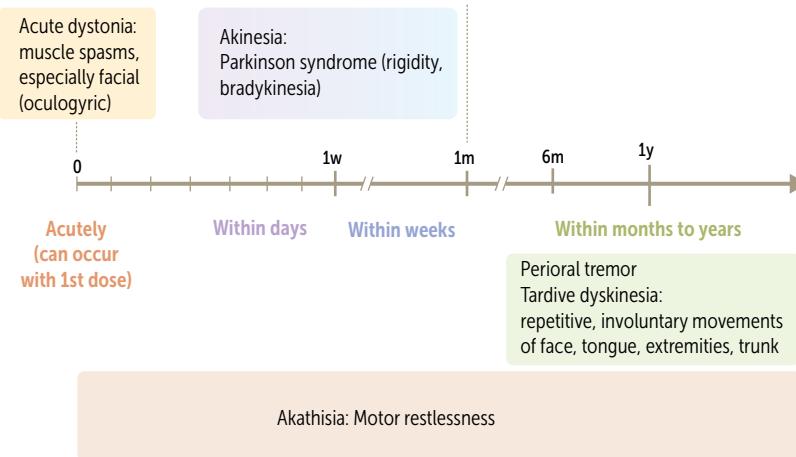
### Complications

- If left untreated, schizophrenia will lead to a “downward drift” in socioeconomic class. Schizophrenia alone ↑ mortality, primarily from suicide, as well as from ↑ risk of cardiovascular disease (hypertension, hyperlipidemia, diabetes, obesity, metabolic syndrome) and associated undertreatment of chronic medical disorders.
- Long-term use of typical antipsychotics (eg, haloperidol) can lead to **tardive dyskinesia** (ie, involuntary choreoathetoid movements of the face, lips, tongue, and trunk). Tardive dyskinesia should be treated by minimizing doses of neuroleptics or by switching to an atypical neuroleptic (eg, olanzapine, risperidone, quetiapine). The effects may be permanent, even after discontinuation of the offending agent (Figure 15.3).

## DELUSIONAL DISORDER

Patients with delusional disorder have a fixed false belief (delusion) that is nonbizarre.

- **Symptoms:** The delusion is often highly specific and organized into a system (ie, patients can describe wide and varying evidence to support the delusion). This leads to hypervigilance and hypersensitivity. There is usually a relative lack of other symptoms, and patients often remain high functioning otherwise.



**FIGURE 15.3. Timeline of appearance of extrapyramidal motor symptoms in antipsychotic toxicity.** Of the four types of effects, tardive dyskinesia can become permanent even after cessation of the offending agent. (Reproduced with permission from USMLE-Rx.com.)

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### ANSWER

Stop haloperidol and start an atypical antipsychotic (eg, olanzapine, quetiapine, risperidone). This patient has likely been on typical antipsychotics (haloperidol) for several years, placing him at risk for tardive dyskinesia. If his symptoms cannot be controlled on atypical antipsychotics, his dose of haloperidol can be ↓. Alternatively, his tardive dyskinesia can be treated with a non-selective β-blocker or a benzodiazepine, but this would not constitute first-line therapy.

- **Differential:**
  - **Schizophrenia:** Patients often have a history of auditory hallucinations or other psychotic symptoms, such as prominent ⊖ symptoms (affective flattening, avolition, alogia, asociality). Frequently, there is greater functional impairment.
  - **Substance-induced delusions:** Particularly associated with amphetamine and cannabis.
  - **Medical conditions:** Hyper-/hypothyroidism, Parkinson, Huntington, Alzheimer, CVAs, metabolic causes (hypercalcemia, uremia, hepatic encephalopathy), other causes of delirium.
- **Management:** Patients are often likely to refuse treatment or medications. **Low-dose atypical antipsychotics** may be helpful. Do not pretend that the delusion is true, but do not argue with patients in attempts to prove it false. Instead, gently remind them of your **goal of maximizing functionality**.
- **Complications:** Many patients do not seek treatment, leading to progressive isolation and to a ↓ in productivity and/or functional status.

**KEY FACT**

Delusional disorder is far less common than schizophrenia and is less responsive to medications.

## Substance Use Disorders

### CHRONIC ABUSE/DEPENDENCE

Substance use disorder is a maladaptive pattern of use that occurs despite adverse consequences. Dependence is abuse and physiologic tolerance.

#### Diagnosis

All the dependencies are characterized by **relapsing and remitting** patterns.

#### Management

- Optimal treatment varies from patient to patient but usually involves a **combination** of the following therapies:
  - **Pharmacologic substitutes:** Replace the substance of abuse with a longer-acting and less addictive pharmacologic equivalent. Examples include methadone or buprenorphine/naloxone for heroin, chlordiazepoxide (Librium) for alcohol, and clonazepam for short-acting benzodiazepines. Agents can be used either in a detoxification program (eg, 21 days) or as maintenance therapy (eg, methadone maintenance).
  - **Pharmacologic antagonists:** ↓ the pleasurable response associated with the substance of abuse. Examples include:
    - **Disulfiram (Antabuse):** Blocks the efficacy of alcohol dehydrogenase, causing buildup of acetaldehyde.
    - **Naltrexone:** Thought to ↓ alcohol craving and ↓ enjoyment from binge drinking behavior.
  - **Nonpharmacologic treatments:**
    - **Therapeutic communities:** Provide a safe, structured environment in which to boost attempts at maintaining early sobriety. Can be inpatient (residential) or outpatient, brief or long term.
    - **Self-help organizations:** Offer a regular and ongoing community of peers to maintain ongoing sobriety. Examples include Alcoholics Anonymous (AA) and Narcotics Anonymous (NA).
    - **Family support/education:** Provide support to family members; offer an environment in which to learn from and commiserate with others. An example is Al-Anon.
    - **Individual counseling/therapy:** Various techniques focus on:
      - Understanding and eliminating triggers for relapse.
      - **Harm reduction approach:** Minimizing use of the substance, which reduces its functional impact on patients' lives.

- **Abstinence model:** Getting patients to accept that they cannot minimize use but must abstain to improve their functional quality of life.
- **Psychoeducation:** Educating patients regarding issues such as the cycle of relapses and remissions; the chronic nature of the illness; and available resources.
- For further information on the treatment of acute intoxication or withdrawal syndromes, see the “Hospital Medicine” chapter.

### Complications

Chronic substance dependence leads to significant loss of productivity, functionality, and quality of life.

## Other Disorders

### SOMATIZATION, FACTITIOUS DISORDER, AND MALINGERING

When patients complain of **physical symptoms** that have no clear medical etiologies, consider evaluating for a somatoform or factitious disorder. **Somatoform disorders** include somatization disorder, conversion disorder, pain disorder, hypochondriasis, and body dysmorphic disorder. These are unconscious and patients believe they are ill. In contrast, patients with **factitious disorder and malingering** consciously feign illness for **primary or secondary gain** (Table 15.3). Certain subtypes are more common in women (eg, conversion disorder, pain disorder); others are more common in men (eg, factitious disorder, malingering). All generally occur more often in those with lower socioeconomic status and education.

### Symptoms

- Vary across the specific disorders, but all are insufficiently explained by medical causes or substance use alone.
- Demonstrate inconsistent findings and often lead to many unnecessary hospitalizations, procedures, and workups. Specific subtypes include the following:
  - **Somatization disorder:** Multiple vague complaints in multiple organ systems (at least **two** organ systems—GI, reproductive, neurologic, pain).
  - **Conversion disorder:** Complaints are in the **neurologic system** (sensory or motor), often in setting of a psychological stressor (**converting** a psychologic problem into a neurologic one).
  - **Pain disorder:** Complaints are predominantly of pain with no identifiable etiology.
  - **Hypochondriasis:** Complaints and fear of serious diseases for at least 6 months.
  - **Body dysmorphic disorder:** Complaints are about a perceived defective body or body part.
  - **Factitious disorder:** Complaints are **consciously simulated by the patient** (vs somatization disorder) to assume the sick role (**primary gain**). No external incentives. **Munchausen syndrome** is a type of factitious disorder with predominantly physical complaints (eg, iatrogenic insulin, diuretic, blood thinner use; feigning hematemesis). **Munchausen syndrome by proxy** is when symptoms are feigned in somebody else under one’s care to assume the sick role by

TABLE 15.3. Symptoms Without an Identifiable Cause

	SOMATOFORM	FACTITIOUS	MALINGERING
Consciously produced	No	Yes	Yes
Secondary gain	No	No	Yes

proxy. While Munchausen syndrome is not a crime, Munchausen syndrome by proxy is a reportable offense.

- **Malingering:** Complaints are **consciously simulated by the patient with specific secondary gain** as a primary motivator (vs factitious disorder). Examples include avoiding police, obtaining room and board, obtaining medications (eg, narcotics).

### Diagnosis

Eliminate likely medical etiologies through standard medical workups. A balance must be struck between sufficient workup to rule out realistic causes and exhaustive workup to rule out extremely rare causes. Psychiatric consultation can help clarify specific diagnoses and can therefore elucidate potential treatment options that could be most helpful.

### Management

- Minimize the number of providers involved in the care of the patient.
- Avoid unnecessary procedures or hospitalizations.
- Establish and maintain a **long-term, trusting doctor-patient relationship**; schedule regular outpatient visits and routinely inquire about psychosocial stressors.
- On each visit, perform at least a partial physical exam directed at the organ system of complaint, and gradually change the agenda to inquire about psychosocial issues in an empathic manner.
- Refer patients to a mental health professional to help them express their feelings, thereby minimizing physical symptoms as a proxy for those feelings.
- Treat any **2° depression** (ie, depression due to the sense of hopelessness associated with having somatoform disorder).
- For conversion disorder, hypnosis, relaxation, and mindfulness techniques can help.
- For body dysmorphic disorder and pain disorder, SSRIs can help.
- Some patients may benefit from the use of an anxiolytic agent (eg, alprazolam).
- Be aware that some patients will develop psychological dependence on medications, so prescribe selectively.

### ATTENTION-DEFICIT HYPERACTIVITY DISORDER

In attention-deficit hyperactivity disorder (ADHD), patients have persistent problems (>6 months) with **inattention** and/or **hyperactivity and impulsivity**.

### Diagnosis

Table 15.4 lists characteristic behaviors required for diagnosis of ADHD.

**TABLE 15.4. Diagnostic Criteria for ADHD**

INATTENTION	HYPERTHYMIA-IMPULSIVITY
Diagnosis requires at least six of the following:	Diagnosis requires at least six of the following:
<b>1.</b> Poor attention to tasks, play activities, or schoolwork.	<b>1.</b> Fidgetiness.
<b>2.</b> Poor listening skills.	<b>2.</b> Leaving rooms in which sitting is expected.
<b>3.</b> Poor follow-through on instructions.	<b>3.</b> Excessive running/climbing.
<b>4.</b> Poor organizational skills.	<b>4.</b> Subjective restlessness.
<b>5.</b> Avoidance of tasks requiring sustained mental effort.	<b>5.</b> Difficulties with leisure activities.
<b>6.</b> Frequent loss of things.	<b>6.</b> Acting as if "driven by a motor."
<b>7.</b> Easy distractibility and forgetfulness.	<b>7.</b> Talking excessively.
<b>8.</b> Frequent careless mistakes.	<b>8.</b> Interrupting others often.

### KEY FACT

Informal "curbside" consults of specialists can be quite helpful for somatoform disorders and are preferable to the formal introduction of yet another medical provider.

### KEY FACT

For an adult to be diagnosed with ADHD, symptoms must have been present in childhood and must cause functional impairment.

### KEY FACT

Adults tend to have less hyperactivity than do children in ADHD. Instead, they tend to present with inattention.

### QUESTION

A 21-year-old woman is brought to the ED following an episode of syncope at home. The patient's mother notes that her daughter is very thin and has not been eating well. She is awake and alert in the ED and has a BMI of 15.5 kg/m<sup>2</sup>. Lab results show hematocrit, 28%; serum potassium, 2.9 mEq/L; serum phosphorus, 1.8 mg/dL; albumin, 3.0 g/dL; and INR, 1.5. The patient wants to go home. What finding puts her at the highest risk for an adverse outcome that would warrant hospitalization?

### Differential

- **Medication-seeking behavior:** Patients often present with a history of substance abuse (especially amphetamine or cocaine abuse).
- **Bipolar affective disorder:** Inattention/racing thoughts occur only during manic episodes; are accompanied by a lack of need for sleep and by grandiosity/euphoria; and are cyclical in nature.
- **Substance-induced symptoms:** Especially common with amphetamine intoxication. Look for associated signs and symptoms of substance abuse.

### Management

- **Stimulants** (eg, methylphenidate): ↑ the dose as needed.
- **Nonstimulants** (eg, atomoxetine).
- **Antidepressants:** If there is a risk of abuse/dependence, bupropion (Wellbutrin) is a nonaddictive and reasonable first-line agent.
- **Behavioral therapy:** Focus on changing maladaptive behaviors and on learning more effective ones.

## EATING DISORDER

Marked disturbances in eating behavior are the hallmarks of an eating disorder. There are **two** major types:

- **Anorexia nervosa:** Patients have misperceptions of body weight, weigh <85% of their ideal body weight, and self-impose severe dietary limitations. The male-to-female ratio is 1:10 to 20. More common in developed/Western societies and in more affluent socioeconomic strata. There are two subtypes of anorexia nervosa, **restricting type** (restricts intake) and **binging/purging type** (binges, then purges).
- **Bulimia nervosa:** Episodic uncontrolled binges of food consumption at least twice a week for 3 months, followed by compensatory weight loss strategies (eg, self-imposed vomiting, laxative and diuretic abuse, excessive exercise). Patients have **normal weight**.

### Symptoms

Both anorexia and bulimia involve a marked misperception of body image and poor self-esteem. Distinguished as follows:

- **Anorexia only:** Actual body weight must be <85% of ideal body weight (for height and age). Also presents with **lanugo**, dry skin, lethargy, bradycardia, hypotension, cold intolerance, hypothermia, and hypercarotenemia (↑ level of carotene in blood resulting in yellowing of skin).
- **Bulimia only:** Patients must have at least **3** months of binge-purging activity that occurs at least **twice a week**. They must also have a sense of **loss of control** during food consumption binges. Patients often have signs of frequent vomiting (eg, low chloride levels, pharyngeal lesions, **tooth enamel decay**, scratches on the dorsal surfaces of the fingers) and **enlarged parotid glands**.

### Diagnosis

Diagnose by history. A collateral history obtained from other family members is often helpful.

### Management

- Correct electrolyte abnormalities. May require hospitalization to monitor for refeeding syndrome.
- Vitamin supplementation: calcium, vitamin D, thiamine.
- Psychotherapy. Anorexia nervosa typically requires long-term treatment.
- **Antidepressants:** SSRIs.

### KEY FACT

Patients with ADHD describe stimulants as slowing them down rather than making them "high."

### KEY FACT

Anorexia nervosa is distinguished from bulimia by low body weight (<85% ideal body weight).

### KEY FACT

The "female athlete triad" is disordered eating, amenorrhea, and osteoporosis.

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### ANSWER

**Hypophosphatemia.** This patient has several features that would warrant hospitalization, but having hypophosphatemia puts her at high risk for **refeeding syndrome**, which could result in cardiovascular collapse. Refeeding syndrome (↑ intake of carbohydrates) leads to ↑ insulin production, causing a shift of potassium, magnesium, and phosphate *into* cells, which further lowers serum levels of these electrolytes.

## Complications

- Anorexia: 2° **amenorrhea**, anemia, osteopenia/osteoporosis, electrolyte abnormalities leading to arrhythmias, refeeding syndrome during treatment (from re-initiation of carbohydrate intake).
- Bulimia: **Acid-induced dental disease**, esophageal tears, hypokalemic metabolic alkalosis (from excessive vomiting).

## SLEEP DISORDERS

Sleep disorders are very common and include 1° and 2° sleep disorders. 1° sleep disorders are described below, and can be divided into **dyssomnias** (disorders of amount, quality, or timing of sleep), and **parasomnias** (abnormal events during sleep). Parasomnias are predominantly seen in children. 2° sleep disorders are due to a mental illness, medical illness, or substance use.

### Symptoms/Exam

Most commonly, patients (or their partners) complain of unrestful sleep. Remainder of symptoms vary based on the specific sleep disorder.

### Differential

There are a variety of sleep disorders (Table 15.5). See the Ambulatory Medicine chapter for more on insomnia.

### Diagnosis

Clinical diagnosis based on history. Remember to ask about **medications and substance use (including caffeine intake)**. Severity is based on impact on daytime function (mood, fatigue, muscle aches, concentration), **not** the total amount of sleep. Other diagnostic modalities include:

- Sleep diaries** are very helpful. Shares insights on sleep-wake patterns, napping, use of drugs, daytime activity.
- EEGs** are sometimes useful in diagnosis and characterize stages of sleep.

### Management

- Depends on sleep disorder (see Table 15.5).
- Sleep hygiene** is often helpful—maintain regular sleep schedule, avoid daytime naps, exercise early in the day, limit caffeine or large meals around bedtime, remove distractions from bedroom (ie, limit the bed to sex and sleep).

## PERSONALITY DISORDERS

A personality disorder is characterized by persistent maladaptive characteristic patterns of behavior that have been present since childhood and cause significant impairment in patients' functioning in society.

### Symptoms

There are several types, most often subdivided into clusters.

- Cluster A** (the “weird” personality disorders):
  - Schizoid:** Not interested in close or sexual relationships and prefer to be alone (social withdrawal), often perceived as eccentric and reclusive.
  - Schizotypal:** Magical thinking (clairvoyance, telepathy, superstitions), eccentric behavior, and social anxiety. Similar to schizophrenia, but less severe with sustained psychotic symptoms. May later develop schizophrenia.



### KEY FACT

Sleep patterns vary with age. With ↑ age, total sleep time naturally ↓ and there are greater transient arousals and fragmentation of sleep (naps).



### KEY FACT

Delayed sleep phase is common in adolescence; advanced sleep phase is common in elderly.



### KEY FACT

When one complains of restless legs, always rule out **iron deficiency** as a cause and treat if low (even if not at anemic levels).

TABLE 15.5. Common Sleep Disorders

SLEEP DISORDER	CLINICAL FEATURES	TREATMENT
<b>DYSSOMNIAS</b>		
1° insomnia	<ul style="list-style-type: none"> <li>■ &gt;1 month of difficult initiating or maintaining sleep, or sleep is nonrestorative</li> <li>■ Significant daytime impairment</li> <li>■ Exclude medication or substance-related</li> </ul>	<ul style="list-style-type: none"> <li>■ Nonpharmacologic: good sleep hygiene, relaxation therapy, behavior modification (reduce stimuli), sleep restriction therapy</li> <li>■ Pharmacologic: sedative-hypnotic medications (eg, eszopiclone, zolpidem)</li> </ul>
Sleep apnea	<ul style="list-style-type: none"> <li>■ Cessation of airflow for &gt;10 seconds during sleep, terminated by awakening</li> <li>■ Excessive daytime sleepiness</li> <li>■ Depression, fatigue, difficulty concentrating</li> <li>■ Partner complains of loud snoring</li> <li>■ Central (rare): lack of respiratory drive</li> <li>■ Obstructive (common): obstruction of upper airway. Risk factors: small jaw, short neck, obese, large tonsils, large tongue</li> </ul>	<ul style="list-style-type: none"> <li>■ Weight loss</li> <li>■ <b>Avoid CNS depressants (eg, benzodiazepines)</b></li> <li>■ CPAP</li> <li>■ Surgery</li> </ul>
Narcolepsy	<ul style="list-style-type: none"> <li>■ Sudden, unexpected REM during wakefulness</li> <li>■ Excessive daytime sleepiness</li> <li>■ Cataplexy (temporary loss of muscle tone), sleep paralysis, hypnagogic hallucinations</li> <li>■ Nocturnal sleep: short REM latency, frequent arousals</li> </ul>	<ul style="list-style-type: none"> <li>■ Scheduled naps</li> <li>■ Dopaminomimetic stimulants</li> <li>■ Modafinil (<math>\alpha_1</math>-agonist)</li> </ul>
Restless leg syndrome	<ul style="list-style-type: none"> <li>■ Repetitive, brief leg jerks in regular 2-4 second intervals</li> <li>■ Desire to move limbs and restlessness when not moving</li> <li>■ Associated with <b>pregnancy, iron deficiency anemia, uremia</b></li> <li>■ Chronic and progressive, leads to severe pain and discomfort, insomnia, excessive daytime sleepiness</li> </ul>	<ul style="list-style-type: none"> <li>■ Benzodiazepines</li> <li>■ Dopaminomimetics (L-dopa, ropinirole)</li> </ul>
Circadian rhythm disorders (Delayed sleep phase syndrome, advanced sleep phase syndrome, jet lag, shift work)	<ul style="list-style-type: none"> <li>■ Delayed sleep phase syndrome: sleep phase delayed beyond desired sleep time; more common in young adults</li> <li>■ Advanced sleep phase syndrome: sleep phase advanced before desired time of sleep, wake up too early without being able to fall back asleep; more common in elderly</li> <li>■ Jet lag/shift work: mismatch between circadian rhythm and external demands on waking behavior, leading to insomnia or hypersomnolence</li> </ul>	<ul style="list-style-type: none"> <li>■ Promote good sleep hygiene</li> <li>■ Light therapy may help for shift work type</li> </ul>

(continues)

TABLE 15.5. Common Sleep Disorders (continued)

SLEEP DISORDER	CLINICAL FEATURES	TREATMENT
<b>PARASOMNIAS</b>		
Nightmare disorder	<ul style="list-style-type: none"> <li>■ Repeated <b>awakenings</b> from frightening dreams causing distress; patients <b>are aware</b></li> <li>■ Happens during REM</li> <li>■ Most often in children, during stress or illness</li> </ul>	<ul style="list-style-type: none"> <li>■ Reassurance</li> <li>■ TCAs can help</li> </ul>
Night terror disorder	<ul style="list-style-type: none"> <li>■ Repeated episodes of apparent fearfulness during sleep (eg, screaming, anxiety); patients <b>do not recall</b></li> <li>■ Happens during non-REM sleep</li> <li>■ Most often in children, often associated with <b>sleepwalking disorder</b></li> </ul>	<ul style="list-style-type: none"> <li>■ Reassurance</li> <li>■ Diazepam can help</li> </ul>
Sleepwalking disorder	<ul style="list-style-type: none"> <li>■ Repeated episodes of walking during sleep; patients <b>do not recall</b></li> <li>■ Most often in children</li> </ul>	<ul style="list-style-type: none"> <li>■ Ensure safe environment</li> </ul>

- **Paranoid:** Pervasive distrust and suspiciousness of others, blames others for own problems, bears long grudges. Unlike paranoid schizophrenia, patients with paranoid personality disorder **do not** have fixed delusions and are **not** frankly psychotic.
- **Cluster B (the “wild” personality disorders):**
  - **Borderline:** Unstable self-image, relationships, affect, and behaviors. Often splits.
  - **Histrionic:** Dramatic, attention-seeking, extroverted but unable to form meaningful relationships. Often revert to **childlike behaviors**.
  - **Narcissistic:** Sense of superiority and need for admiration, fragile self-esteem. High risk of **depression**.
  - **Antisocial:** Begins in childhood as **conduct disorder**. Refuse to conform to social norms, impulsive, lacks empathy, often violate the law.
- **Cluster C (the “wimpy” personality disorders):**
  - **Dependent:** Excessive need to be taken care of and feel helpless when alone, low self-confidence.
  - **Obsessive-compulsive:** Preoccupied with perfection and orderliness, inflexibly so. **Do not** have obsessions or compulsions, as in **obsessive-compulsive disorder**.
  - **Avoidant:** Intense fear of rejection; desire relationships (unlike **schizoid**) but are very shy and fragile. Unlike **social phobia** or **social anxiety disorder**, patients with avoidant personality disorder generally are shy since childhood, and fear is of *rejection*, not *embarrassment*.

### Differential

Developmental delay (patients have below-normal intelligence), substance abuse, mood or psychotic disorders (may be comorbid).

### Diagnosis

Without a significant amount of collateral information, it is difficult to diagnose a personality disorder in patients on a single visit. Because there must be a persistent pattern of behavior, patients should ideally be observed over time to ensure accurate diagnosis and referral.

### KEY FACT

People with cluster B personality disorders will sometimes “split” medical personnel—ie, they tend to view things in black-and-white and view individual medical staff as either “the best ever” or “the worst ever.” Their impressions of staff can frequently change, frustrating caregivers and making it difficult for many to provide empathetic care.

### Management

- Personality disorders are both long-standing and pervasive and are thus **resistant to treatment**. Patients generally are **not aware** they need help.
- **Psychotherapy and group therapy** are usually the most helpful. Pharmacotherapy has limited usefulness. Do not refer patients with antisocial personality disorder to group therapy modalities. They do not typically benefit and often exploit or victimize peers in this setting.
- **Dialectical behavioral therapy** has been shown to be an effective treatment of **borderline personality disorder**. Brief **CBT** groups may also maximize effective coping strategies and minimize functional impact on patients' lives.
- **Mood stabilizers** (eg, valproic acid, lithium, carbamazepine) may be of use in **antisocial and borderline personality disorders**. **SSRIs** (eg, fluoxetine, sertraline, paroxetine) may be useful in treating **borderline, dependent, and avoidant personality disorders**.

### Patient Competence and Decision-Making Capacity

#### KEY FACT

**Competence** is a legal assessment made by a judge; patient **decision-making capacity** can be determined in the health care setting (ie, by clinicians). Capacity is determined for a specific clinical decision or treatment encounter.

Patient **competence** refers to a patient's ability to make medical decisions on his/her own behalf on a regular basis. It involves a legal assessment and is generally a long-term decision made outside the hospital or clinic setting. Patient capacity refers to the ability of a person to make an **informed decision** about a clinical recommendation (eg, to operate or not) and always occurs in the context of a specific treatment encounter. Therefore, the fundamental question with **patient** decision-making capacity is, "Is the patient able to decide on his/her own behalf, or should you (or someone else) make the decision for him/her?" The answer depends on the **context** of care. See the Ambulatory Medicine chapter for more on decision-making **capacity**.

- **Patients with acute/emergent medical issues** (eg, massive hemorrhage): In most states, doctors have the right to perform emergent medical care. Although not explicitly defined, the term *emergent* is generally thought of as "when there is an imminent loss of life or limb." Technically, without explicit patient or representative consent, you must confine your care to the treatment of emergent conditions.
- **Patients with acute psychiatric issues** (eg, those who are actively psychotic, floridly manic, or acutely suicidal): Again, laws vary from state to state, but most states allow for emergent psychiatric treatment. This may include medications (IM or IV if necessary), locked hospitalization, locked seclusion, and/or physical restraints.
- **Patients with subacute medical conditions** (eg, nonemergent medical or surgical procedures) have the right to refuse recommended treatment as long as they:
  - **Know and can repeat** the nature of the medical condition.
  - **Know and can repeat** the benefits/risks of and alternatives to the recommended treatment.
  - **Consistently** express the rationale for their decision.
- **Patients with subacute psychiatric conditions** (eg, schizophrenic but not actively psychotic; depressive but not actively suicidal; bipolar but not floridly manic):
  - Recommended medical treatment should be offered just as if there were no psychiatric condition (see above).
  - Laws regarding recommended psychiatric care vary significantly across states. Some states allow clinicians significant power in mandating unwanted treatment, while others give patients significant rights to refuse, which can be overturned only in a court of law.
  - Remember that if/when the condition becomes acute or emergent, most states allow psychiatric treatment.

- **Patients with advance directives**—by definition, patients may sign advance directives only when they have the mental capacity to do so, and when the directive:
  - Explicitly addresses the recommended/anticipated treatment, physicians must adhere to the patient's pre-stated wishes even if those wishes will lead to a worse outcome (including death).
  - Does not explicitly address an emergent or subacute medical condition (and the patient cannot respond), staff and/or the patient's family/friends must attempt to infer what the patient's wishes would be and treat accordingly.

## Confidentiality in Psychiatry

The following are some exceptions to confidentiality in psychiatric practice:

- If the patient is **suicidal or homicidal**, protective steps may have to be taken that breach confidentiality.
- **Child abuse** must be reported to protective services. In most states, laws similarly require reporting for abuse of older adults.
- If the plaintiff in a lawsuit has made his or her medical or psychiatric condition an issue, the defendant has the right to know about and to obtain the records of the plaintiff's evaluation and treatment.
- A court may order a physician to disclose confidential information. If working at a hospital or with a large practice, it is recommended physicians contact Risk Management in this event.
- The results of a court-ordered pretrial evaluation may be available to the defense attorney, the prosecuting attorney, and the judge.
- The results of a disability evaluation will be available to the attorney or agency that requested the evaluation.

## Special Populations in Psychiatry

### GERIATRIC PATIENTS

See the Geriatric Medicine chapter.

### ADOLESCENT PATIENTS

Mid- to late adolescence is the most common time for early signs of schizophrenia or bipolar disorder to begin, with significant impairments in functioning tending to occur in the late teens to early 20s.

- **Depression:** In adolescents (and children), irritability can often be more prominent than sadness or anhedonia when diagnosing depression.
- **Suicidality:** Adolescents are more prone to impulsive acts, so close monitoring when beginning antidepressant medications (which can sometimes cause anxiety or agitation as side effects) is crucial.

### PATIENTS WITH HIV/AIDS

Psychomotor slowing and personality change can sometimes be seen in HIV-associated cognitive impairment. Some antiretroviral medications (eg, efavirenz) can have significant psychiatric side effects. Also consider whether an opportunistic infection (such as toxoplasmosis) or malignancy (such as CNS lymphoma) could be contributing, depending on the context.



### QUESTION

A 30-year-old man on quetiapine for schizophrenia presents to the ED with cough and shortness of breath. He is febrile with an ↑ WBC; a CXR reveals necrotizing pneumonia. The patient is told to remain in the hospital for IV antibiotics but refuses to stay. He claims to understand his medical condition and the potential risks of repeating the alternative therapy (PO antibiotics) at home. The admitting physician feels strongly that the patient should be hospitalized and notes that he should not be able to refuse treatment, as he is schizophrenic and thus cannot make appropriate decisions. The physician asks your opinion. What is your response?



### KEY FACT

Adolescents on psychiatric medicines should be closely monitored for agitation or anxiety side effects.

**A****ANSWER**

If the patient is not actively psychotic, his schizophrenia should be disregarded in any issues regarding decision-making capacity. Since he meets all other criteria for decision-making capacity, he should be evaluated for active psychosis and then discharged with PO antibiotics.

**Therapeutic Drugs in Psychiatry****ADVERSE EFFECTS**

Table 15.6 outlines both common and potentially serious adverse effects associated with psychiatric drugs.

- **Serotonin syndrome and neuroleptic malignant syndrome (NMS):** Both may cause autonomic instability, hyperthermia, rhabdomyolysis, metabolic acidosis in context of offending drugs (Table 15.7). Serotonin syndrome causes hyperkinesia and myoclonus; NMS causes bradykinesia and “lead pipe” rigidity. In serotonin syndrome, onset and offset tend to be faster (<24 hours), whereas in NMS, onset tends to be slower (1-3 days) and altered mental status and elevated CK are more likely to occur.

**T A B L E 15 . 6 . Adverse Effects of Commonly Administered Psychiatric Drugs**

EXAMPLES	COMMON ADVERSE EFFECTS	MEDICALLY SERIOUS ADVERSE EFFECTS
<b>SSRIS</b>		
Paroxetine (Paxil), fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox)	Sedation, weight gain, GI discomfort, sexual dysfunction	<b>Serotonin syndrome</b> (tachycardia, hypertension, fever, hyperthermia, myoclonus, convulsions, coma)
<b>OTHER ANTIDEPRESSANTS</b>		
Bupropion (Wellbutrin)	Insomnia, “jitteriness”	Lowered seizure threshold
Venlafaxine (Effexor)	Constipation, dizziness	Lowered seizure threshold, hypertension
<b>MOOD STABILIZERS</b>		
Lithium	Cognitive dulling, tremor, sedation, nausea, diarrhea, T-wave flattening	Lithium toxicity (altered mental status, arrhythmias, GI symptoms), hypothyroidism (with long-term use), nephrogenic diabetes insipidus
<b>MOOD STABILIZERS/ANTICONVULSANTS</b>		
Valproic acid (Depakote)	Weight gain, sedation, cognitive dulling, hair loss	Thrombocytopenia
Carbamazepine (Tegretol)	Same as above	SIADH, agranulocytosis, Stevens-Johnson rash
<b>TYPICAL HIGH-POTENCY ANTIPSYCHOTICS</b>		
Haloperidol (Haldol), fluphenazine (Prolixin), trifluoperazine (Stelazine)	Sedation	Acute dystonic reactions, <b>neuroleptic malignant syndrome</b> , tardive dyskinesia (with long-term use); QTc prolongation leading to torsades de pointes with high doses of haloperidol
<b>TYPICAL MIDPOTENCY ANTIPSYCHOTICS</b>		
Perphenazine (Trilafon), thiothixene (Navane)	Sedation, anticholinergic side effects (dry mouth, constipation, urinary retention, tachycardia)	Acute dystonic reactions, neuroleptic malignant syndrome, tardive dyskinesia (with long-term use)
<b>TYPICAL LOW-POTENCY ANTIPSYCHOTICS</b>		
Thioridazine (Mellaril), chlorpromazine (Thorazine)	Sedation, orthostatic hypotension	Acute dystonic reactions, neuroleptic malignant syndrome, tardive dyskinesia (with long-term use)

(continues)

**TABLE 15.6.** Adverse Effects of Commonly Administered Psychiatric Drugs (*continued*)

EXAMPLES	COMMON ADVERSE EFFECTS	MEDICALLY SERIOUS ADVERSE EFFECTS
<b>ATYPICAL ANTIPSYCHOTICS</b>		
Olanzapine (Zyprexa)	Weight gain, sedation	Hypercholesterolemia, possible DM
Risperidone (Risperdal)	Weight gain	Hyperprolactinemia; side effects of typical antipsychotics (when used in high doses)
Clozapine (Clozaril)	Drooling, weight gain	Agranulocytosis
Quetiapine (Seroquel)	Sedation, orthostasis	Hypotension QTc prolongation
Ziprasidone (Geodon)	Sedation	QTc prolongation
Aripiprazole (Abilify)	Restlessness	—

- **Antipsychotic extrapyramidal symptoms:** Characterized by rapid-onset muscle spasms, tend to be localized to neck, tongue, and jaw.

### IMPORTANT DRUG-DRUG INTERACTIONS

- **Carbamazepine:**
  - An autoinducer of cytochrome P-450 isoenzyme, so levels must be rechecked and the dose often ↑ after several weeks of use.
  - ↓ serum level of OCPs.
  - Erythromycin, isoniazid, and H<sub>2</sub> blockers all ↑ carbamazepine levels.
  - HLA-B\*1502 found in many Chinese patients make them susceptible to carbamazepine-induced Steven-Johnson syndrome and toxic epidermal necrolysis; consider an alternate medication or genetic testing in these patients.
- **Valproic acid:** Levels are ↑ by ASA and anticoagulants.
- **Benzodiazepines:**
  - Levels are ↑ by disulfiram, ketoconazole, valproic acid, erythromycin, and cimetidine.
  - Diazepam (Valium) and alprazolam (Xanax) ↑ levels of digoxin and phenytoin.

### NONPSYCHIATRIC MEDICATION CLASSES WITH PSYCHIATRIC ADVERSE EFFECTS

- **Antiretrovirals** (eg, efavirenz): Delirium, mania, irritability, cognitive impairment.
- **Dopamine agonists** (eg, pergolide, carbidopa-levodopa): Hallucinations, paranoia.
- **Antihistamines** (eg, diphenhydramine, hydroxyzine): Delirium, cognitive impairment.
- **Anticholinergics** (eg, benzatropine, oxybutynin): Delirium, cognitive impairment.
- **Corticosteroids** (eg, prednisone): Mania, psychosis, elation, depression.

**TABLE 15.7.** Drugs Associated With Serotonin Syndrome

Monoamine oxidase inhibitors (eg, isocarboxazid, phenelzine)
SSRIs
Tricyclic antidepressants
Meperidine
Sumatriptan
Lithium
Procarbazine
Linezolid
Cocaine

## NOTES

# CHAPTER 16

## Rheumatology

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**KEY FACT**

Arthritis of the DIP joints has a very limited differential diagnosis: think osteoarthritis, gout, or psoriatic arthritis.

**Approach to Arthritis**

Figure 16.1 and Tables 16.1 and 16.2 outline general approaches to the differential diagnosis of arthritis and other rheumatic diseases. **Contraindications to arthrocentesis** include overlying soft tissue infection or cellulitis, severe coagulopathy, and bleeding disorder (INR > 3.0).

**Rheumatoid Arthritis**

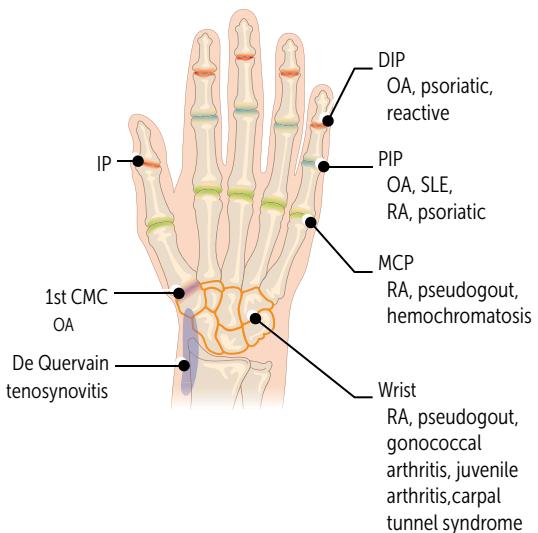
RA is a symmetric, inflammatory arthritis that has been present for >6 weeks and involves the MCP and wrist joints. It has female-to-male predominance of 3:1. Prevalence ↑ with age, with a typical age at onset of 20 to 40 years.

**Symptoms/Exam**

- Morning pain and/or stiffness for >60 minutes for at least 6 weeks.
- Symmetric inflammatory polyarthritis improves with joint use and worsens with prolonged inactivity.
- Typically involves >3 joints; predominately affecting these seven sites: MCP, PIP, wrist, elbow, knee, ankle, and MTP (Figure 16.3) (TIP: The hands are involved in almost all patients with RA; however, RA spares the DIP joints).
- Characteristic hand deformities include **ulnar deviation** of the fingers at the MCPs, **swan neck deformities**, and boutonniere deformities.
- RA commonly affects the cervical spine—be aware of the risk of C1-C2 (“atlanto-axial”) subluxation in patients with chronic RA and obtain cervical spine x-ray prior to tracheal intubation to assess for this. C1-C2 subluxation may be asymptomatic or produce occipital headaches or cervical myelopathy.
- Look for **rheumatoid nodules** over bony prominences on extensor surfaces (Figure 16.4).
- Extra-articular findings of RA are outlined in Table 16.3.

**Diagnosis**

- Classification criteria were revised in 2010 and are outlined in Table 16.4.
- Classic radiographic findings: Periarticular osteopenia, joint space narrowing, juxta-articular erosions, erosions of the ulnar styloids (Figures 16.5 and 16.6). Early radiographic RA findings can often be seen first in the feet, particularly fifth MTP joint.



**FIGURE 16.1. Diagnosis of rheumatic diseases based on joint distribution.**

TABLE 16.1. Differential Diagnosis of Arthritis

DISEASE	JOINT PATTERN	PERIPHERAL JOINT INVOLVEMENT	SPINAL DISEASE	KEY DISTINGUISHING FEATURES
Rheumatoid arthritis (RA)	Symmetric/polyarticular	Wrist/MCPs, <b>PIP</b> s/ <b>MTP</b> s, ankles, knees; <b>DIP</b> s are spared	No (except C-spine)	Polyarticular, symmetric, small joints, ulnar deviation, boutonnière deformity, rheumatoid nodules
Systemic lupus erythematosus (SLE)	Symmetric/polyarticular	Wrist/MCPs/PIP	No	Extra-articular manifestations of SLE
Ankylosing spondylitis	Usually oligoarticular	Hips, shoulders, knees	<b>Yes</b>	Low back pain, progressive limitation of back motion; sacroiliitis
Psoriatic arthritis	Asymmetric/oligoarticular	Dactylitis, <b>DIP</b> s	Yes	History of cutaneous psoriasis, nail pitting
Reactive arthritis	Asymmetric/oligoarticular	Larger, weight-bearing joints; knees/ankles	Yes	History of URTI, diarrheal illness, or STI
IBD-associated arthritis	Oligoarticular	Larger joints	Yes	GI manifestations (eg, diarrhea, bloody stools)
Gout	Monoarticular, polyarticular	First MTP, ankle, knee, MCPs/PIP	No	Acute, exquisitely painful to touch, cellulitis
Osteoarthritis (see Figure 16.2)	Monoarticular/oligoarticular, polyarticular	<b>DIP</b> s, first carpal-metacarpal, knees, hips	Yes	<b>Noninflammatory</b> (worse at end of day and with activity; improves with rest); Bouchard nodes, Heberden nodes



A



B



C

**FIGURE 16.2. Osteoarthritis.** (A) Plain x-ray shows joint space narrowing, osteophytes, and subchondral degenerative cysts involving the interphalangeal joints with sparing of the MCP and carpal joints. (B) Frontal x-ray of the right knee shows medial joint space narrowing, subchondral sclerosis of the medial tibia, and marginal osteophytes consistent with osteoarthritis. (C) Anteroposterior x-ray of the pelvis with bilateral hip osteoarthritis. (Images A and B reproduced with permission from USMLE-Rx.com; image C source: Islam KA, et al. An unusual cause for a painful Birmingham hip resurfacing. *Ann R Coll Surg Engl*. 2013;95(1):e10-e11.)



## QUESTION

A 35-year-old woman presents with 3 months of morning stiffness, wrist swelling, and pain. Exam notable for MCP and wrist synovitis. Lab results:  $\ominus$  ANA,  $\ominus$  RF, and  $\oplus$  anti-CCP. Hand x-rays show marginal erosion of the MCP. What is the most likely diagnosis?

RHEUMATOLOGY

TABLE 16.2. Characteristics of Synovial Fluid

SIGN	NORMAL	GROUP 1: NONINFLAMMATORY (OSTEOARTHRITIS, HYPOTHYROIDISM)	GROUP 2: INFLAMMATORY (RA, GOUT, CPPD, SPONDYLOARTHROITIS, SLE)	GROUP 3: SEPTIC
Clarity	Transparent	Transparent	Slightly opaque	Opaque
Color	Clear	Yellow	Yellow-opalescent	Yellow-green
Viscosity	High	High	Low	Usually low
Culture	⊖	⊖	⊖	Often ⊕
WBCs/mm <sup>3</sup>	<200	200-2000	2000-100,000	>50,000
PMNs (%)	<25	<25	>50	>75

**KEY FACT**

Anti-CCP is more specific but less sensitive than RF for diagnosing RA. When used together, the two tests maximize the sensitivity and specificity of a diagnosis of RA.

**KEY FACT**

Most extra-articular manifestations of RA are observed in patients who are “seropositive” (meaning RF ⊕ and/or anti-CCP ⊕) and have long-standing erosive articular disease.

**KEY FACT**

In a patient being treated with methotrexate for RA who presents with new-onset dyspnea and interstitial infiltrates on CXR, consider opportunistic infection and hypersensitivity pneumonitis from methotrexate and discontinue the drug.

**KEY FACT**

Infliximab is associated with higher rates of infusion reactions and of neutralizing antibodies than other TNF inhibitors because it is a chimeric (mouse and human) antibody.

**A****ANSWER**

RA. RF is ⊕ in 85% of cases, but only 33% of cases are ⊕ in the first 6 months of disease. Anti-CCP has 90% to 95% specificity for RA, is detected in early RA more commonly than RF, and has significant predictive value when combined with RF.



**FIGURE 16.3. Clinical progression of rheumatoid arthritis.** Typical ulnar deviation of the MCP joints and swelling of the PIP joints in a patient with RA. (Source: NIH Senior Health Web site, National Library of Medicine. <https://nihseniorhealth.gov/>.)

**TABLE 16.3. Extra-articular Manifestations of RA**

ORGAN	PRESENTATION
Cardiac	Pericarditis, myocarditis, atherosclerosis
Pulmonary	Pleural effusion, interstitial lung disease, pulmonary nodules, Caplan syndrome
Eyes	Episcleritis, scleritis, keratitis, uveitis, Sjögren syndrome
Renal	Amyloid renal disease
Nerve	Mononeuritis multiplex, cervical myelopathy, carpal tunnel syndrome
Skin	Rheumatoid nodules (usually extensor surface)
Blood	Anemia of chronic disease, thrombocytosis, Felty syndrome (RA, neutropenia, and splenomegaly)
Other	Vasculitis, AA amyloidosis (2° amyloidosis)

**FIGURE 16.4. Rheumatoid nodules on the extensor surface of the forearm.**

(Reproduced with permission from USMLE-Rx.com.)

- Biologic DMARDs: TNF- $\alpha$  inhibitors, tocilizumab, abatacept, rituximab, tofacitinib.
- **Recommended protocol:** Table 16.5 outlines indications for the various antirheumatic drugs as well as their appropriate dosages, contraindications, and potential side effects. The recommended protocol is as follows (see Figure 16.7):
  - **First-line DMARDs:** Methotrexate for most patients with RA. Leflunomide is an alternative first-line agent if methotrexate is not tolerated. Hydroxychloroquine and sulfasalazine can be used alone, but more often in combination with methotrexate.
  - **Second-line DMARDs:** Combination therapy with two or three first-line DMARDs (“triple therapy” = methotrexate + hydroxychloroquine + sulfasalazine; more efficacious than double therapy) or a TNF- $\alpha$  inhibitor.
  - **Third-line DMARDs:** If no response is achieved after 3 to 6 months of a TNF- $\alpha$  inhibitor, consider changing to a different class of biologic medication or adding azathioprine. Note: patients given azathioprine require monitoring for low thiopurine methyltransferase (TPMT) activity, which is associated with a high risk of drug toxicity.
  - **Flares:** Steroid as a bridge until DMARDs. NSAIDs can ameliorate RA symptoms, but lack disease-modifying activity.
  - **Surgery:** Reserved for patients unresponsive to pharmacologic management with severe joint destruction, intractable pain, or ruptured tendons.

**TABLE 16.4. Criteria for the Classification of RA<sup>a</sup>**

CRITERION	DESCRIPTION	POINTS
Joint involvement (swollen, tender, or erosions seen on x-ray)	1 large joint 2-10 large joints 1-3 small joints 4-10 small joints >10 joints	0 1 2 3 5
Serology	Negative RF and anti-CCP ⊕ RF or anti-CCP at low level ⊕ RF or anti-CCP at high level	0 2 3
Acute-phase reactants	Elevated CRP or ESR	1
Duration	$\geq 6$ weeks	1

**KEY FACT**

For patients with RA or SLE, prednisone and hydroxychloroquine are the preferred anti-inflammatory agents during pregnancy.  
**(Remember the 3P's: For Pregnancy, use Prednisone or Plaquenil).**

<sup>a</sup>The diagnosis of RA requires a score of 6 or higher and no other disease to explain the symptoms.

TABLE 16.5. Comparison of the Most Commonly Used Antirheumatic Drugs

DRUG	INDICATION	DOSAGE	INITIAL MONITORING	ROUTINE MONITORING	CONTRAINdications	SIDE EFFECTS
Methotrexate	First-line DMARD	Weekly	CXR, hepatitis serologic tests, CBC, LFTs, Cr	CBC, LFTs every 4-8 weeks	Renal disease, hepatic disease, EtOH abuse, pregnancy/trying to conceive	Myelosuppression, hepatotoxicity, cirrhosis, teratogenicity (F and M), GI intolerance, stomatitis, alopecia, hypersensitivity pneumonitis, pulmonary fibrosis
Sulfasalazine	First- or second-line DMARD	Daily	CBC, G6PD (if suspected)	CBC, LFTs	G6PD deficiency (can cause hemolysis), sulfite allergy	GI intolerance, transaminitis, neutropenia, thrombocytopenia
Leflunomide	First- or second-line DMARD	Daily, but $t_{1/2}$ is >2 weeks	Hepatitis serologic tests, CBC, LFTs, Cr	CBC, LFTs, Cr	Pregnancy/trying to conceive, EtOH abuse, hepatic disease	Myelosuppression, hepatotoxicity, rash, diarrhea, alopecia, teratogenicity
Hydroxychloroquine	First- or second-line DMARD	Daily		Yearly eye exam		Retinopathy, especially with renal dysfunction
Corticosteroids	First-line DMARD, but use lowest dose possible and wean off to prevent long-term complications	Daily oral; joint injections are very helpful for symptoms	BP, glucose, metabolic panel, lipids	Bone densitometry (DEXA), glucose, lipids	Caution in osteoporosis, severe diabetes	Glucose intolerance, hypertension, cataracts, osteoporosis, avascular necrosis
TNF- $\alpha$ inhibitors	Second-line DMARDs/ biologics; usually added after 3-6 months if there is little or no response to other DMARDs	<b>Infliximab:</b> Infusion q 6-8 weeks <b>Adalimumab:</b> SQ injection q 2 weeks <b>Etanercept:</b> SQ injection 1-2 per week <b>Certolizumab:</b> SQ injection 1-2 per month <b>Golimumab:</b> SQ injection 1 per month	PPD or IGRA, CXR, CBC, LFTs, hepatitis serology testing	CBC, LFTs	Malignancy; active or untreated latent TB	With all agents: Immunosuppression with an ↑ incidence of opportunistic infections and malignancy; all can cause drug-induced lupus (+ anti-ds-DNA)

(continues)

TABLE 16.5. Comparison of the Most Commonly Used Antirheumatic Drugs (*continued*)

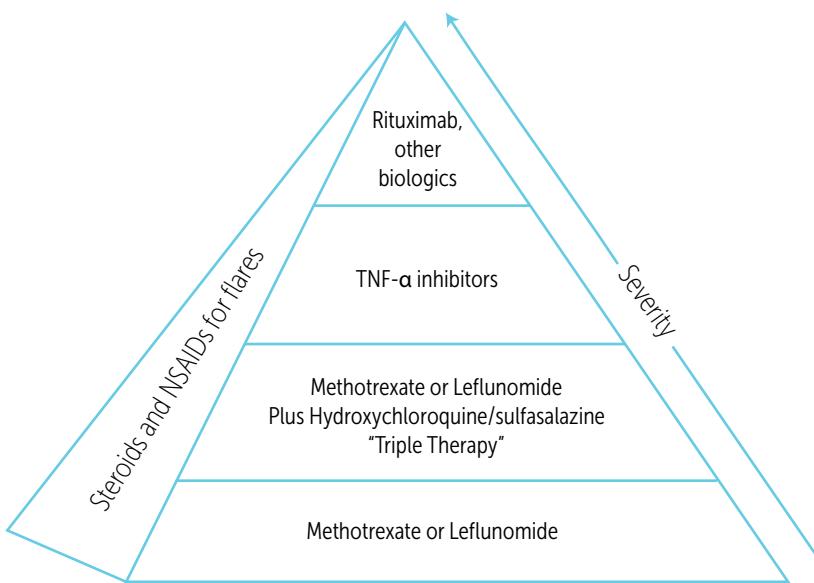
DRUG	INDICATION	DOSAGE	INITIAL MONITORING	ROUTINE MONITORING	CONTRAINdications	SIDE EFFECTS
Azathioprine	Used for severe/refractory RA	Daily	CBC, LFTs, Cr, low TPMT activity	CBC with change in dose, LFTs	Not to be used concomitantly with allopurinol	Myelosuppression, immunosuppression, hepatotoxicity, lymphoproliferative disorders
Tocilizumab	Used for severe RA, IL-6 receptor inhibitor	Monthly	PPD or IGRA, CBC, chemistry, LFTs, hepatitis serology testing	CBC, chemistry, LFTs, lipids	ANC <2000 Platelets <100,000 Active hepatic disease, malignancy, active or untreated latent TB	URTI, GI infection, hepatotoxicity, lymphoproliferative disorders, SJS, demyelinating CNS disorders
Other biologics	Use if refractory to TNF- $\alpha$ inhibitors	<b>Rituximab:</b> 3-4 months <b>Abatacept:</b> Monthly <b>Tofacitinib:</b> Oral twice daily <b>Anakinra:</b> Daily	<b>Rituximab:</b> PPD or IGRA, chemistry, LFTs <b>Abatacept:</b> LFTs, hepatitis serology testing <b>Tofacitinib:</b> Oral twice daily <b>Anakinra:</b> Daily	CBC, Chemistry, LFTs	Malignancy; active or untreated latent TB	With all agents: Hepatotoxicity, lymphoproliferative disorders, infusion reaction, PML, SJS, pulmonary toxicity <b>Abatacept:</b> COPD exacerbation, headache



FIGURE 16.5. Radiographic appearance of rheumatoid arthritis. AP bilateral hand radiograph in a patient with advanced RA shows joint space narrowing involving the carpal, MCP, and PIP joints as well as subluxation at multiple MCP joints (circle) and periarticular erosions (arrow). (Reproduced with permission from USMLE-Rx.com.)



FIGURE 16.6. Radiographic findings of erosive rheumatoid arthritis. AP radiograph (A) and CT (B) of 2nd MCP joint show juxta-articular bony erosion. (Source: Dohn UM, et al. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther.* 2006;8(4):R110.)



**FIGURE 16.7. Treatment pyramid for RA.** Start with treatments at the bottom and work your way up as determined by disease severity. (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Thanh C. Tran.)

**TABLE 16.6. Serologic Results in SLE and Other Rheumatic Diseases**

CONDITION	AUTO-ABS WITH HIGH SENSITIVITY <sup>a</sup>	AUTO-ABS WITH HIGH SPECIFICITY <sup>b</sup>	COMMENTS
RA	RF (70%-90%)	Anti-cyclic citrullinated peptide (CCP) (95%)	Anti-CCP appears earlier than RF in RA; associated with the development of erosive RA
SLE	ANA	Anti-dsDNA, anti-Sm	⊖ ANA test virtually excludes SLE Anti-dsDNA titer generally correlates with SLE disease activity <b>Low complement level (C3,C4, CH50)</b>
Drug-induced lupus	ANA, antihistone	–	Anti-dsDNA seen in drug-induced lupus from <b>anti-TNF agents and interferon-α</b>
Sjögren syndrome	Anti-Ro/SSA (75%)	–	Anti-Ro/SSA also associated with <b>neonatal lupus</b>
Mixed connective tissue disease	ANA, anti-RNP	–	Anti-RNP must be present to make the diagnosis
Scleroderma (limited and diffuse)	ANA (85%-95%)	Anti-centromere (more associated with limited), Anti-Scl-70 (more associated with diffuse)	Anti-centromere associated with a lower likelihood of interstitial lung disease
Granulomatosis with polyangiitis (Wegener granulomatosis)	ANCA (60%-90%)	c-ANCA pattern (by immunofluorescence) + PR3-ANCA (by ELISA)	ANCA also seen in drug-induced lupus from <b>minocycline, hydralazine</b>
Polymyositis/dermatomyositis	ANA (80%-95%)	Anti-Jo-1 (20%-30%)	Anti-Jo-1 associated with <b>antisynthetase syndrome</b> , a subset of dermatomyositis patients

<sup>a</sup>Sensitivity is the probability that a patient with the disease will test positive.

<sup>b</sup>Specificity is the probability that a patient without the disease will test negative.

## Systemic Lupus Erythematosus and Drug-Induced Lupus

### SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is characterized by arthralgias, photosensitivity, dermatologic lesions (malar rash, oral ulcers; Figure 16.8), pancytopenia, serositis, and nonerosive arthritis (Figure 16.9). Lymphadenopathy and splenomegaly may also be seen. Has a female-to-male predominance of 9:1. ↑ prevalence among African Americans, Hispanics, and Asians compared with Caucasians. Both genetic and environmental factors are involved. Nearly 90% of patients have joint involvement.

#### Diagnosis

- Four of the 11 clinical and laboratory criteria listed in Table 16.7 can classify patients as having SLE.
- ANA testing is nearly 100% sensitive but is not specific for SLE (see Table 16.6). There is no role for following ANA titers in established lupus, as levels do not correlate with disease activity.
- Antibodies to dsDNA and Smith are specific (>90% and >95%, respectively) but not sensitive (50%-60% and 30%, respectively).
- Only antibody titers to dsDNA can correlate with disease activity, particularly renal disease.
- Depressed serum complement levels (CH50, C3, C4) can be seen in lupus flares.

#### Management

- **Mild disease** (skin/joint involvement, oral ulcers, serositis):
  - NSAIDs for mild arthritis.
  - Topical corticosteroids for skin disease.
  - Low-dose oral corticosteroids (<10 mg/day).
  - **Hydroxychloroquine** should be initiated for nearly every patient with mild SLE.
  - All patients should be counseled about sun protection/avoidance.
- **Moderate disease** (cytopenias/hemolytic anemia, serositis, mild pneumonitis, mild myocarditis):
  - Moderately dosed systemic corticosteroids (~ 0.5 mg/kg/day).



A



B



C

**FIGURE 16.8. Mucocutaneous manifestations of SLE.** (A) Malar rash. This type of rash is typically photosensitive and spares the nasolabial folds. (B) Discoid rash. (C) Oral ulcer. (Image A source: Wikimedia Commons, Fig. 14-20. Image B source: Kole AK, et al. Cutaneous manifestations of systemic lupus erythematosus in a tertiary referral center. *Indian J Dermatol*. 2009;54(2):132-136. Image C reproduced with permission from Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill, 2008, Fig. 156-8C.)

**KEY FACT**

Don't be tricked with Jaccoud-like arthropathy in SLE. It mimics RA with MCP involvement and ulnar deviation, yet unlike in RA, the deformities are reducible.



**FIGURE 16.9. Jaccoud-like arthropathy in SLE.** Characteristic ulnar deviation at the MCP joints with subluxation at multiple joints. Note the absence of bony erosions. (Reproduced with permission from Chen MY, et al. *Basic Radiology*. New York: McGraw-Hill, 2004, Fig. 7-43.)

**KEY FACT**

The leading causes of death in patients with SLE:

Early: Active organ disease and infection.  
Late: Accelerated atherosclerosis, end-stage organ disease (especially renal), and infection.

- Steroid-sparing agents such as azathioprine, methotrexate (good for skin and arthritis), and mycophenolate mofetil.
- **Severe disease** (nephritis, severe CNS disease, vasculitis, pulmonary hemorrhage, pneumonitis, myocarditis):
  - High-dose corticosteroids (pulse steroid, follow by prednisone 60 mg oral).
  - IV cyclophosphamide or mycophenolate mofetil for nephritis.
  - Azathioprine.
  - Rituximab.
  - Belimumab if refractory to conventional therapy.
  - IVIG (for antibody-mediated cytopenias).

### Complications

In addition to disease-related organ-specific damage, complications are as follows:

- **Accelerated atherosclerosis; CAD.**
- An ↑ risk of venous thromboembolism with antiphospholipid antibodies.
- Cyclophosphamide is associated with transitional cell carcinoma, ovarian failure, and hematologic malignancies.
- Opportunistic infections (due to immunosuppressive therapy).

### DRUG-INDUCED LUPUS

- Hallmarks that distinguish drug-induced lupus from SLE include the following:
  - Equal prevalence in both sexes.
  - Renal and neurologic involvement are uncommon.
  - Frequently normal levels of serum complement.
  - Abatement of clinical and laboratory features on discontinuation of the inciting agent.
- Unique auto-antibody associations as follows:
  - **Antihistone:** Seen in drug-induced lupus caused by procainamide, hydralazine, chlorpromazine, and quinidine.
  - **Anti-dsDNA:** Minocycline, statins, anti-TNF- $\alpha$ , and interferon.
  - **ANCA:** Minocycline and antithyroid drugs.
  - **Anti-Ro:** CCBs, thiazide, and ACEIs.

TABLE 16.7. 1997 Classification Criteria for SLE<sup>a</sup>

VARIABLE	CRITERIA	COMMENTS
<b>Skin/Sunlight</b>	1. Malar rash 2. Discoid rash 3. Photosensitivity	Malar rash is a butterfly-shaped rash across the cheek and bridge of the nose that spares the nasal folds, unlike rosacea
<b>Serosa/mucous membranes</b>	4. Oral ulcers 5. Serositis (pleuritis/pericarditis)	Painless oral ulcers compared to painful ulcers in Behçet disease
<b>Synovitis</b>	6. Arthritis	Usually polyarticular, Jaccoud arthropathy mimics RA with MCP involvement and ulnar deviation, yet unlike in RA, the deformities are reducible
<b>Seizures, "S"yphosis</b>	7. Neurologic disease	Seizure, stroke, depression, confusion, fatigue
"S"ellular casts, proteinuria	8. Renal disease (any one of the following): a. >0.5 g/day proteinuria b. ≥3+ dipstick protein c. Cellular casts	Usually nephritic, but can have nephrotic range proteinuria
"S"ytopenias	9. Hematologic disorders (any one of the following): a. Hemolytic anemia b. Leukopenia (<4000/mL) c. Lymphopenia (<1500/mL) d. Thrombocytopenia (<100,000/mL)	Often autoimmune destruction of cell lines; leukopenia, not leukocytosis, is usually seen with a flare
<b>Serologic tests</b>	10. + ANA 11. Immunologic abnormalities (any one of the following): a. Antibodies to native DNA b. Anti-Smith antibodies c. Antiphospholipid antibodies: (1) False + serologic test for syphilis (2) Evidence of anticardiolipin antibodies (3) Evidence of lupus anticoagulant	Only antibody titers to dsDNA can correlate with disease activity

<sup>a</sup>Four out of 11 yield high specificity in classifying a patient as having SLE.**KEY FACT**

The medications most commonly associated with drug-induced lupus are hydralazine, procainamide, INH, quinidine, methyldopa, anti-TNF agents, and chlorpromazine.

**KEY FACT**

In a patient taking hydralazine who has pericardial effusion, arthralgias, and + ANA and antihistone antibodies, suspect drug-induced lupus and stop the hydralazine.

**QUESTION 1**

A 25-year-old woman presents with 3 weeks of diffuse arthritis, ecchymosis, and a facial sunburn. Exam is notable for tender MCP, an erythematous facial rash sparing the nasolabial folds, painless oral ulcers, bibasilar crackles, and splenomegaly. Lab results show pancytopenia. What is the most likely diagnosis?

**QUESTION 2**

A 40-year-old woman with history of RA on methotrexate and infliximab presents with worsening diffuse arthritis, pleuritic chest pain, and a malar rash. Exam reveals hand synovitis and a pericardial rub. What is causing the patient's symptoms?

### PREGNANCY-RELATED LUPUS

- Disease should be controlled for 6 months prior to conception. Pregnancy and postpartum periods are associated with higher rates of SLE flares. Higher risk in patients with active disease 6 months prior to conception, history of lupus nephritis, and discontinuation of hydroxychloroquine.
- **Recommended preconception evaluation of women with SLE who wish to become pregnant should include:** Lupus anticoagulant, anticardiolipin, anti-β2-glycoprotein, anti-Ro, anti-La, dsDNA antibodies, complement level, renal function, CBC, and LFTs.
- **Management:**
  - Glucocorticoids: Use lowest possible dose. Associated with cleft lip when used in the first trimester.
  - Hydroxychloroquine: Continue during pregnancy. Has been shown to reduce the number of flares during pregnancy.
  - NSAIDs: Not strongly associated with congenital anomalies. Discontinue during third trimester to avoid premature closure of ductus arteriosus.
  - Azathioprine: Considered relatively safe during pregnancy. Do not exceed 2 mg/kg/day.
  - Cyclosporine and tacrolimus: Considered relatively safe during pregnancy.
  - Antihypertensives: Methyldopa, labetalol, nifedipine, and hydralazine are safe to use.
  - Contraindicated medications during pregnancy: Cyclophosphamide, mycophenolate, methotrexate, and leflunomide.
- **Complications:**
  - Preeclampsia: One of the most common complications in pregnant women with SLE.
  - Fetal loss: Slight ↑ in risk, especially with history of antiphospholipid syndrome.
  - Neonatal lupus:
    - A photosensitive rash, **complete heart block**, hepatitis, thrombocytopenia, and hemolytic anemia.
    - Passive transfer of maternal **anti-Ro/SSA and anti-La/SSB antibodies** in utero associated with permanent complete heart block.
    - Most features remit when titers of antibodies wane in the neonate.

### KEY FACT

Neonatal lupus is classically associated with maternal anti-Ro/SSA and anti-La/SSB antibodies and may cause complete heart block, which is irreversible.

A

### ANSWER 1

SLE. She meets 4 of the 11 criteria: photosensitive rash that spares the nasolabial folds, arthritis, oral ulcers, and pancytopenia. The next appropriate test would be ANA.

### KEY FACT

Patients with Sjögren syndrome are have a >40-fold ↑ risk of developing lymphoma—be on the lookout for new lymphadenopathy as a potential clue to lymphoma.

A

### ANSWER 2

Drug-induced SLE, most likely from the anti-TNF agent infliximab, which should be discontinued. About 20% of RA patients treated with anti-TNF agents become ANA +, and drug-induced lupus may develop. Corticosteroid therapy may be needed to treat the arthritis, pericarditis, and rash.

## Sjögren Syndrome

### Symptoms/Exam

Clinical characteristics of Sjögren syndrome: Xerostomia, keratoconjunctivitis sicca, parotid gland enlargement, lacrimal gland enlargement, and mucosal dryness.

- Look for these associations:
  - Interstitial lung disease (ILD).
  - Type 1 RTA.
  - **Lymphoma (44-fold ↑ risk of non-Hodgkin lymphoma).**
  - MALT lymphoma.
- Other autoimmune disease: RA, SLE, autoimmune thyroiditis.
- Waldenström macroglobulinemia.

### Diagnosis

- **Lab results:** ANA, RF, and anti-SSA/anti-SSB antibodies are frequently + (see Table 16.6); hypergammaglobulinemia.
- **Biopsy** of lip/salivary gland remains the gold standard for diagnosis.
- **Other:** Ancillary testing can demonstrate ↓ tear production and low salivary flow.

## Management

Seek symptom relief with the following:

- Ocular sicca: Artificial tears, **topical cyclosporine**, punctal plugs.
- Oral sicca: Artificial saliva, sugar-free candies, pilocarpine, **cevimeline**.
- Associated rash or arthritis: NSAIDs, hydroxychloroquine, or low-dose steroid.
- Organ involvement: Methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, or high-dose steroid.

## Seronegative Spondyloarthritis

Seronegative spondyloarthritis encompasses four disorders: Ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and IBD-associated arthritis (Table 16.8).

### ANKYLOSING SPONDYLITIS

A systemic inflammatory disorder in which sacroiliac damage can occur 6 to 12 months after disease onset. Extra-articular manifestations include aortitis with aortic insufficiency, upper lobe pulmonary fibrocystic disease, 2° amyloidosis, cardiac conduction disease, and recurrent uveitis. Predominance of **males over females**; characterized by an early age of onset (generally <35 years). Prevalence is 0.2% to 0.5% among Caucasians in the United States (has a higher prevalence among Scandinavians).

#### Symptoms/Exam

- Morning inflammatory low back pain or stiffness that **worsens with inactivity but improves with exercise**.
- Progressive limitation of spinal mobility.
- ↓ lumbar lordosis; ↓ chest expansion diameter.
- Limited range of motion of the neck.
- Enthesitis: Tenderness to palpation over site where tendon inserts into bone (Figure 16.10).

**TABLE 16.8. Features of Seronegative Spondyloarthritis**

DISEASE	JOINT INVOLVEMENT	% WITH $\oplus$ HLA-B27	OTHER MANIFESTATIONS
Ankylosing spondylitis	SI joints and spine are most common; hips, shoulders less common	90%	Uveitis, <b>aortitis</b> , restrictive lung disease
Psoriatic arthritis	Mainly peripheral; often asymmetric and polyarticular; $\pm$ SI joints	75%	Skin disease in 80% of cases; enthesitis; dactylitis; <b>DIP arthritis is common</b>
Reactive arthritis	Mainly peripheral, asymmetric large joint oligoarthritis (knee, shoulder, ankle); usually self-limited but can become chronic	80% of Caucasians, 50%-60% of African Americans	The classic triad is <b>conjunctivitis, urethritis, and arthritis</b> (more commonly of larger peripheral joints than of the spine); keratoderma blennorrhagicum (a pustular rash on the soles of the feet); uveitis
IBD-associated arthritis	Mainly peripheral joints (spine and SI less common)	50% (when sacroiliitis is present)	GI disease is usually present; <b>more commonly Crohn</b> disease than ulcerative colitis



### QUESTION

A 50-year-old woman presents with a 20-lb weight loss, night sweats, and dental caries. Exam reveals dry eyes, dry mucous membranes, enlarged parotid glands, and splenomegaly. Lab results:  $\oplus$  ANA,  $\oplus$  Anti-Ro, and increased gamma globulin on serum protein electrophoresis. What diagnostic study should be done next?



### KEY FACT

The four seronegative spondyloarthritis diseases are grouped because:

**"Seronegative" = serologies  $\ominus$  for ANA, CCP, and RF.**

"Spondyo-" = spinal arthritis.



### KEY FACT

Apical pulmonary fibrosis in ankylosing spondylitis can look like TB.

A

## ANSWER

CT of the chest and abdomen to look for non-Hodgkin lymphoma and other associated lymphoproliferative conditions. 1° Sjögren syndrome occurs in women 40 to 60 years of age. Patients often have  $\oplus$  antibodies, including ANA and RF, along with hypergammaglobulinemia.



**FIGURE 16.11. Ankylosing spondylitis.** Radiograph of the lumbar spine showing long-standing ankylosing spondylitis resulting in fusion of the SI joints, squared vertebral bodies and thin syndesmophytes bridging the entire spine referred to as “bamboo spine,” and ossification of the interspinous/supraspinous ligaments, which is known as the “dagger sign.” (Source: Wikipedia/Stevenfruitsmaak.)



## KEY FACT

Patients with psoriatic arthritis may have an elevated uric acid level due to rapid skin cell turnover. Don’t be tricked into thinking gout if the clinical picture fits psoriatic arthritis better!



**FIGURE 16.10. Enthesitis.** Lateral foot radiograph in a patient with sacroiliitis and heel pain, most commonly due to ankylosing spondylitis or reactive arthritis. Note the prominent calcaneal spur representing enthesopathic change (abnormalities at bony insertion points of tendons, in this case the plantar fascia tendon) (arrow). (Reproduced with permission from Chen MY, et al. *Basic Radiology*. New York: McGraw-Hill, 2004, Fig. 7-44.)

## Diagnosis

- Diagnosed in the setting of a consistent history and imaging.
- **Imaging:** Start with a plain radiography SI joint to look for evidence of sacroiliitis and/or spinal involvement (Figure 16.11).
- Bilateral sclerosis of the SI joints can be seen.
- Squared-off, bamboo like syndesmophytes, and “shiny corners” of vertebral bodies.
- **Labs:** Positive HLA-B27 is supportive but **not diagnostic**. ↑ ESR and ⊖ RF.

## Management

- First line: NSAIDs to reduce SI and spine inflammation, plus exercise and physical therapy to preserve mobility.
- Second line: TNF- $\alpha$  inhibitors.
- Peripheral arthritis: Sulfasalazine, hydroxychloroquine, or methotrexate.

## Complications

All of the following are classic associations:

- Anterior uveitis—most common extra-articular manifestation.
- Aortitis and aortic regurgitation (more rarely, cardiac conduction system involvement).
- Apical pulmonary fibrosis (mimics TB—be careful!).

## PSORIATIC ARTHRITIS

Peripheral arthritis, dactylitis, and enthesitis (inflammation of the tendinous insertions to bones; seen with other HLA-B27-related diseases as well) are characteristic of psoriatic arthritis. Found in 10% to 20% of patients with psoriatic skin disease. Skin disease precedes arthritis in 80% of cases.

- **Symptoms/Exam:** The clinical presentation of psoriatic arthritis is outlined in Table 16.9.
- **Diagnosis:** Table 16.10 lists the key clinical features of the Classification Criteria for Psoriatic Arthritis (CASPAR).

TABLE 16.9. Five Major Patterns in Psoriatic Arthritis

PATTERN	JOINT INVOLVEMENT
DIP involvement	Can be monoarticular or asymmetric (Figure 16.12); nail pitting (Figure 16.13) and onycholysis
Pseudorheumatoid	Symmetric, smaller-joint polyarthritis
Oligoarticular	Marginal erosive arthritis, dactylitis ("sausage digit")
Arthritis mutilans	Severe, osteolytic, deforming (telescoping digits, which appear as "pencil in cup" deformities on x-ray)
Spondylitis	Usually asymmetric sacroiliitis and/or ankylosing spondylitis

- **Management:** Pharmacologic treatments are the same as ankylosing spondylitis. Avoid corticosteroids if possible (tapering can cause skin disease to flare).

### REACTIVE ARTHRITIS

- Men (particularly young men) are affected more often than women. Eighty percent of Caucasian and 50% to 60% of African American patients are HLA-B27  $\oplus$ . May be idiopathic or may develop within days to weeks of antecedent infection:
  - GI disease: *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*.
  - GU disease (urethritis): *Chlamydia* and *Ureaplasma*.
- **Symptoms/Exam:**
  - Typically presents with asymmetric involvement of larger, weight-bearing joints of the lower extremities that occurs 2 to 6 weeks after an infection.
  - Approximately 50% of patients have upper extremity joint involvement.
  - May see conjunctivitis, uveitis, urethritis, cervicitis, enthesitis, dactylitis, asymmetrical sacroiliitis, and keratoderma blennorrhagicum (pustular eruptions on the palms and soles; see Figure 16.14).
- **Diagnosis:** Inflammatory pattern is seen on arthrocentesis, and cultures of joint fluid are sterile. Test urine for chlamydia to rule out persistent infection.

**A****B**

**FIGURE 16.12. Psoriatic arthritis, DIP predominant.** (A) AP radiograph of the hands shows periarticular erosions involving the PIP and DIP joints with sparing of the carpal and carpometacarpal joints and absence of periarticular osteopenia. (B) Magnified, cropped view of the interphalangeal joints of the right hand better demonstrates the joint space narrowing and marginal erosions that predominate in the DIP joints but also affect the PIP joints. (Reproduced with permission from USMLE-Rx.com.)

TABLE 16.10. CASPAR Criteria

- Inflammatory articular disease with joint, spine, and/or enthesal involvement
- Plus ≥3 of the following findings:
  - Psoriasis
  - Psoriatic nail dystrophy
  - Dactylitis (sausage digits)
  - Negative RF
  - Radiographic evidence of juxta-articular new bone formation

### KEY FACT

Before initiating TNF inhibitors, screen for TB (PPD placement or IGRA) and viral hepatitis; if PPD or IGRA are positive, treat for latent TB.

### KEY FACT

Psoriasis precedes most cases (80%) of psoriatic arthritis. The severity of skin disease does not correlate with severity of arthritis.



### QUESTION

A 30-year-old man presents with worsening lower back pain and buttock pain when seated. Exam reveals uveitis, tenderness of the SI joint and lumbar spine, and a 2/6 diastolic murmur. His ESR is 100 mm/hr and a pelvic x-ray shows SI joint erosion. What is the most likely diagnosis?



**FIGURE 16.13. Psoriasis of the nails.** Pitting describes punctate depressions. The brownish

to salmon discolorations of the nails of the fourth and fifth digits represent “oil stains.”

(Reproduced with permission from Wolff K, Johnson RA. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill, 2009, Fig. 3e-PS-50.)

#### KEY FACT

Antibiotics are not effective for reactive arthritis except in cases of persistent infection.

#### ■ Management:

- Resolves spontaneously in over 50% of patients within 6 months, but may need NSAIDs or intrarticular steroid injection for symptomatic relief. In a minority of patients, reactive arthritis progresses to chronic or recurrent arthritis.
  - Sulfasalazine, methotrexate, and other DMARDs for recalcitrant peripheral arthritis.
- **Complications:** Aortitis and aortic regurgitation (rare).



#### A

#### ANSWER

Ankylosing spondylitis.

**FIGURE 16.14. Keratoderma blennorrhagicum in reactive arthritis.** Hyperkeratotic scaled erythematous plaques of the hand of a 33-year-old man with eye irritation, joint pain, and a recent history of diarrhea. (Reproduced with permission from USMLE-Rx.com.)

## INFLAMMATORY BOWEL DISEASE-ASSOCIATED ARTHRITIS

Twenty percent of patients with IBD have associated arthritis. Associated more often with Crohn disease than with ulcerative colitis. Arthritis usually appears after the onset of GI disease.

- **Symptoms/Exam:**

- Peripheral arthritis, enthesitis, and dactylitis:
  - Type I (oligoarticular): Asymmetric, nonerosive, lower extremity, large joint arthritis.
  - Type II (polyarticular): Asymmetric, nonerosive, small upper extremity arthritis.
- Spinal arthritis: Asymmetric inflammatory sacroiliitis and spondylitis.
- **Management:** Treatments for IBD will also help the arthritis:
  - First-line: Methotrexate and sulfasalazine to treat both arthritis and IBD.
  - Second-line: TNF- $\alpha$  inhibitors (except etanercept).

### KEY FACT

In IBD-associated arthritis, NSAIDs have limited use due to risk of IBD flare.

## Diffuse Idiopathic Skeletal Hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is a variant of osteoarthritis (OA) that results in the noninflammatory bony remodeling of the spine. It is distinguished from 1° OA of the spine by flowing anterolateral osteophytes of the vertebrae with preservation of the disk space. DISH can also be associated with peripheral enthesitis and tendinitis. Prevalence ↑ with age, but it is more common in men than women.

- **Symptoms/Exam:** Tendinitis or enthesitis, bone spurs (heel spurs), thoracic spine tenderness.
- **Diagnosis:** Plain radiography of the spine shows the following:
  - Preservation of the intervertebral disk space.
  - Flowing calcification or osteophytes bridges along four or more continuous vertebrae (thoracic spine most common).
  - Absence of sacroiliitis.
- **Management:** Same as for OA: acetaminophen, NSAIDs, intra-articular glucocorticoid injection.

### KEY FACT

Asymptomatic hyperuricemia usually does not need to be treated. In most patients with hyperuricemia, gout does not develop.

## Crystalline-Induced Arthropathies

Include gout and calcium pyrophosphate dihydrate deposition (CPPD) disease.

### HYPERURICEMIA

The causes of hyperuricemia and its relation to gout are delineated in Table 16.11.

### GOOT

Usually associated with abnormal uric acid metabolism and hyperuricemia; can be associated with uric acid stones and urate nephropathy (renal toxicity). Men are affected more often than women (9:1). Onset is generally after age 30 years; almost always postmenopausal in women.



### QUESTION 1

A 55-year-old man with a 3-year history of psoriatic arthritis has worsening functional capacity and new areas of joint inflammation with extensive cutaneous psoriasis. He has been on oral methotrexate 20 mg weekly after an unsuccessful trial of naproxen. Exam reveals swelling, erythema, and tenderness over the PIPs and DIPs of both hands as well as the wrists; dactylitis of the toes; and bilateral knee effusions. The patient also has lower lumbar and SI tenderness, limited ROM of the torso, and difficulty in turning his head. What is the next best treatment?



### QUESTION 2

An 18-year-old boy with history of gastroenteritis presents with uveitis and knee and ankle swelling. Exam reveals effusion of the right knee and tenderness of the Achilles tendon. Lab results are notable for  $\ominus$  hepatitis serology,  $\ominus$  RF, and ESR of 70 mm/hr. What is the most likely diagnosis?

**TABLE 16.11. Causes of Hyperuricemia**

**OVERPRODUCTION OF URIC ACID (<10%)**

Genetic metabolic defects:

- Lesch-Nyhan syndrome
- Glycogen storage diseases
- Psoriasis

Myeloproliferative disorders/large tumor burden malignancies/tumor lysis syndrome

Idiopathic

**UNDEREXCRETION OF URIC ACID (>90%)**

Idiopathic

CKD

Medication induced:

- Thiazide diuretics
- Loop diuretics
- Cyclosporine

Metabolic:

- Lactic acidosis
- Alcoholism
- Ketoacidosis

Lead nephropathy (saturnine gout)

**A**

**ANSWER 1**

Add anti-TNF agent. This patient has severe, active, destructive psoriatic arthritis that is unresponsive to full-dose methotrexate and NSAIDs. Anti-TNF therapy produces excellent clinical responses for the spinal inflammation of psoriatic arthritis and ankylosing spondylitis.

**KEY FACT**

Gout and hyperuricemia are strongly associated with metabolic syndrome, hypertension, thiazide diuretic use, alcohol abuse, and CKD.

**A**

**ANSWER 2**

Reactive arthritis, which is characterized by large joint oligoarthritis ( $\leq 4$  joints), enthesitis involving tendon insertion sites, and extra-articular manifestations, including uveitis. It is triggered by infections in the intestines, the urogenital tract, and, less commonly, the throat or respiratory tract.

**Symptoms**

- **Acute gouty arthritis:** Sudden-onset, self-limited, and recurrent monoarticular or oligoarticular arthritis. Most common location is first MTP (podagra), other common locations include midfoot, ankle, heel, and knee.
- **Intercritical gout:** Asymptomatic period that can last for years between gout attacks.
- **Chronic recurrent and tophaceous gout:** Recurrent attacks that can result in tophi formation in joints, bone, tendon, cartilage, and subcutaneous tissues.

**Exam**

- Inflammatory monoarticular or oligoarticular arthritis, often hot, red, and exquisitely tender to touch.
- Look for the presence of **tophi** on the external ears, elbows, hands, and feet (Figure 16.15).
- Fever is common but rarely exceeds  $39^{\circ}\text{C}$  ( $102.2^{\circ}\text{F}$ ).

**Diagnosis**

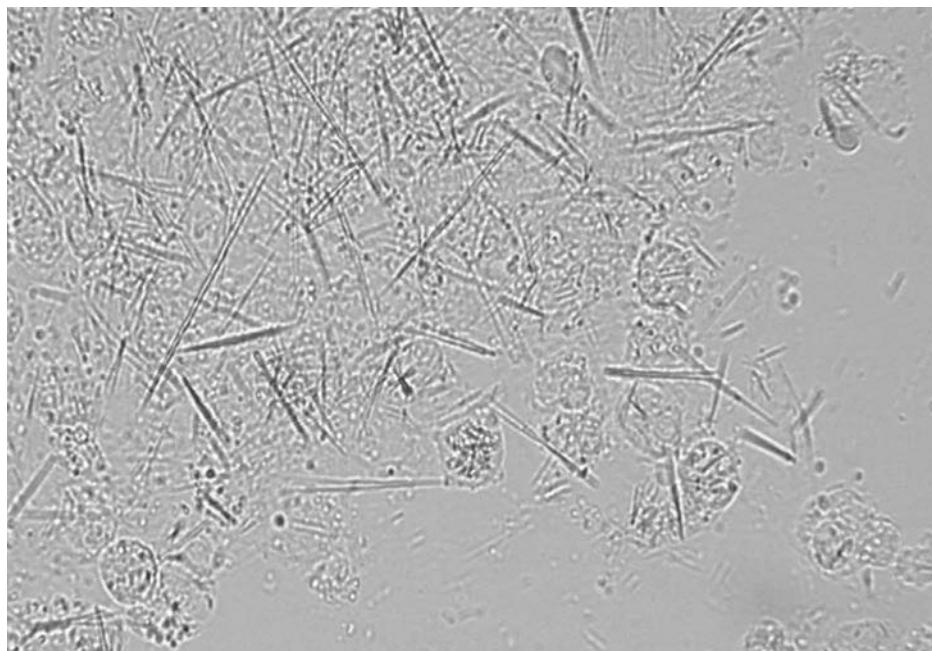
- Hyperuricemia is supportive, but **not diagnostic**. May have low or normal uric acid level during acute flare.
- Synovial fluid aspiration is the gold standard and reveals the following:
  - A sterile, inflammatory, neutrophil predominant pattern.
  - Negatively birefringent, needle-like crystals (think **yELLow = paraLLel**; Figure 16.16). Radiographs of chronic tophi show “rat-bite” erosions adjacent to affected joints (Figure 16.17).

**Management**

Guidelines for the treatment of gout are outlined in Table 16.12.



**FIGURE 16.15. Tophaceous gout.** (A) Affected hand, the right great toe and finger interphalangeal joints are shown. Note the asymmetrical swelling and yellow-white discoloration. (B) AP radiograph showing the severe consequences of long-standing gout, including large, nonmarginal erosions with overhanging edges of bone (red arrows), soft tissue swelling, and destruction of the first MTP joint (arrowhead). Note the subtle calcification of a gouty tophus (orange arrow). (Images reproduced with permission from USMLE-Rx.com.)



**FIGURE 16.16.** Gout crystals.

**TABLE 16.12. Treatment of Gout**

DRUG	USAGE
<b>Acute attack:</b>	
NSAIDs (naproxen, COX-2 inhibitor)	Use until symptoms resolve (1-2 weeks); avoid in CKD and PUD
Colchicine	Use within 48 hours of onset of attack (1.2 mg followed by 0.6 mg 1 hour later); avoid in CKD
Corticosteroids	Oral steroids in NSAID-intolerant patients; intra-articular injections for monoarticular disease
<b>In between attacks:</b>	
Nothing	Many patients experience few if any future attacks and choose to discontinue uric acid therapy
Diet	Low purine; low fructose, high dairy, alcohol avoidance
Medication management	Discontinue precipitating medications (eg, thiazides, low-dose salicylates, niacin)
Colchicine prophylaxis	Give 0.6 mg QD BID to prevent future attacks and continue 3-6 months after urate levels return to normal; give 0.6 mg/day $\times$ 1-2 weeks while initiating uric acid-lowering therapies
<b>Urate Lowering Prophylaxis Therapy</b>	
Allopurinol	Best for uric acid overproducers, tophaceous gout, and urate nephropathy
Febuxostat	Use if the patient cannot tolerate allopurinol or has CKD, causes less hypersensitivity reactions
Probenecid	Best for uric acid underexcreters (promotes uricosuria)
Pegloticase	Uricase analog, given IV, reserved for severe tophaceous gout not controlled with xanthine oxidase inhibitors



**FIGURE 16.17.** Osteolysis of the fifth digit and PIP, MCP, and carpal erosions due to tophaceous gout.

#### KEY FACT

Initiate urate lowering therapy (eg, allopurinol or febuxostat) in patients with two or more attacks annually or one attack in patients with CKD, visible tophi, and history of urolithiasis. Goal is to achieve serum urate level of <6 mg/dL (or <5 mg/dL if tophi are present).

#### KEY FACT

Synovial fluid with leukocyte count  $>50,000/\mu\text{L}$  and monosodium urate crystal raise suspicion for a concurrent bacterial infection with gout.

#### MNEMONIC

Switch from thiazides to **LO**sartan to **LO**wer serum urate in patient with gout and hypertension.

#### KEY FACT

Use a COX-2 inhibitor in patient with a gout attack and  $\uparrow$  risk of GI bleed.

#### QUESTION

A 60-year-old man with hypertension and gout has had three episodes of left knee pain in the past year. He is on HCTZ and lisinopril. Lab results: normal CBC, uric acid of 10.4 mg/dL, and arthrocentesis with urate crystals. In addition to low-dose colchicine, what is the next appropriate step?

**KEY FACT**

When starting urate-lowering therapy (eg, allopurinol or febuxostat), prescribe it concurrently with prophylactic low-dose NSAIDs, low dose prednisone, or colchicine for the first 3 to 6 months to prevent the precipitation of acute gout attacks.

**KEY FACT**

Suspect CPPD in a patient who has very severe OA or OA in atypical locations. CPPD may be part of an underlying metabolic disorder:

- Hemochromatosis
- Hypophosphatemia
- Hypomagnesemia
- Hyperparathyroidism
- Hypothyroidism
- Diabetes



**FIGURE 16.18. Chondrocalcinosis of menisci (left side of image at joint).**

(Source: Wikidoc.org.)

**A****ANSWER**

Given the frequent, severe attacks of gout and hyperuricemia, it would be reasonable to start allopurinol with a target uric acid level of  $\leq 6$  mg/dL, checking levels every 3 to 4 weeks after a change in dose. Low-dose colchicine prophylaxis may be discontinued if tophi resolve, uric acid levels stabilize, and the patient has no gout attacks for 6 months.

**Complications**

Complications associated with treatment are as follows:

- **Allopurinol:** Initiation of allopurinol can provoke acute gout attack if it is not used concomitantly with prophylactic NSAIDs, colchicine, or corticosteroid for 6 months. Hypersensitivity syndrome may also be seen ( $\uparrow$  in renal disease). Severe cutaneous drug reactions are more common in patients who are HLA-B\*5801 positive. Allopurinol  $\uparrow$  the effect and toxicity of azathioprine by blocking its metabolism.
- **Probenecid:** Precipitates urate nephropathy and nephrolithiasis if used in tophaceous gout or in patients with a history of urate calculi.
- **Pegloticase:** Risk of serious hypersensitivity reaction.

**CALCIUM PYROPHOSPHATE DEPOSITION DISEASE**

Arthritis associated with calcium pyrophosphate deposition disease (CPPD), also known as pseudogout, may be hereditary or associated with metabolic disease, or it may be due to aging. Four percent of the adult population are found to have articular CPPD deposits at the time of death, and by the ninth decade nearly half of the population have been found to have chondrocalcinosis.

**Symptoms/Exam**

CPPD can be mono- or oligoarticular and can affect the fibrocartilage of the knee, symphysis pubis, glenoid and acetabular labra, and wrist as well as the elbow and MCP (ie, atypical distribution of OA). There are four patterns of CPPD disease outlined in Table 16.13.

**Differential**

Be aware of the separate but unrelated condition **basic calcium phosphate deposition**. Basic calcium phosphate crystals (including hydroxyapatite) can cause cartilage calcification and arthropathy. A classic manifestation is the **Milwaukee shoulder syndrome**—painful, swollen glenohumeral joint and rotator cuff, often very destructive, usually seen in women  $>70$  years.

**Diagnosis**

- Serum urate level is normal.
- **Chondrocalcinosis** is visualized on radiographs of the knees and wrists (Figure 16.18).
- Synovial fluid aspiration reveals the following:
  - Inflammatory fluid profile in acute attacks.
  - Weakly positively birefringent **rhomboid-shaped crystals** (the opposite of urate; Figure 16.19).

**TABLE 16.13. Types of CPPD**

TYPES	CLINICAL PRESENTATION
Cartilage calcification (chondrocalcinosis)	Asymptomatic with linear calcification of cartilage on x-ray
Acute CPP crystal arthritis (pseudogout)	Inflammatory arthritis of the knee, wrist, shoulder (Podagra uncommon)
Chronic CPP crystal arthritis (pseudo-RA)	Joint involvement resembles RA distribution, but negative RF and anti-CCP
OA with CPPD (pseudo-OA)	Knee arthritis most common with accelerated OA in non-weight-bearing joints (MCP, wrist, shoulder joints)

## Management

- There are no drugs that ↓ CPPD crystal formation (except treatment of the underlying metabolic etiology, if there is one).
- Acute CPPD crystal arthritis: NSAIDs, colchicine and intra-articular corticosteroid injection (similar to treatment of acute gout attack).
- Chronic CPPD crystal arthritis: Same as acute. Can also consider systemic steroids, methotrexate, or hydroxychloroquine for severe disease.
- Prophylaxis: Initiate when ≥3 attacks. Start with low-dose colchicine or NSAIDs. There is no role for urate-lowering medications such as allopurinol in CPPD.

## Inflammatory Myopathies

Presumed immune-mediated diseases of skeletal muscles. Major types of inflammatory myopathies are **polymyositis**, **dermatomyositis**, and **inclusion body myositis**, each of which has distinctive patterns of muscle weakness, associated symptoms, and muscle pathology. May be confused with polymyalgia rheumatica. Table 16.14 outlines the clinical characteristics of various inflammatory myopathies.

### POLYMYOSITIS

Targets the proximal musculature, typically in women 40 to 60 years of age. Associated with ↑ rates of malignancy.

#### Symptoms/Exam

- Progressive symmetrical, painless proximal muscle weakness** involving the deltoids, arm/hip flexors, and neck flexors.
- May have dysphagia or ILD-induced shortness of breath.



### QUESTION

A 68-year-old man with hyperparathyroidism presents with worsening left knee pain and swelling of 1 week's duration; he reports having similar episodes intermittently for the past 4 years. Between attacks, he experiences knee stiffness and discomfort. Exam reveals synovitis, suprapatellar joint effusion, and tenderness of the left knee. An x-ray of the knee shows linear deposits of calcium in the articular space and marked joint space narrowing. What is the most likely diagnosis?



**FIGURE 16.19. Pseudogout.**

Positively birefringent calcium pyrophosphate dihydrate crystals from a joint aspirate. (Source: Wikimedia; courtesy of David Iberri.)

**TABLE 16.14. Characteristics of Inflammatory Myopathies and Polymyalgia Rheumatica**

	POLYMYOSITIS	DERMATOMYOSITIS	INCLUSION BODY MYOSITIS	POLYMYALGIA RHEUMATICA
Age at onset	30-50	40-60	>60	>50
Gender	Women >> men	Women >> men	<b>Men &gt;&gt; women</b>	Women > men
Key features	Proximal muscle weakness <b>without skin findings</b>	Proximal muscle weakness <b>and skin findings:</b> Gottron papules, heliotrope rash, "mechanic hands"	Insidious onset with prominent wasting of the <b>finger and forearm flexors and quadriceps</b>	Proximal shoulder and pelvic muscle <b>pain without weakness</b>
CK	Elevated	Elevated	<b>Normal</b>	<b>Normal</b>
EMG	Myopathic	Myopathic	<b>Myoneuropathic</b>	<b>Normal</b>
Biopsy	CD8 lymphocytes, Microinfarction	CD4 lymphocytes, myofibril necrosis	<b>Rimmed vacuoles, eosinophils and basophilic inclusions</b>	<b>Normal</b>
Response to steroids	Good	Good	<b>Poor</b>	<b>Excellent</b>
Comments	Biopsy distinguishes polymyositis from dermatomyositis	Strongest association with <b>underlying malignancy</b>	Most patients lose the ability to walk within 10 years of diagnosis	Look for signs of giant cell arteritis

## A

## ANSWER

CPPD as demonstrated by chondrocalcinosis of the fibrocartilage of the knee, joint space narrowing, and the episodic nature of the attacks. Arthrocentesis would show calcium pyrophosphate crystals.



## MNEMONIC

Remember the pentad: Hair, Chair, Stair, Air, and Beer. Classically, patients will have difficulty combing their hair, rising from a chair, climbing stairs, getting air (ILD), and drinking a beer (dysphagia).



## KEY FACT

Elevated AST and ALT may be due to myositis and should not be confused for liver disease.

## Diagnosis

- Elevated muscle enzymes (CK, aldolase, LDH).
- Myositis specific auto-antibodies (eg, anti-Jo-1, anti-SRP, and anti-Mi-2) are found in 60% of patients with immune-mediated myopathy.
- MRI shows muscle edema, fibrosis, myositis, and calcification. (MRI is particularly useful to identify best site for muscle biopsy.)
- EMG is nonspecific and shows abnormal polyphasic potentials, fibrillations, and high-frequency action potentials.
- **Gold standard is a muscle biopsy** that shows CD8 lymphocytic infiltrate with myofibril necrosis.
- Be prepared to recognize the **antisynthetase syndrome**—a subtype of dermatomyositis and polymyositis associated with poorer prognosis and characterized by ILD, Raynaud phenomenon, arthritis, and **anti-Jo-1 antibodies**.

## Management

- High-dose corticosteroids until muscle enzymes normalize.
- DMARDs (methotrexate, azathioprine, mycophenolate mofetil) for steroid-sparing or recalcitrant disease.

## Complications

- **Malignancy:** Not as high a risk as it is for dermatomyositis.
- **Other:** Myocarditis, respiratory muscle failure, swallowing difficulties and aspiration.

## DERMATOMYOSITIS

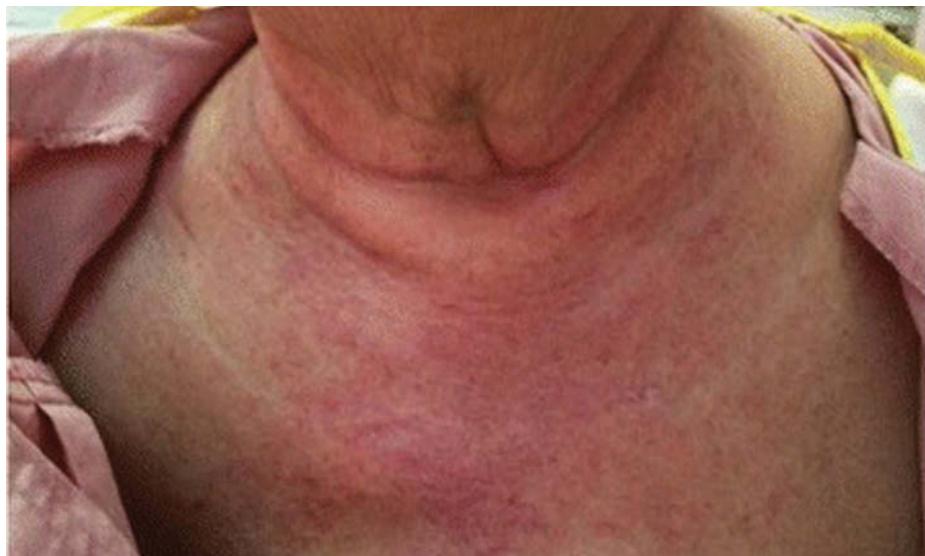
Often associated with **occult malignancy**. Amyopathic dermatomyositis is a variant with a characteristic skin disease but no clinically apparent muscle involvement.

## Symptoms/Exam

- Symptoms similar to those of polymyositis.
- Additional features are as follows:
  - **Gottron papules:** A scaly rash over the extensor surfaces of the MCP and IP joints (Figure 16.20).
  - **Shawl sign:** Erythema in a sun-exposed V-neck or shoulder distribution (Figure 16.21).



**FIGURE 16.20. Gottron papules, nail fold telangiectasias, and dystrophic cuticles in dermatomyositis.** (Reproduced with permission from USMLE-Rx.com; courtesy of Dr. Christopher Crosby.)



**FIGURE 16.21. Shawl sign in dermatomyositis.** (Source: Ng YRY, et al. Paraneoplastic cerebellar degeneration and dermatomyositis as first manifestations of underlying breast malignancy: a report of two cases and a brief review of the subject. *Surg Case Rep*. 2015;1:59.)

- **Heliotrope rash:** A violaceous rash over the eyelids, sometimes with periorbital edema (Figure 16.22).
- **Facial erythema:** A diffuse, dusky rash that involves the nasolabial folds.
- **Mechanic hands:** Dystrophic cuticles of the hands.
- **Holster sign:** A violaceous rash over the lateral thighs.
- **Other:** Periungual erythema and dilated periungual capillaries.

### Diagnosis

- Similar to polymyositis.
- Muscle biopsy shows perivascular and perifascicular CD4 lymphocytic infiltrate with microinfarction.

### Management

- Similar to that of polymyositis.
- IVIG for severe/refractory cases, especially with dysphagia.
- Age-appropriate and symptom-directed cancer screening. Consider screening women for ovarian cancer with pelvic ultrasound and/or CA-125 level.
- Treat underlying malignancy (if present).

### INCLUSION BODY MYOSITIS

- Characterized by **distal** more than proximal muscle weakness; weakness is more often **asymmetric** than symmetric. Older Caucasian men are more frequently affected. More insidious in onset than polymyositis or dermatomyositis.
- **Diagnosis:** CK levels may be normal or ↑. Characteristic eosinophilic and basophilic inclusion bodies and rimmed vacuoles are seen on muscle biopsy.
- **Management:** “Treatment resistant” compared to other inflammatory myopathies (does not respond as well to steroids).

## Other Myopathies

### METABOLIC MYOPATHIES

Hyperthyroidism, hypothyroidism, and glucocorticoid excess, whether endogenous (eg, Cushing syndrome) or exogenous (eg, steroid treatment), may all produce myopathy.

### DRUG-INDUCED AND TOXIC MYOPATHIES

Many medications are associated with toxic myopathies, and the condition is usually reversible upon withdrawal of the offending toxin. Common offending medications include **statins**, **colchicine**, cimetidine, penicillamine, hydroxychloroquine, niacin, corticosteroids, and zidovudine (AZT). Other toxins associated with myopathy include alcohol and heroin.

## Systemic Sclerosis (Scleroderma)

The clinical characteristics of systemic sclerosis are outlined below and in Table 16.15. Generally, skin involvement proximal to elbows or knees indicates progressive (or “diffuse”) systemic sclerosis. Face can be involved in either limited or diffuse disease.

- **Management:** There is no disease-modifying treatment for scleroderma. Therapy for scleroderma involves systematic management of end-organ involvement.



**FIGURE 16.22. Heliotrope rash of dermatomyositis.** (Source: Dhoble A, et al.

Dermatomyositis and supraventricular tachycardia. *Int Arch Med.* 2008;1:25.)

### KEY FACT

The risk of malignancy is ↑ in **dermatomyositis**, and to a lesser extent in polymyositis and inclusion body myositis—suspect malignancy in any patient not responding to treatment. Patients require aggressive screening for malignancy, including the consideration of pelvic imaging and CA-125 in women.

### KEY FACT

Inclusion body myositis involves asymmetric weakness of distal more than proximal muscles and is seen more often in men than in women.

### KEY FACT

Hypothyroid myopathy is characterized by muscle pain, cramps, stiffness, fatigue, paresthesias, and a delay in the relaxation phase of the muscle stretch reflex. CK levels may be 10 to 100 times normal. Check TSH before EMG or muscle biopsy.



### QUESTION

A 55-year-old woman presents with 4 months of generalized weakness, especially when she climbs stairs or reaches for things overhead. She also has myalgias and dyspnea on exertion. She takes prednisone for severe asthma. Exam reveals proximal muscle and neck flexor weakness. CK level is 5000 U/L. Needle EMG shows diffuse spontaneous fibrillations, repetitive discharges, and positive sharp waves. What is the most likely diagnosis?

**FIGURE 16.23. Raynaud**

**phenomenon.** This condition can cause pain, numbness, and a characteristic discoloration in the affected extremities. Initially, there is a reduction of blood flow that results in pallor or white skin. When oxygen is depleted, the skin becomes cyanotic or blue. In the final stage, there is reperfusion and the skin turns rubor or red. (Source: Wikimedia/Jamclaassen.)

**TABLE 16.15. Characteristics of Systemic Sclerosis**

DISEASE TYPE	FREQUENCY OF CASES	ORGANS INVOLVED	ANTIBODIES
Limited scleroderma	80%	CREST, <b>pulmonary hypertension</b>	ANA, <b>anticentromere</b> , anti-Th/To
Progressive systemic sclerosis	20%	Proximal skin, kidney, heart, <b>lung (ILD)</b> , GI tract	ANA, <b>anti-SCL-70</b> , anti-RNA polymerase III, anti-U3-RNP

- **Complications:** Lung disease is the most common cause of morbidity and mortality in systemic sclerosis. Pulmonary hypertension and ILD can occur independently or together.

### LIMITED SCLERODERMA

- **Symptoms/Exam:** Characterized primarily by CREST syndrome: Calcinosis, Raynaud phenomenon (Figure 16.23), Esophageal dysmotility, Sclerodactyly (sclerodermatous skin changes confined to the upper extremity distal to the wrist; Figure 16.24), and Telangiectasias. Lung disease tends to be **pulmonary hypertension**.
- **Management:** Treatment is outlined in Table 16.16.
- **Complications:** The prognosis is generally more favorable than that of diffuse scleroderma, but later-onset pulmonary hypertension and other vasculopathic processes affect mortality.

### PROGRESSIVE (DIFFUSE) SYSTEMIC SCLEROSIS

- **Symptoms/Exam:** Presents with skin involvement that includes areas **proximal to the wrists** (Figure 16.25), the arms, chest, abdomen, neck, and face (Figure 16.26). Other features outlined in Table 16.17.
- **Management:** Treatment is outlined in Table 16.18.

A

### ANSWER

Polymyositis with characteristic findings; respiratory symptoms may be related to an associated ILD. Steroid myopathy would have normal CK levels and a normal EMG but similar weakness.



**FIGURE 16.24. Sclerodactyly.** The hands and fingers are edematous (nonpitting); the skin is without skin folds and taut. The distal fingers are tapered (“madonna fingers”). (Reproduced with permission from Wolff K, Johnson RA. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill, 2009, Fig. 14-28.)

**TABLE 16.16. Symptomatic Treatment of Limited Scleroderma**

DISORDER	TREATMENT
Raynaud phenomenon	Body-warming techniques, CCBs
Digital ulcerations	Raynaud therapies as above; ASA, sildenafil, topical nitrates, prostacyclin analogs
Esophageal dysmotility	Elevate the head of the bed and avoid late-night meals; H <sub>2</sub> blockers or PPIs
Pulmonary hypertension	O <sub>2</sub> , CCBs, sildenafil, prostacyclin analogs, endothelin receptor antagonists



**FIGURE 16.25. Scleroderma acrosclerosis.** “Rat-bite” necrosis and ulceration of fingertips.  
(Reproduced with permission from USMLE-Rx.com.)

- Complications:** Patients with a long history of Raynaud phenomenon and diffuse or limited cutaneous scleroderma are at risk for pulmonary vascular disease (accentuated pulmonic component of S2, JVD, tricuspid regurgitation). Pulmonary artery catheterization is indicated to diagnose PAH and to assess responsiveness to vasodilator therapy.

**TABLE 16.17. Features of Scleroderma**

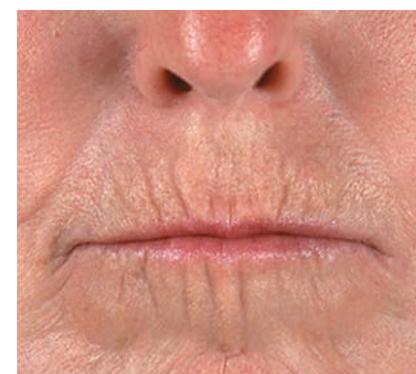
ORGANS	MANIFESTATIONS
Skin	Skin thickening, swollen hands, limited oral aperture, <b>hand pruritus</b>
Musculoskeletal	Arthralgia, myalgia, <b>tendon friction rub</b>
Vascular	<b>Raynaud phenomenon, dilated nailfold capillaries, digital ulcerations</b>
Gastrointestinal	<b>GERD, Barrett esophagus, dysphagia, gastric antral vascular ectasia, pseudo-obstruction, blind loop syndrome</b>
Renal	<b>Scleroderma renal crisis</b>
Pulmonary	Aspiration, COPD, <b>ILD</b>
Cardiac	Cardiac fibrosis, pulmonary hypertension

**QUESTION 1**

A 30-year-old woman with dermatomyositis diagnosed 2 years ago presents with 6 months of progressive lower extremity muscle weakness. She takes prednisone 20 mg/day. On exam, she has proximal thigh and hip muscle weakness but no rashes. CK level 150 U/L. What is the most likely cause of her recurrent weakness?

**QUESTION 2**

A 60-year-old woman with a 15-year history of limited cutaneous systemic sclerosis presents with abdominal pain and diarrhea for a week preceded by a week of constipation and fecal incontinence. She takes nifedipine for Raynaud phenomenon and omeprazole, and reports no recent antibiotic use, travel, or contact with anyone having similar symptoms. On exam, she is mildly orthostatic and has hyperactive bowel sounds, distention, and diffuse abdominal tenderness but no rebound or guarding. CBC, chemistry, and upright AXRs are normal. What is the most appropriate next step?



**FIGURE 16.26. Facial features in scleroderma.** Note the thinning of the lips, or microstomia (which is more evident when patients attempt to open the mouth), along with radial perioral furrowing. Also note the sharp, beaklike nose. (Reproduced with permission from Wolff K, Johnson RA. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill, 2009, Fig.14-29B.)

**A****ANSWER 1**

Corticosteroid-induced myopathy, particularly in the lower extremities, after a ↓ in or normalization of muscle enzyme levels. Muscle wasting and upper extremity involvement may be seen, but there is usually no tenderness.

**A****ANSWER 2**

Oral ciprofloxacin (7-10 days) for small bowel bacterial growth from GI dysmotility. In scleroderma, smooth muscle disease may lead to chronic intestinal pseudo-obstruction of the small bowel. Coverage for gram-negative rods and anaerobes is indicated. Opioid antidiarrheal therapy may worsen intestinal motility disorders.

**TABLE 16.18. Symptomatic Treatment of Diffuse Scleroderma**

ORGAN	COMPLICATIONS	TREATMENT
Kidney	Renal crisis (malignant hypertension, renal failure, and microangiopathic hemolytic anemia)	ACEIs
Lung	Interstitial pneumonitis, interstitial fibrosis	Corticosteroids, <sup>a</sup> cytotoxic (eg, cyclophosphamide) and immunosuppressant therapies
Heart	Myocarditis, myocardial fibrosis, heart failure, pericardial effusions, conduction system disease	Corticosteroids, <sup>a</sup> immunosuppressants, CHF therapy, pacemakers
GI	Delayed gastric emptying, intestinal malabsorption, bacterial overgrowth	Frequent small meals, promotility agents, antibiotics

<sup>a</sup>Corticosteroids are usually avoided in scleroderma (unless severe organ-related disease leaves little other choice) because they may precipitate a renal crisis.

## Vasculitis

### APPROACH TO VASCULITIS

Table 16.19 categorizes vasculitis by vessel size. Etiologies include:

- **Infections:** Particularly indolent, chronic infections such as subacute bacterial endocarditis and HCV.
- **Medications:** Hypersensitivity vasculitis, leukocytoclastic vasculitis, ANCA-associated vasculitis.
- **Other:** Collagen vascular disease, malignancy.

### 1° VASCULITIS SYNDROMES

#### Granulomatosis With Polyangiitis (Wegener Granulomatosis)

A necrotizing **granulomatous** arteritis of small- to medium-sized arteries, arterioles, and capillaries. Granulomatosis with polyangiitis (GPA), also known as Wegener granulomatosis, is characterized by cavitating **nodules of the upper and lower respiratory tract (lungs and sinuses)** and by **glomerulonephritis**. Organs and systems affected include the upper and lower respiratory tract, kidney, eye, ear, nerves, skin, gingiva, and joints.

#### Symptoms/Exam

- Upper respiratory tract: Sinusitis (Figure 16.27), epistaxis, otitis media, gingivitis, stridor, mastoiditis, saddle nose.
- Lungs: Cough, hemoptysis, diffuse alveolar hemorrhage, dyspnea, tracheal stenosis.
- Kidneys: Rapidly progressive crescentic glomerulonephritis (RPGN), hematuria.
- Other: Arthritis, scleritis, skin rashes.

TABLE 16.19. Classification of Vasculitis

VESSEL SIZE			
	SMALL	MEDIUM	LARGE
Disorders	Microscopic polyangiitis Henoch-Schonlein purpura Cutaneous leukocytoclastic angiitis Behçet syndrome Hypersensitivity Cryoglobulinemia Associated with connective tissue disease (SLE, RA) Drug-induced Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) Granulomatosis with polyangiitis (GPA)	Polyarteritis nodosa (PAN) Behçet syndrome	Takayasu arteritis Giant cell arteritis/temporal arteritis Behçet syndrome
Skin	Palpable purpura, digital infarcts	Nodules, ulcers, gangrene, livedo reticularis	Mimics severe atherosclerosis, gangrene
Kidney	Rapidly progressive crescentic glomerulonephritis	HTN, aneurysms	HTN
Cardiovascular	CHF, pericarditis	MI	MI
GI	Pain, nausea/vomiting, GI bleeding	Pain, nausea/vomiting, GI bleeding, infarction, aneurysms	Intestinal angina (pain out of proportion to exam), infarction
Testes	–	Pain (classic for PAN)	–
Peripheral nervous system	Sensory polyneuropathy	Sensory/motor neuropathy; mononeuritis multiplex	–
CNS	Meningitis	TIA	Stroke
Systemic symptoms (fever, weight loss)	++	++++	++++

## Diagnosis

- **Labs:**
  - ↑ ESR; normal serum complement levels.
  - ⊕ c-ANCA (anti-proteinase 3) more than p-ANCA (anti-myeloperoxidase [MPO]).
  - Biopsy shows vasculitis and necrotizing granuloma (characteristic of GPA only).
- **Imaging:** CXR and chest CT show pulmonary nodules or cavities (see Figure 16.27).
- UA with active sediment.

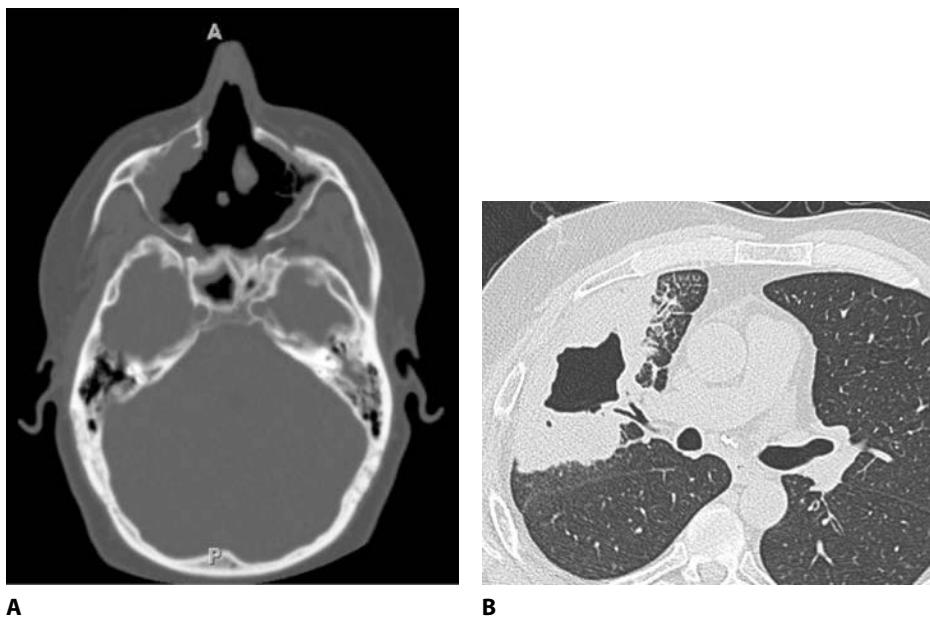
## Management

- **Induction:** Cyclophosphamide, corticosteroids, and/or rituximab.
- **Remission:** Methotrexate, azathioprine.
- Rapid diagnosis and treatment of GPA is critical, as RPGN can quickly lead to irreversible kidney failure, and diffuse alveolar hemorrhage can develop suddenly and be life threatening.



### KEY FACT

Hemorrhagic cystitis is a possible complication of oral cyclophosphamide therapy, presenting with hematuria without erythrocyte casts or protein on UA. Patients also have an ↑ risk of transitional cell carcinoma of the bladder even years after treatment has been discontinued. For this reason, lifelong screening for bladder cancer with cystoscopy is indicated.



**FIGURE 16.27. Granulomatosis with polyangiitis.** (A) Unenhanced CT scan of the paranasal sinuses shows moderate mucoperiosteal thickening throughout with destruction of the adjacent bony structures in a patient with GPA and severe chronic sinusitis. (B) Chest CT scan shows a large cavitary lesion in the right upper lobe. (Reproduced with permission from USMLE-Rx.com.)

### KEY FACT

The triad of asthma, eosinophilia, and a  $\oplus$  **p-ANCA** strongly suggests EGPA. If there is no eosinophilia, the diagnosis is probably not EGPA.

### Eosinophilic Granulomatosis With Polyangiitis (Churg Strauss Syndrome)

A small- and medium-vessel necrotizing vasculitis that presents as eosinophilic pneumonia and corticosteroid-dependent asthma. Neuropathic, cardiac, renal, and GI symptoms can also occur. Men are affected more often than women.

#### Symptoms/Exam

- **Asthma**, nasal polyps, allergic rhinitis.
- Mono- and peripheral neuropathy (**mononeuritis multiplex**).
- Fever, rash, myalgias, arthralgias, weight loss.
- **Cough, dyspnea**, angina pectoris (due to myocarditis or coronary artery involvement).
- Glomerulonephritis is less common than in other ANCA-associated diseases.

#### Diagnosis

- **Labs:** Peripheral eosinophilia; normal serum complement levels;  $\oplus$  **p-ANCA** (anti-MPO), although not specific for the disease.
- **Imaging:** CXR shows fleeting pulmonary infiltrates.
- Biopsy of affected tissue demonstrates extravascular eosinophils.

#### Management

- High-dose corticosteroids.
- Immunosuppressants for renal or nerve/CNS involvement or for steroid-unresponsive disease.

### Microscopic Polyangiitis

A medium- or, more commonly, small-vessel nongranulomatous vasculitis and capillaritis characterized by pulmonary hemorrhage and by glomerulonephritis and renal failure. Organs and systems affected include the lung, kidney, nerve, and skin. Often confused with polyarteritis nodosa (PAN). See Table 16.20.

**TABLE 16.20. Polyarteritis Nodosa Versus Microscopic Polyangiitis**

	POLYARTERITIS NODOSA	MICROSCOPIC POLYANGIITIS
Vessel size	Medium	Medium and small
Skin	Ulcer/nodule/livedo reticularis	Palpable purpura
Lung	<b>Rare</b>	Capillaritis/alveolar hemorrhage
Renal	Renal artery aneurysms/renal infarction	Glomerulonephritis

■ **Symptoms/Exam:**

- Fever, malaise, myalgias, arthralgias, weight loss.
- Hemoptysis, dyspnea.
- Hematuria/active sediment.
- Mono-/polyneuropathy; skin rashes (palpable purpura).

■ **Diagnosis:**

- **Labs:** ↑ ESR, normal serum complement levels,  $\oplus$  p-ANCA (anti-MPO).
- Tissue biopsy demonstrates alveolar hemorrhage/necrotizing capillaritis/ glomerulonephritis.

■ **Management:** Corticosteroids; cytotoxic agents.

 **KEY FACT**

Microscopic polyangiitis, "MPA," typically involves the lung and kidney with less involvement of the upper respiratory tract. Remember **MPA** is positive for **MPO** antibodies.

### Polyarteritis Nodosa

A necrotizing arteritis of small and medium-sized vessels. Active infection with **HBV** predisposes to the development of PAN (prevalent in 5%-10% of patients). Organs affected include the kidney, nerves, GI/mesentery, brain, skin, heart, testes, and joints. Often confused with microscopic polyangiitis (see Table 16.20).

■ **Symptoms/Exam:**

- Fever, malaise, weight loss, hypertension, **testicular pain, abdominal pain after eating**.
- Arthralgias, myalgias.
- Look for **mononeuropathies**: Foot or wrist drop.
- **Skin rash** (livedo reticularis, nodules, ulcerations).

■ **Diagnosis:**

- **Labs:** ↑ ESR or CRP; majority of cases are ANCA  $\ominus$ ; normal serum complement levels;  $\oplus$  HBV serology.
- **Imaging:** Angiography shows aneurysmal dilations of affected arteries (commonly renal and mesenteric).
- Site-directed biopsy.

■ **Management:**

- High-dose corticosteroids.
- Cytotoxic immunosuppressive agents (eg, cyclophosphamide).
- Plasma exchange and antiviral therapy for patients with HBV infection.

 **KEY FACT**

In a patient with newly diagnosed PAN, check for evidence of hepatitis B infection, which is associated with PAN.

### Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR) is associated with proximal/axial skeletal pain and stiffness; fever, malaise, and weight loss; and an ↑ ESR. Very rare before age 50 years; usually affects **older women**. Associated with giant cell (temporal) arteritis.

■ **Symptoms/Exam:**

- Joints affected include the shoulders, hip girdles, and low back and, less commonly, the peripheral joints.
- **No muscular weakness is seen** (this is different from polymyositis).
- Fever, malaise, and weight loss can be profound.

 **QUESTION**

A 30-year-old man presents with 2 months of epistaxis, intermittent night sweats, cough, and a 10-pound weight loss without any recent travel. Exam reveals a large perforation of the nasal septum. UA reveals 3+ protein, erythrocytes, and erythrocyte casts, and a CT of the chest shows bilateral cavitary nodules. What is the most likely diagnosis?

**KEY FACT**

CK is normal in PMR, and there is no weakness. Remember that poly**myalgia** is not poly**myositis**.

**KEY FACT**

Up to 20% of PMR patients have giant cell arteritis, and up to 60% of giant cell patients have PMR.

**KEY FACT**

Patients with PMR experience rapid and dramatic improvement when prednisone is initiated (often >90% improvement after the first few doses). However, prednisone must be tapered very gradually in PMR (often over the course of 1-3 years) to reduce risk of recurrence/flares.

**KEY FACT**

Failure to consider GCA as a cause of new fever, headache, or vision loss in the elderly can result in permanent vision loss if high-dose steroids are delayed. If you suspect GCA, start steroids immediately then get a bilateral temporal artery biopsy within 2 weeks.

**KEY FACT**

Takayasu arteritis is also known as "pulseless disease" because the arteries it involves—the aorta and its branches—can narrow, resulting in ↓ radial and femoral pulses and BP.

**ANSWER**

Granulomatosis with polyangiitis.

- **Diagnosis:** See Table 16.14. ↑ ESR (>40 mm/hr). Normal muscle enzymes.
- **Management:** Small to moderate doses of corticosteroids (prednisone 5-20 mg/day), tapered very gradually, often over the course of 1 to 3 years.

**Giant Cell Arteritis**

Granulomatous arteritis of large and medium-sized vessels of the extracranial branches of the carotid artery. The most common vasculitis in North America and Europe; affects patients >50 years of age. Blindness results from involvement of posterior ciliary arteries/ischemic optic neuritis. Has a strong association with PMR.

**Symptoms/Exam:**

- Head: Severe headache, scalp tenderness or ulceration, temporal artery tenderness.
- Neck: Jaw claudication, tongue tenderness.
- Vision: Diplopia, amaurosis fugax, ptosis.
- Constitutional symptoms: Fever, malaise, and weight loss.

**Diagnosis:**

- Age >50 years.
- ↑ ESR (>50 mm/hr).
- Typical clinical features (especially new headache and/or tender, nodular, or pulseless temporal artery).
- Characteristic angiographic findings.
- Characteristic temporal artery biopsy showing mononuclear cell infiltration with occasional giant cells.

**Management:** High-dose corticosteroids (prednisone 40-60 mg/day) usually for 1 to 2 years, titrated based on symptoms and ESR.**Complications:** Vision loss, aortic aneurysm.**Takayasu Arteritis**

A pulseless aortitis and vasculitis of the large vessels/branches of the aorta. Most prevalent in East Asia; women <40 years of age are most commonly affected.

**Symptoms/Exam**

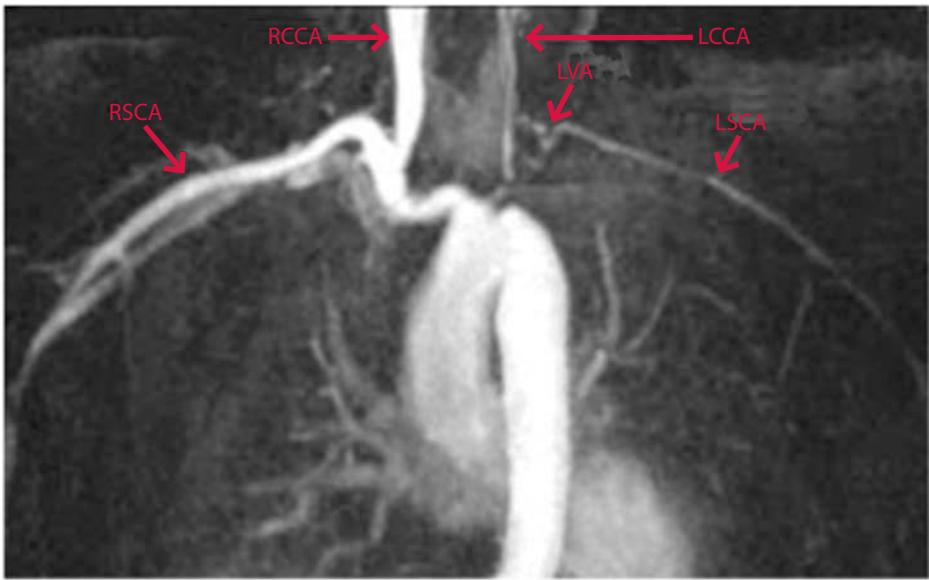
- Fever, malaise, myalgias, arthralgias, weight loss, progressive claudication.
- Evidence of limb and/or organ ischemia.
- Hypertension, bruits, and abnormal pulses; **systolic BP discrepancies measured between limbs**; aortic valvular regurgitation murmur.

**Diagnosis**

- ↑ ESR is common but not universal.
- CXR may suggest aortic abnormalities.
- Does not require biopsy—diagnosed via angiography of the aorta/branches showing stenoses and aneurysms (Figure 16.28).
- Biopsy (if performed) reveals granulomatous arteritis ± variable numbers of giant cells.

**Management**

- High-dose corticosteroids, methotrexate, TNF-inhibitors.
- Aggressive BP control.
- Surgical bypass of ischemic vessels once systemic disease is controlled.



**FIGURE 16.28. Takayasu arteritis.** Coronal MIP image from an MRA shows normal appearance of the right subclavian and common carotid arteries (RSCA, RCCA) but severe diffuse narrowing of the left common carotid artery (LCCA) and occlusion of the origin of the left subclavian artery (LSCA), which is diffusely narrowed distally but fills via retrograde flow from the left vertebral artery (LVA) (“subclavian steal”). (Reproduced with permission from USMLE-Rx.com.)

### OTHER VASCULITIDES

#### Cryoglobulinemia

- Cryoglobulinemia and associated small vessel vasculitis are characterized by Raynaud phenomenon, a palpable purpuric rash, abnormal LFTs, arthritis, neuropathy, glomerulonephritis, cryoglobulins, and a C4 level that is ↓ to a greater extent than the C3 level. All cryoglobulins are immune complexes that precipitate at ≤4°C. Cryoglobulinemias are divided into three types (Table 16.21).
- Management:** Treat the underlying cause.

#### Buerger Disease (Thromboangiitis Obliterans)

- Thromboses of medium-sized arteries and veins, usually of the hands or feet. Most commonly affects men who smoke heavily.
- Management:** Treat by discontinuing smoking.

**TABLE 16.21. Classification of Cryoglobulinemias**

TYPES	ANTIBODIES	UNDERLYING CONDITIONS
I	Monoclonal IgM	Hematological malignancy (eg, multiple myeloma and Waldenström macroglobulinemia)
II	Monoclonal IgM against polyclonal immune targets	Chronic infection (eg, HIV and HCV, which is the most common cause of cryoglobulinemia in the United States)
III	Polyclonal IgM/IgG against polyclonal immune targets	Autoimmune disease (eg, SLE, RA, Sjögren syndrome)



#### QUESTION 1

A 60-year-old woman presents with 2 weeks of progressive dyspnea and a productive cough with blood-streaked sputum. She has no history of asthma and was born in the United States. On exam, she is hypertensive and has bilateral crackles at the lung bases, 1+ edema of the extremities, and a palpable petechial rash. Lab results: CBC with no eosinophils, Cr 4 mg/dL, C3 100 mg/dL, and C4 30 mg/dL; numerous dysmorphic erythrocytes and erythrocyte casts are found on UA. CXR shows bilateral pulmonary infiltrates. What is the most likely diagnosis?



#### QUESTION 2

A 60-year-old woman presents with 6 months of inability to fully raise her left foot along with painful paresthesias on the dorsum of that foot and in her right hand. She has also had fevers, night sweats, arthralgias without joint swelling or stiffness, myalgias, and a 20-pound weight loss. Exam reveals fever 38.8°C (102°F), BP of 175/96 mm Hg, and livedo reticularis on the lower extremities. Lab results: ESR 110 mm/hr, Hg 11g/dL, Cr 1.9 mg/dL, AST 90 U/L, ALT 80 U/L, + hepatitis B surface antigen and core antibody but - surface antibody, normal UA. What is the most likely diagnosis?



#### QUESTION 3

A 62-year-old woman presents with 6 months of fatigue, malaise, and significant shoulder and hip pain, especially in the morning. She cannot do her usual daily exercise and is unable to sleep at night because of pain. On exam, she has full ROM of shoulders and hips, albeit with discomfort, along with tenderness at the deltoid and trochanteric areas. ESR is 70 mm/hr and CK 100 U/L; CBC and LFTs are normal. What is the most likely diagnosis?

**A****ANSWER 1**

Microscopic polyangiitis causing a pulmonary-renal syndrome, with alveolar bleeding from capillaritis—75% of patients have a  $\oplus$  ANCA (usually MPO $\oplus$ ). Complement levels would be abnormal in cryoglobulinemia or lupus. Classic polyarteritis nodosa typically spares the lungs.

**KEY FACT**

Behçet's is a clinical diagnosis with no specific blood test.

**A****ANSWER 2**

PAN presents with mononeuritis multiplex in up to 60% of affected patients and frequently involves the renal arteries, GI tract, and skin as well. Patients with PAN often have a  $\oplus$  hepatitis B surface antigen.

**KEY FACT**

Three rheumatic diseases associated with oral ulcers are Behçet's, SLE, and reactive arthritis.

**A****ANSWER 3**

Polymyalgia rheumatica, which is characterized by pain and stiffness in the axial joints and proximal muscles, usually with normal muscle strength and lack of swelling/warmth/erythema. Patients typically have an  $\uparrow$  ESR and a normal CK and are almost always  $>50$  years of age.

**KEY FACT**

The differential diagnosis for saddle-nose deformity is granulomatous with polyangiitis (Wegener granulomatosis) relapsing polychondritis, congenital syphilis, cocaine abuse, and leprosy.

**Behçet Disease**

A multisystem inflammatory disease characterized by recurrent aphthous oral ulcers and at least two or more of the following: recurrent painful genital ulceration, eye or cutaneous lesions, or  $\oplus$  findings on pathergy testing. Rare vasculitis prevalent in patients of Turkey and Middle Eastern ancestry.

■ **Symptoms/Exam:** Look for the following clinical features:

- Recurrent oral and genital ulcerations.
- Skin: Ulcerations, pathergy (worsening of ulcerations with provocation), erythema nodosum.
- Ocular disease: Uveitis, keratitis, hypopyon, retinal vasculitis, blindness.
- CNS abnormalities: Cerebral vasculitis, meningoencephalitis, myelitis, cranial neuropathies.
- Other: Vasculitis of any size vessel, pulmonary artery aneurysms, thrombosis (DVT, PE, dural venous sinuses).
- Features associated with the greatest morbidity or mortality include CNS disease, ocular disease, vascular thrombosis, arterial aneurysms, and GI disease (ulcers in the terminal ileum, cecum, and ascending colon).

■ **Management:** Treat with corticosteroids, colchicine, dapsone, or thalidomide for aphthous and mucocutaneous disease, and/or immunosuppressants such as azathioprine in severe ocular or CNS disease.

**Relapsing Polychondritis**

Relapsing polychondritis is a systemic inflammatory connective tissue disease characterized by inflammation and destruction of cartilaginous structures. May be idiopathic or due to another autoimmune, collagen vascular, or malignant disease.

■ **Symptoms/Exam:**

- Inflammatory episodes involving the cartilage of the ears (Figure 16.29), nose, larynx, and trachea.
- Noncartilaginous involvement includes fever, polyarthritides, scleritis, uveitis, middle/inner ear inflammation, hearing loss, and vasculitis.

■ **Management:** Treat with corticosteroids, dapsone, colchicine, and immunosuppressants (for refractory disease).



**FIGURE 16.29. Relapsing polychondritis.** Swelling and erythema of the cartilaginous part of the ear, sparing the lobule, which lacks cartilage. (Source: Sosada B, et al. Relapsing polychondritis. *Case Rep Dermatol Med*. 2014;2014:791951.)

- Complications:** Include chronic deformities of the ear (cauliflower ear), nasal septum collapse (**saddle nose**), laryngotracheal chondritis and stenoses, hearing loss, vertigo, tinnitus, and valvular heart disease.

## Infectious Arthritis

### NONGONOCOCCAL ARTHRITIS

Acute-onset, **monoarticular** joint pain, swelling, warmth, and erythema is characteristic of nongonococcal arthritis. The knee is the most commonly involved joint (affecting 50% of cases). Gram-positive species (*S aureus*, *Streptococcus*) are common causative organisms. Gram-negative species (*E coli*, *Pseudomonas*) are less commonly involved. Risk factors are listed in Table 16.22.

- Symptoms/Exam:** Fevers, chills, inability to bear weight, severe pain with active or passive joint motion, hot, red, and swollen joint.
- Diagnosis:**
  - Blood cultures are  $\oplus$  in <50% of cases.
  - Arthrocentesis reveals leukocytosis (usually  $>50,000/\mu\text{L}$  with  $>90\%$  PMN predominance) and a  $\oplus$  synovial fluid culture in 70% to 90% of cases; Gram stain is  $\oplus$  in only 75% of cases (*S aureus*).
  - X-rays are nonspecific but may reveal demineralization, bony erosions, joint narrowing, and periosteal reactions.
- Management:**
  - IV antibiotics are started while awaiting culture results; often needed for up to 6 weeks.
  - Serial arthrocentesis if effusion reaccumulates; surgical drainage if the patient medical therapy or the disease involves inaccessible sites (eg, the hip).
- Complications:** Articular destruction; septicemia. The mortality rate for in-hospital septic arthritis is 7% to 15% despite antibiotic therapy.

### GONOCOCCAL ARTHRITIS (DISSEMINATED INFECTION)

Suspect gonococcal arthritis (disseminated infection) in a sexually active woman with asymmetric migratory arthralgias, oligoarthritis, and tenosynovitis, with or without skin lesions. Most common in patients <40 years of age; women are more frequently affected than men.

- Symptoms/Exam:** Two forms of disseminated gonococcal infections:
  - Arthritis-dermatitis syndrome:** **Dermatitis** consisting of papular, pustular, or vesicular lesions, which can be subtle with often only a few skin lesions (Figure 16.30); **tenosynovitis**, commonly on the dorsa of the hands or feet; and **nonpurulent migratory polyarthritis**.
  - Purulent arthritis** without skin lesions.
- Diagnosis:**
  - Arthrocentesis reveals leukocytosis (commonly  $>50,000/\mu\text{L}$ , but can be lower than  $<25,000/\mu\text{L}$ ); don't be reassured by a  $\ominus$  synovial fluid culture! Gram stain is  $\oplus$  only 10% of the time, and culture is  $\oplus$  <50% of the time.
  - Blood cultures, rectal and throat swab cultures, urethral cultures (70%-86% sensitive).
- Management:**
  - Give IV antibiotics (third-generation cephalosporin) until clinical improvement is seen, followed by the oral equivalent or a quinolone antibiotic for a 7- to 10-day total course.
  - Screening for chlamydia, HIV, and other STDs should be performed once gonorrhreal infection is established.

### KEY FACT

Suspect septic arthritis in all patients with otherwise unexplained acute inflammatory mono- or oligoarthritis. Remember that septic arthritis and gout can exist concurrently—even if you see crystals in the synovial fluid, it doesn't automatically eliminate the possibility of septic arthritis!

### KEY FACT

Prosthetic infections: Think *S epidermidis*.

### QUESTION 1

A 40-year-old female former IV drug user has had a lower leg rash for 4 months and a year of Raynaud's cold-induced acral cyanosis. On exam, she is hypertensive and has hepatomegaly, 1+ lower extremity edema, and a purpuric rash. Lab results: Hg 10 g/dL, Cr 1.5 mg/dL, C3 80 mg/dL, C4 10 mg/dL, AST 50 U/L, and ALT 80 U/L. UA shows 3+ hematuria, 1+ protein, and dysmorphic erythrocytes. What is the most likely cause of her renal disease?

### QUESTION 2

A 30-year-old woman presents with a week of headache and left eye pain along with a vaginal ulcer; she has also had intermittent oral ulcers for the past 2 years. She is monogamous, takes no medications, and has no fevers, neck stiffness, or joint pain. The left eye is inflamed with ciliary flush and hypopyon. Leukocyte count is 16,000/ $\mu\text{L}$ , head CT is normal, and LP shows a leukocyte count of 15/ $\mu\text{L}$  (100% lymphocytes) with a  $\ominus$  Gram stain. What is the most likely diagnosis?

### QUESTION 3

A 40-year-old woman presents with acute-onset shortness of breath and nasal pain. She has been treated for left ear cellulitis in the past year. On exam, she is in respiratory distress, has stridor localized to the trachea, and has a collapsed nasal bridge with early saddle-nose deformity. CBC, chemistry, UA, and a CXR are all normal. Laryngoscopy shows dynamic laryngeal collapse with inspiration but normal mucosa. What is the most likely diagnosis?

**TABLE 16.22. Risk Factors for Septic Arthritis (Nongonococcal)**

- Age >80 years
- Diabetes mellitus
- IV drug use
- Endocarditis
- Recent joint surgery
- Skin infection
- RA
- Joint prostheses

**A****ANSWER 1**

Cryoglobulinemic glomerulonephritis. Hepatitis C is highly associated with cryoglobulinemia and should be strongly suspected in this former IV drug user with an abnormal ALT. ESR may be ↑ and RF can be +.



**FIGURE 16.30. Disseminated gonorrhea skin lesions.** Lesions may be a clue to the etiology of migratory arthritis and tenosynovitis. (Reproduced with permission from USMLE-Rx.com.)

**A****ANSWER 2**

Behcet disease. This patient has two features associated with high morbidity: aseptic meningitis and anterior uveitis with hypopyon.

**TUBERCULOUS ARTHRITIS**

- Most common in children, immunosuppressed patients, and the elderly. Can occur shortly after 1° infection or as a reactivation phenomenon. Fewer than 50% of patients with tuberculous arthritis will have an abnormal CXR. Patients with spinal disease (Pott disease) rarely have extraspinal involvement.
- **Symptoms/Exam:**
  - Insidious onset, subacute or chronic monoarticular arthritis often of the hip or knee.
  - **Pott disease** presents as insidious vertebral osteomyelitis.
- **Diagnosis:**
  - Isolation of acid-fast bacilli from joint fluid or synovial biopsy.
  - PPD may be - especially in immunocompromised patients.
- **Management:** As for pulmonary TB, but a longer treatment course may be necessary.
- **Complications:** Joint destruction, invasion of adjacent soft tissues and bone, paraplegia (from Pott disease).

**A****ANSWER 3**

Relapsing polychondritis with a history of auricular inflammation, saddle-nose deformity, and collapse of the tracheal cartilage. The most common presenting feature is auricular chondritis.

**LYME ARTHRITIS**

**Early Lyme disease** (stages 1 and 2) may have migratory arthralgias and myalgias along with flulike symptoms and an erythema migrans rash. **Advanced Lyme disease** (stage 3) presents as an **acute monoarthritis of the knee**; oligo- or polyarthritis is less common.

- **Diagnosis:**
  - **Arthrocentesis:** PMN-predominant leukocytosis (average ~ 25,000/µL); cultures for *Borrelia burgdorferi* are typically -.
  - **American College of Physicians recommendations for diagnosis include** objective arthritis with both ELISA IgG and Western blot confirmatory test for

*B burgdorferi*. ELISA IgM not recommended because usually  $\ominus$  early in disease when arthritis present; a  $\oplus$  IgM more likely to be false-positive.

- **Management:** Treat advanced Lyme arthritis (stage 3) with doxycycline (4 weeks) or ceftriaxone (2-4 weeks).

## Fibromyalgia

### Diagnosis

Perform serologic tests to exclude potential mimickers of fibromyalgia: CBC, chemistry panel, TSH, ESR, CRP. The 2010 American College of Rheumatology diagnostic criteria for fibromyalgia requires that a patient have the following:

- **Widespread pain index (WPI)  $\geq 7$  and symptom severity (SS) scale score  $\geq 5$**  (or WPI 3-6 and SS scale score  $\geq 9$ ).
  - WPI (scores from 0 to 19): Quantifies areas of tenderness over the last week.
  - SS scale (scores from 0 to 12): Grades severity of fatigue, feeling “refreshed” after sleep, and cognitive symptoms. Each symptom has a score from 0 to 3.
- Symptoms persistent for at least 3 months.
- No other disorder to explain the pain.
  - For Board exam, be prepared to make a diagnosis of fibromyalgia based on clinical features and limited number of tests to exclude mimickers. Avoid testing for ANA, RF, anti-CCP, or muscle enzymes if patient fits classic picture of fibromyalgia.

### Management

- **Nonpharmacologic treatment:**
  - Education; cognitive behavioral therapy.
  - Treat sleep disturbances and depression if present.
  - **Aerobic exercise:** “Start low and go slow” with a focus on adherence to a life-long program.
  - **Complementary therapies:** Acupuncture, hypnotherapy, relaxation techniques (yoga, Tai Chi, and meditation), and osteopathic manipulation appear to have some efficacy.
- **Pharmacologic treatment:** Options include low-dose TCAs (eg, amitriptyline), SNRIs (eg, milnacipran), SSRIs (eg, fluoxetine), and pregabalin. **Opiates are not indicated.**

### Complications

The adverse impact of fibromyalgia on the patient, family, and society is high. More than 25% of patients receive some type of disability or other compensation payment.

## Miscellaneous Diseases

### ADULT-ONSET STILL DISEASE

- **Symptoms/Exam:** Adult-onset Still disease presents with daily high-spiking fevers, diaphoresis, chills, sore throat, an evanescent **salmon-colored rash** coincident with fevers, **erosive arthritis**, serositis, **lymphadenopathy**, and **splenomegaly**.
- **Diagnosis:**
  - Distinguishing laboratory findings include striking **leukocytosis** (often  $>15,000/\mu\text{L}$ ), seronegativity ( $\ominus$  ANA and RF), transaminitis,  $\uparrow$  LDH and  **ferritin levels  $>1000 \text{ ng/mL}$**  (exceeds 10,000 ng/mL in 30% of cases).
    - Requires five of the Yamaguchi diagnostic criteria (Table 16.23).
- **Management:** Tends to be self-limited. Patients often benefit from NSAIDs and corticosteroids. Methotrexate for refractory disease.

### KEY FACT

Recurrent bouts of disseminated gonococcal infection should prompt evaluation for complement deficiency (C5-C9).

### KEY FACT

Western blot confirmation of Lyme disease necessary to exclude cross-reactive antibodies from conditions such as SLE, RA, other rickettsial infections, or false-positive IgG.

### KEY FACT

The joint most commonly involved in Lyme arthritis (stage 3) is the knee; this stage occurs several months after the initial infection if the condition is left untreated.



### QUESTION 1

A 70-year-old woman has difficulty walking from severe right hip pain of 1 week's duration. Two weeks ago, she had extensive dental surgery. Hip x-rays show mild joint space narrowing. On exam, temperature is  $38.1^\circ\text{C}$  ( $100.6^\circ\text{F}$ ); ROM testing elicits right groin pain that limits mobility. Blood cultures are drawn. What is the next best diagnostic step?



### QUESTION 2

A 20-year-old sexually active woman with an acutely painful, swollen right wrist and left knee and migratory joint pains is given IV ceftriaxone while waiting for results of blood, pharyngeal, cervical, rectal, and left knee cultures. Gram stain is  $\ominus$ . Two days later she is only minimally improved and cultures are  $\ominus$ . What is the most appropriate next step?

**TABLE 16.23. Yamaguchi Criteria for Adult-Onset Still Disease Diagnosis**

**MAJOR CRITERIA  
(AT LEAST TWO OF FIVE REQUIRED)**

- Arthralgia >2 weeks
- Fever >39°C (102°F) lasting ≥ 1 week
- WBC >10,000/ $\mu$ L (>80% granulocytes)
- Nonpruritic, salmon-colored macular or maculopapular rash predominantly on trunk or proximal limb

**MINOR CRITERIA**

- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- $\ominus$  ANA or RF
- Abnormal LFTs

**KEY FACT**

Lung or lymph node biopsy is typically not required for diagnosis of sarcoidosis if the patient presents with classic Löfgren syndrome.

**KEY FACT**

Consider adult-onset Still disease in a young adult with fever of unknown origin and markedly ↑ serum ferritin (usually >1000 ng/mL) whose workup for infection, malignancy, and other autoimmune disease is  $\ominus$ .

A

**ANSWER 1**

Imaging-guided hip joint aspiration with ultrasound or fluoroscopy to rule out septic arthritis. This patient's dental surgery likely led to bacteremia, a common precursor to septic arthritis. Radiographic evidence is often delayed 7 to 10 days.

A

**ANSWER 2**

There is a high suspicion of disseminated gonococcal infection in this sexually active woman with asymmetric migratory arthralgias, oligoarthritis, and tenosynovitis in the wrist. The rash is not always present. Continue ceftriaxone, as a complete response to appropriate antibiotic therapy for disseminated gonorrhea may take up to 72 hours. Gonorrheal infection must be excluded by  $\ominus$  culture results and a lack of response to antibiotic therapy before a diagnosis of reactive arthritis is established.

**SARCOIDOSIS**

Arthritis associated with sarcoidosis is either acute or chronic. See the Pulmonary and Critical Care chapter for nonarticular manifestations of sarcoidosis.

- **Symptoms/Exam:** Acute sarcoid arthritis = Löfgren syndrome, which presents with **periarthritides** (most commonly of the ankle/knee), **erythema nodosum**, and **hilar adenopathy** on CXR.
- **Management:**
  - Resolution of acute disease occurs in 2 to 16 weeks with conservative therapies such as NSAIDs or colchicine.
  - **Chronic sarcoid arthritis** usually involves minimally inflamed joints with synovial swelling/granulomata. Treat with NSAIDs, corticosteroids, and immunosuppressants.

**FAMILIAL MEDITERRANEAN FEVER**

Pathology is due to mutation of the *MEFV* gene that upregulates the production of IL-1. Release of IL-1 from damaged cells or through neutrophils, mast cells, or macrophages causes symptoms. In up to 75% of patients, first episode occurs before age 10 years, and in about 90% by age 20 years. Often seen in those with Mediterranean ancestry (eg. Armenians, Turks, Greeks, Italians) and  $\oplus$  family history.

- **Symptoms/Exam:**
  - Recurrent fevers with accompanying abdomen, chest, or joint pain—arthritis may resemble septic arthritis.
  - Rash: Similar to that of erysipelas.
  - Serositis: Pleuritis, peritonitis, pericarditis, pleuritis.
  - Other possible findings: Uveitis, lymphadenopathy, splenomegaly.
- **Diagnosis:**
  - ↑ inflammatory markers: ESR, CRP, AA amyloidosis, fibrinogen,  $\beta$ -2 microglobulin.
  - *MEFV* gene:  $\oplus$  in 80% of patients.
- **Management:**
  - First line: Colchicine is very effective, with 70% response rate.
  - Second line: Etanercept, infliximab, anakinra, thalidomide.

## MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD) is comprised of symptoms from SLE, scleroderma, and polymyositis. Women are three times more likely to develop the disease compared to men with onset of symptoms between 15 and 25 years of age.

- **Symptoms/Exam:**
  - **Neurologic:** Hearing loss, trigeminal neuralgia.
  - **Cardiac:** Pericarditis, myocarditis, conduction blocks.
  - **Pulmonary:** ILD, pulmonary arterial hypertension, alveolar hemorrhage.
  - **Gastrointestinal:** Esophageal hypomotility.
  - **Renal:** Membranous nephropathy.
  - **Musculoskeletal:** Arthritis, myositis, sclerodactyly, swollen hands.
  - **Skin:** Raynaud phenomenon, acrosclerosis.
- **Diagnosis:** Suspect MCTD in patients with  $\oplus$ ANA,  $\oplus$ anti-RNP, and clinical features of at least two of the following: SLE, scleroderma, and inflammatory myositis.
- **Management:**
  - Steroid: Efficacious in patients with SLE features (eg, pleurisy, pericarditis) and myositis. Less efficacious in patients with scleroderma-dominant symptoms (Raynaud phenomenon). Avoid long-term use.
  - Steroid sparing: Hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide.
  - Limited role for TNF- $\alpha$  inhibitors.

## IGG4-RELATED DISEASE

Recently recognized syndrome characterized by IgG4-producing plasma cells infiltrating organs. Most patients are men >50 years of age. Can affect almost any organ. See Table 16.24 for clinical manifestations.

- **Diagnosis:**  $\uparrow$  IgG4 level in 70% of patients. Requires tissue biopsy, which reveals the following:
  - Dense lymphoplasmacytic infiltrate with CD4 T cells in germinal centers.
  - IgG4 plasma cells.
  - Storiform fibrosis (spokes on a wheel-appearing).
  - Obliterative phlebitis.

**TABLE 16.24. Clinical Manifestations of IgG4-Related Disorders**

ORGAN	CLINICAL MANIFESTATION
Salivary glands	Swelling of the submandibular and/or parotid glands
Lacrimal gland, orbits	Swelling of the lacrimal glands, orbital pseudotumors, proptosis
Thyroid	Riedel thyroiditis (fibrosis and woody enlargement)
Lymph nodes	Tender and nontender lymphadenopathy
Thorax	Ascending aortitis, aortic aneurysm/dissection, fibrosing mediastinitis
Abdomen/pelvis	Abdominal aortic aneurysm, retroperitoneal fibrosis
Lungs	Cough, dyspnea
Biliary tree	Sclerosing cholangitis
Pancreas	Autoimmune pancreatitis
Kidneys	Tubulointerstitial nephritis, mass-like lesions



### QUESTION 1

A 30-year-old woman presents with 2 years of diffuse myalgias and arthralgias, difficulty getting out of bed in the morning, difficulty concentrating, and chronic headaches that are not relieved by ibuprofen or acetaminophen. On exam, she has soft-tissue tenderness to palpation at multiple sites but no weakness or synovitis. CBC, ESR, LFTs, chemistries,  $B_{12}$  level, and TSH are normal; head CT is normal. What is the most appropriate next step in management?



### QUESTION 2

A 30-year-old man presents with 1 month of arthralgia, fevers, sore throat, and rash that occurs during fevers. On exam, he appears ill and is febrile; he has a pink macular rash on his extremities, cervical and axillary lymphadenopathy, splenomegaly, and synovitis of the wrists and knees. Lab results: Hg 10 mg/dL, leukocyte count 15,000/ $\mu$ L, AST 110 U/L, LDH 300 U/L, ferritin 4000 ng/mL, iron 90  $\mu$ g/dL, and TIBC 350  $\mu$ g/dL. What is the most likely diagnosis?



### QUESTION 3

A 25-year-old man presents with 1 week of right ankle pain and multiple painful, nonpruritic lumps on his shins. On exam, he has a temperature of 38.3°C (101°F), swollen and tender right ankle, and tender erythema nodosum of the lower extremities. CBC, chemistries, UA, and arthrocentesis are normal. What is the most appropriate next step?



**FIGURE 16.31. Cholesterol emboli.**

Typical appearance of blue toes due to multiple atheromatous emboli to the lower limbs in a patient with extensive atheromatous disease of the aorta.

(Reproduced with permission from Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill, 2008, Fig. 174-5A.)

A

#### ANSWER 1

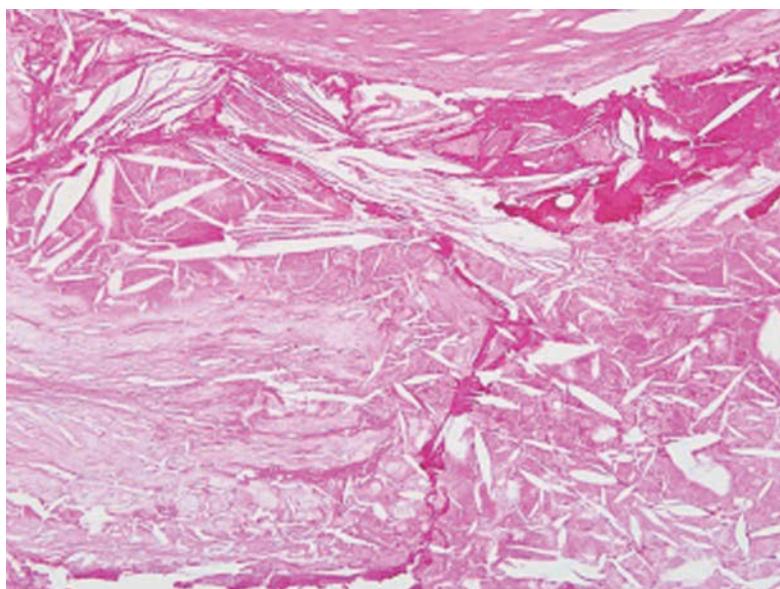
This clinical picture is consistent with fibromyalgia. Graded exercise therapy and cognitive behavioral therapy are the first-line nonpharmacologic options. Patients who do not respond to these measures may receive benefit from TCAs, SSRIs, and pregabalin. Narcotic analgesics are contraindicated.

#### Management:

- Initial treatment is corticosteroid.
- Second-line is cytotoxic agent (azathioprine, methotrexate, mycophenolate mofetil).
- Rituximab for severe refractory cases.

#### CHOLESTEROL EMBOLISM SYNDROME

Precipitated by invasive arterial procedures in patients with atherosclerotic disease. Features include fever, livedo reticularis, cyanosis/gangrene of the digits, vasculitic/ischemic ulcerations, eosinophilia, renal failure, and other end-organ damage (Figures 16.31 and 16.32).



**FIGURE 16.32. Needle-shaped cholesterol clefts**, shown here within an atherosclerotic plaque, may also be seen in skin or kidney biopsy specimens in patients with cholesterol embolism syndrome. (Reproduced with permission from USMLE-Rx.com.)

A

#### ANSWER 2

Adult-onset Still disease. This patient's arthralgia, daily fever, sore throat, rash, leukocytosis, ↑ ferritin and LDH levels, lymphadenopathy, and splenomegaly in the absence of infection or other rheumatic disease are all characteristic of this inflammatory disorder.

A

#### ANSWER 3

Order a CXR to evaluate for hilar lymphadenopathy of Löfgren syndrome, a variant of sarcoidosis characterized by acute erythema nodosum, hilar adenopathy, arthritis or periarthritis, and fever.

## CHAPTER 17

# Women's Health

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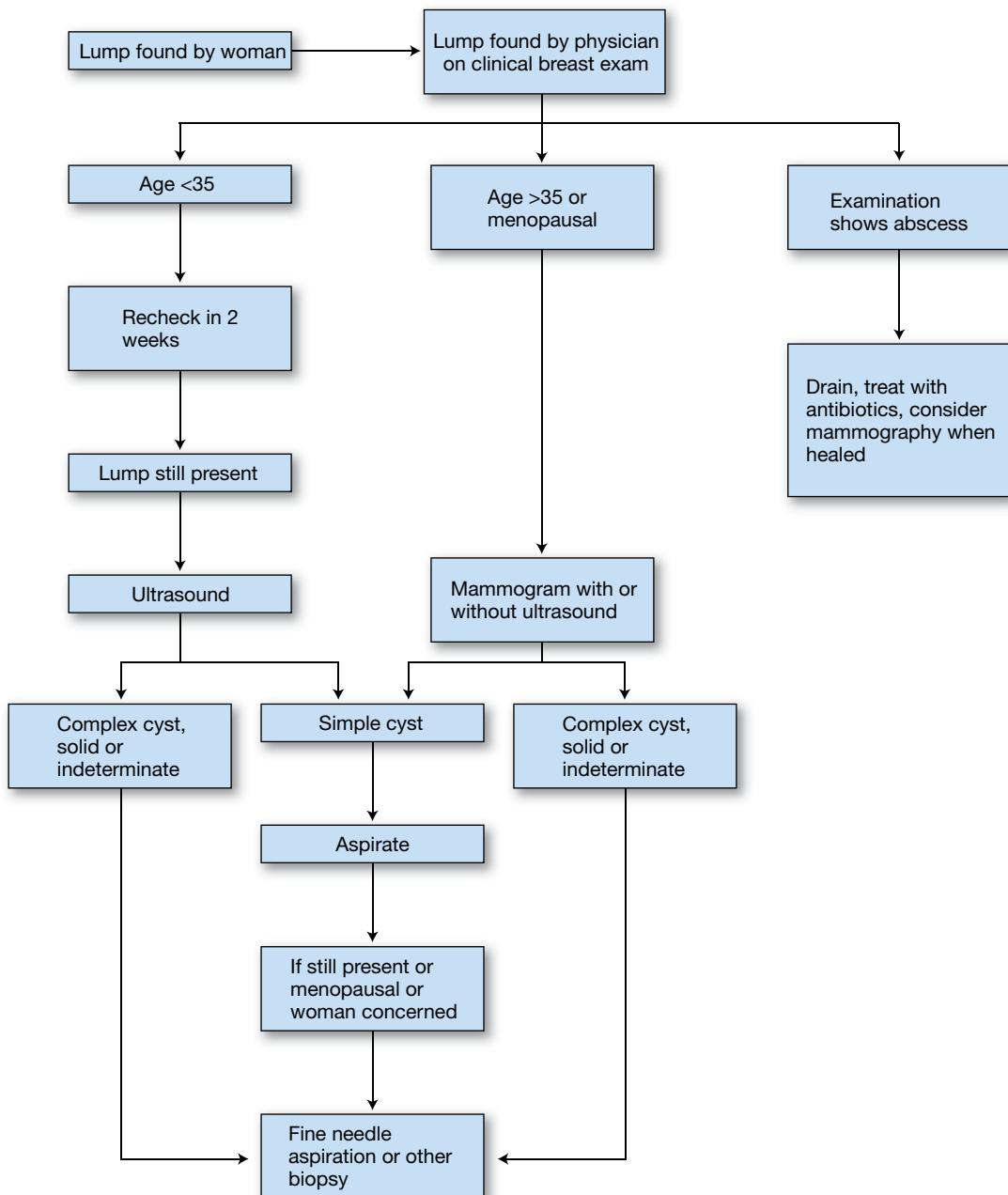
## Breast Masses

### KEY FACT

If there is a persistent palpable abnormality in the breast, a normal mammogram does not rule out cancer; ultrasound or biopsy must be done in these cases.

Benign fibroadenomas or cysts are the most common causes of breast lumps in premenopausal women, but cannot be differentiated by clinical exam from malignancy.

- **Exam:** Ask about associations with menstrual cycle, pain, and risk factors for breast cancer. Breast masses in young women that fluctuate with the menstrual cycle are likely to be fibroadenomas. Painful masses may represent infection but can also suggest inflammatory breast cancer.
- **Diagnosis:** If a dominant mass is present, proceed to mammography ± ultrasound and surgical evaluation for biopsy (Figure 17.1).



**FIGURE 17.1. Evaluation of palpable breast masses.** (Reproduced with permission from South-Paul JE, et al. *Current Diagnosis & Treatment in Family Medicine*, 2nd ed. New York: McGraw-Hill, 2008: 272.)

- Management:** Women with benign findings on imaging and biopsy require close follow-up. Consider excision in the setting of continued growth or patient preference. The management of breast malignancies is discussed in detail in the Oncology chapter.

## Contraception

Table 17.1 describes common contraceptive methods and outlines their contraindications and side effects.

### KEY FACT

Depot medroxyprogesterone (Depo-Provera) can cause bone loss if used >2 years, but bone density recovers after discontinuing the drug.

TABLE 17.1. Contraceptive Methods

METHOD	DESCRIPTION	PROS/CONS
<b>BARRIER METHODS</b>		
Diaphragm, cervical cap	A domed sheet of latex filled with spermicide and placed over the cervix	Allergy to latex or spermicide; ↑ <b>risk of UTI</b> <b>Lower efficacy</b>
Male or female condoms	A latex or polyurethane sheath placed over the penis during intercourse	Allergy to latex or spermicide <b>The only contraceptive method that also prevents STI transmission</b> <b>Lower efficacy</b>
<b>INTRAUTERINE DEVICES (IUDS)</b>		
Copper IUD (ParaGard)	A copper device placed into the endometrial cavity; produces a local inflammatory reaction that has a spermicidal effect and impairs implantation	↑ vaginal bleeding/cramping <b>Most effective contraception</b> , and single device effective up to 12 years
Progestrone-releasing IUD (levonorgestrel [Mirena, Skyla])	Progestin-releasing device placed in endometrial cavity, which thins the endometrium and thickens cervical mucus. Local effects are the same as those of the copper IUD	Amenorrhea may occur; ↓ menstrual blood loss may be beneficial for women with menorrhagia or dysmenorrhea <b>Highly effective</b> , approved for use of up to 5 years
<b>HORMONAL METHODS</b>		
Combined estrogen/progestin contraceptives (OCPs, transdermal ["the patch"], vaginal ring ["the ring"])	Suppress ovulation; thicken cervical mucus; thin endometrium	Nausea, breast tenderness, acne, mood changes, hypertension, hepatic adenoma, weight gain ↑ <b>risk of venous thromboembolism (VTE) and arterial thrombosis (MI, CVA)</b> , particularly among women with other CVD risk factors
Progestin-only oral contraceptive ("mini-pill")		<b>No apparent ↑ in the risk of VTE</b> A good option for women who are intolerant of estrogen or who are <b>breast-feeding</b>
Depot medroxyprogesterone acetate (Depo-Provera)	IM injection lasts 3 months	<b>Irregular vaginal bleeding</b> , depression, weight gain, breast tenderness, osteoporosis, delayed restoration of ovulation after discontinuation (6-18 months), should <b>not be used for &gt;2 years given concern for bone mineral loss</b> Easy for patients
Etonogestrel implant (nexplanon)	A single-rod subdermal implant that is effective for 3 years	Irregular vaginal bleeding; small possibility of device migration and difficult removal

(continues)

TABLE 17.1. Contraceptive Methods (*continued*)

METHOD	DESCRIPTION	PROS/CONS
<b>SURGICAL STERILIZATION</b>		
Vasectomy	The vas deferens is cut	Very low risk of local complications; more than 50% of men with reversed vasectomies are fertile
Tubal ligation	The fallopian tubes are ligated, cauterized, or mechanically occluded	Tubal ligation may result in bleeding, infection, failure, or ectopic pregnancy; the procedure is essentially irreversible

**KEY FACT**

Women >35 years of age who smoke >15 cigarettes daily should not be prescribed estrogen-containing contraceptives because of the ↑ risk of MI and DVT. Other contraindications include uncontrolled hypertension, breast cancer, VTE, liver disease, and migraine with aura.

**KEY FACT**

Drugs that are safe to use in pregnancy include heparins (UFH, LMWH), β-lactam antibiotics, prednisone, and insulin.

Emergency contraception should be taken within 5 days (ideally <24 hours) of unprotected intercourse to suppress ovulation or discourage implantation. Copper IUD insertion is the most effective option, although not always logistically feasible. Ulipristal and levonorgestrel (Plan B) are also effective oral options. Levonorgestrel is less effective in obese women.

**Medical Conditions in Pregnancy****DRUG USE IN PREGNANCY**

Table 17.2 lists certain drugs with adverse effects during pregnancy and their replacements.

**HYPERTENSION IN PREGNANCY**

Table 17.3 lists hypertensive disorders during pregnancy.

TABLE 17.2. Selected Drugs With Adverse Effects During Pregnancy and Their Replacements

TERATOGENIC DRUGS (AVOID IN PREGNANCY)	REPLACEMENT DRUGS (MAY BE USED WITH CAUTION)
Intracellular antibiotics ( <b>quinolones</b> , doxycycline and other tetracyclines, sulfonamides, streptomycin)	β-lactams (eg, erythromycin, azithromycin)
Most antihistamines	Chlorpheniramine
Warfarin: In general, this is avoided unless the woman is at very high risk for thrombosis (eg, mechanical heart valve); in this situation, warfarin can be used at low doses even in the first trimester	Heparins (unfractionated heparin [UFH] and low-molecular-weight heparin [LMWH]) do not cross the placenta
ACE inhibitors ARBs	Methyldopa β-blockers (including labetalol) Hydralazine CCBs
Immunomodulatory/antiangiogenic drugs (eg, methotrexate, thalidomide)	Prednisone: For SLE, RA, or other autoimmune disorders

**TABLE 17.3.** Hypertensive Disorders of Pregnancy

	CHRONIC HYPERTENSION	PREGNANCY-INDUCED HYPERTENSION (PREECLAMPSIA)	GESTATIONAL HYPERTENSION
Timing	Present before pregnancy or persisting >6 weeks postpartum	Onset after 20 weeks' gestation (can occur up to 6 weeks postpartum)	Onset after 20 weeks' gestation. Resolves after delivery
Clinical features	Hypertension prior to pregnancy	<b>Hypertension (&gt;140/90 mm Hg) and proteinuria with onset after 20 weeks</b> Often associated with edema Eclampsia = preeclampsia + seizures	Hypertension without proteinuria during pregnancy
Complications	↑ risk of preeclampsia Intrauterine growth restriction (IUGR), placental abruption, fetal demise	<b>Fetal:</b> IUGR, oligohydramnios, demise <b>Maternal:</b> Edema, <b>HELLP syndrome</b> (hemolysis, elevated liver enzymes, low platelets), seizures, death	May develop into preeclampsia ↑ risk of subsequent essential hypertension
Treatment	Treat BP if >145-150/95-100 mm Hg Target a diastolic BP of 80-100 mm Hg <b>Methyldopa, β-blockers, hydralazine, and CCBs</b> are often used DO NOT use ACEI/ARB in pregnancy	<b>After 36 weeks' gestation:</b> Immediate delivery <b>Before 36 weeks' gestation:</b> Bed rest, close monitoring of mother and fetus, BP management (goal diastolic BP 90-100 mm Hg) Hospitalization and delivery at any stage of gestation for severe preeclampsia, HELLP, or eclampsia Magnesium sulfate is given after delivery to prevent seizures	Same as that for chronic hypertension

### Pregnancy-Induced Hypertension (Preeclampsia)

- Diagnosis is made by the new development of hypertension (BP >140/90 mm Hg) and either proteinuria **or** end-organ dysfunction that develops after 20 weeks of gestation or during the postpartum period. Organ dysfunction can be thrombocytopenia, hepatic and/or renal failure, pulmonary edema, seizures, visual disturbances, or intracerebral hemorrhage.
- **Symptoms/Exam:**
  - Typical presentation is a nulliparous woman presenting with new hypertension (BP >140/90 mm Hg), generalized weight gain, rapid swelling, and proteinuria.
  - Risk factors for preeclampsia: First pregnancy, multiple gestation, advanced maternal age, certain comorbidities (eg, diabetes, hypertension, obesity, autoimmune and renal disease).
  - Can be asymptomatic.
  - Symptoms can include headache or visual changes and clinical conditions such as seizures, thrombocytopenia, multiorgan failure, placental abruption.

### HELLP Syndrome

Hemolysis, Elevated Liver enzymes, and Low Platelets. Considered a variant of preeclampsia. May be associated with renal dysfunction.

- **Diagnosis:**
  - Microangiopathic hemolytic anemia.
  - AST >70 IU/L.
  - Platelets <100K.

### KEY FACT

Pregnant women at high risk for preeclampsia (eg, history of preeclampsia, chronic hypertension, multifetal gestation, diabetes) should be on low-dose aspirin after 12 weeks of gestation.

### QUESTION

A 32-year-old woman seeks advice on her options for contraception. She has migraines with aura and does not smoke. What type of birth control is most appropriate?

- **Management:** Prompt delivery; supportive measures.
- **Complications:** Although most patients recover fully within weeks, there is a 3% to 5% maternal mortality rate.

### DIABETES IN PREGNANCY

Preexisting type 2 DM or impaired glucose tolerance may be unmasked in pregnancy. Guidelines for testing are as follows.

- **High risk:** Administer an oral glucose tolerance test (OGTT) to pregnant women at high risk for gestational DM (GDM). Risk factors include the following:
  - Marked obesity.
  - A personal history of GDM.
  - Previous delivery of a large-for-gestational-age infant.
  - Polycystic ovarian syndrome (PCOS).
  - A strong family history of DM.
- **Average risk:** Test between 24 and 28 weeks' gestation.
- **Low risk:** Women at low risk do not need testing if they:
  - Are <25 years of age.
  - Are of normal weight prior to pregnancy.
  - Are not members of high-risk ethnic groups (ie, not African American, Asian, Hispanic, or Native American).
  - Have no first-degree relatives with DM.
  - Have no history of abnormal glucose tolerance.
  - Have had no prior poor obstetric outcome.

#### KEY FACT

Women who have had GDM have a 35% to 60% risk of developing type 2 DM within 10 years of delivery. All such women should have a repeat OGTT at 6 weeks postpartum as well as periodic surveillance for DM thereafter.

#### KEY FACT

The goal in a mother with preexisting diabetes is good control ( $\text{HbA}_{1c} < 6\%$ ) before conception. If medication is needed during pregnancy, insulin is preferred.

**A**

#### ANSWER

The most appropriate method for this patient is a copper IUD. It may be acceptable to initiate progestin-only pills, long-acting depot medroxyprogesterone, norethisterone implants, or levonorgestrel-releasing IUDs as well, but the risks of continuing these methods may outweigh the advantages of doing so. Avoid combined oral contraceptives, transdermal patch, and vaginal rings in women who have migraines with aura at any age due to ↑ risk of stroke.

### Diagnosis

Oral glucose tolerance test (OGTT): Conduct initial screening with a 50-g glucose load. Then perform a 100-g diagnostic OGTT in patients with a 1-hour glucose level  $\geq 130$  to 140 mg/dL.

### Management

- Maternal and fetal outcomes are improved with tight glycemic control.
- **Tight control should be established before conception ( $\text{HbA}_{1c} < 6\%$ )** in women with preexisting DM.
  - Obese women should be placed on a calorie-restricted diet.
  - **Insulin** is preferred if lifestyle modification does not achieve adequate glycemic control. While metformin can be used, many oral hypoglycemic agents are contraindicated.
  - Fetal size should be monitored, and patients may be referred for cesarean section if macrosomia is present.

### Complications

- **Maternal:** DKA, preeclampsia, preterm labor, polyhydramnios; the need for cesarean section due to fetal macrosomia.
- **Fetal/neonatal:** Macrosomia; cardiac, renal, and neural tube defects; birth injury (shoulder dystocia); neonatal hypoglycemia; perinatal mortality.

### THYROID DISEASE IN PREGNANCY

#### Normal Changes in Thyroid Function During Pregnancy

- ↑ thyroid-binding globulin.
- This will ↑ total serum levels of  $T_4$  and  $T_3$ , but free hormone levels should remain normal.

- The normal range for TSH in pregnancy is lower (<2.5 mIU/L) in the first trimester, and gradually rises to an upper limit of normal of 3 mIU/L by the end of the pregnancy.

## Hyperthyroidism

- Hyperthyroidism affects <1% of pregnant women. In general, Graves disease improves during pregnancy but may **flare in the early postpartum period**.
- Diagnosis:** Similar to the approach in nonpregnant patients except that **radioactive iodine is contraindicated during pregnancy**.
- Management:**
  - Antithyroid medications (thionamides):** All antithyroid medications cross the placenta and have the potential to cause fetal hypothyroidism in the newborn. Of the thionamides, **propylthiouracil (PTU)** is preferred over methimazole (MMI) **in the first trimester** because of concerns about embryogenesis ("P for PTU in first trimester of Pregnancy"). At the start of second trimester, switch to MMI.
  - Other medications:** **Radioactive iodine is contraindicated in pregnancy** since it causes fetal hypothyroidism. **Propranolol** may be used to control cardiovascular symptoms.
  - Surgery:** In the setting of uncontrolled hyperthyroidism, thyroidectomy should be considered and performed during the second trimester if necessary.
- Complications:** Untreated hyperthyroidism may lead to spontaneous abortion, premature delivery, and an ↑ risk of a small-for-gestational-age newborn.

## Hypothyroidism

New-onset hypothyroidism is rare during pregnancy.

- Diagnosis:** Screening TSH is guided by history. Women with a history of thyroid disease already on thyroid hormone replacement, women with other autoimmune disease, history of head/neck radiation, prior thyroid surgery, or strong family history should be screened.
- Management:**
  - Thyroid hormone replacement:** Women with preexisting hypothyroidism may require 30% to 50% higher levothyroxine dosages.
  - Monitor thyroid function closely. Consider an empiric ↑ of levothyroxine by 30% after pregnancy is confirmed. Consider treating subclinical hypothyroidism.
- Complications:**
  - Fetal:** Congenital anomalies, perinatal mortality, impaired mental and somatic development.
  - Maternal:** Anemia, preterm labor, preeclampsia, placental abruption, postpartum hemorrhage.

## CARDIOVASCULAR DISEASE IN PREGNANCY

- Cardiac conditions that are major risk factors for maternal or fetal complications include:
  - Pulmonary hypertension, particularly Eisenmenger syndrome.
  - Cyanotic congenital heart disease.
  - Dilated cardiomyopathy with severe heart failure with ↓ ejection fraction.
  - Marfan syndrome with aortopathy.
  - Severe valvular disease.
- Pregnancy prevention in CVD:**
  - The safest and most effective contraceptive device for cardiac patients is a levonorgestrel-releasing or copper IUD.

### KEY FACT

Maternal hypothyroidism during pregnancy causes developmental delay in the child. Women may need up to 50% more of their usual levothyroxine supplementation dose.

### KEY FACT

Amiodarone is contraindicated as it can cause fetal hypothyroidism.

### KEY FACT

Think of a new diagnosis of mitral stenosis if a pregnant woman presents with atrial fibrillation and edema. Note that digoxin can be used in pregnancy and electrocardioversion is allowed.

**KEY FACT**

Warfarin is generally discouraged during pregnancy due to teratogenesis and the ↑ risk of fetal complications. However, for women at very high risk for thrombosis (eg, mechanical valves), warfarin can be continued in the first trimester if the daily dose is <5 mg, since warfarin is the most effective option in terms of reducing thrombosis risk to the mother. LMWH is a safe alternative.

- Progesterone-only OCPs are another possibility, but they must be used cautiously as Depo-Provera can lead to fluid retention in CHF patients.
- Pregnancy complications in CVD:
  - Women with obstructive valvular disease tend to become more symptomatic due to ↑ blood volume requiring ↑ in cardiac output.
  - **Peripartum cardiomyopathy** is the leading cause of pregnancy-related maternal death in North America.
  - Pregnancy in congenital heart disease impacts both mother and fetus; thus, Obstetrics and Cardiology are responsible for the well-being of both.

**Infertility**

Inability to conceive after 1 year of unprotected intercourse, or 6 months in women ≥35 years of age. Etiologies to consider:

- **Male infertility:** Disorders of sperm transport (posttesticular defects), seminiferous tubule dysfunction, 1° hypogonadism, hypothalamic pituitary disease.
- **Ovulatory disorders:** Hypogonadism, PCOS, ovarian failure, luteal phase defects (implantation problems).
- **Diminished ovarian reserve:** Decline in egg quality due to ↑ age.
- **Uterine abnormalities:** Congenital, diethylstilbestrol exposure, fibroids, polyps, synechiae from prior manipulation.
- **Tubal and peritoneal abnormalities:** Scarring from prior PID, severe endometriosis, adhesions.

**Symptoms/Exam**

Look for hirsutism, goiter, galactorrhea, an abnormal pelvic exam in the female partner, and testicular size/masses in the male partner.

**Diagnosis**

- Semen analysis.
- Check ovarian reserve: Obtain day 3 of menstrual cycle FSH, LH, estradiol, anti-mullerian hormone.
- Consider TSH, prolactin; if virilization, obtain testosterone and DHEA levels.
- Assess ovulation with a basal body temperature chart or a urine LH kit for the female partner.
- Consider hysterosalpingography, pelvic ultrasound, endometrial biopsy, and/or laparoscopy to assess for structural etiologies.

**Management**

Treat the underlying cause:

- Urologic treatment for male factor infertility.
- Ovulation induction (clomiphene, gonadotropins, GnRH).
- Laparoscopy (eg, to remove endometriosis implants).
- Assisted reproductive technologies (intrauterine insemination, IVF).
- Sperm or egg donation.

**Menstrual Disorders****KEY FACT**

Any vaginal bleeding in a postmenopausal woman must be investigated.

**ABNORMAL UTERINE BLEEDING**

Abnormal uterine bleeding is defined as abnormalities in the frequency, duration, volume, and/or timing of menses. Etiologies are listed in Table 17.4. In up to half of cases, no cause can be identified. Subtypes include the following:

**TABLE 17.4.** Causes of Abnormal Uterine Bleeding

CAUSE	UNDERLYING DISORDERS	CLINICAL FEATURES
Anovulation	PCOS, hypothalamic-pituitary-ovarian axis dysfunction, hypothyroidism, prolactinoma, ovarian or adrenal tumor	Irregular cycles. Check for other endocrinologic signs, physical or mental <b>stress, eating disorders, or high-intensity exercise</b>
Cervical lesions	Cervical polyps, cervicitis, dysplasia/malignancy	Spotting, often postcoital; vaginal discharge (infection)
Bleeding disorder	von Willebrand disease; acquired or other congenital coagulopathies	Menorrhagia, intermenstrual heavy bleeding; other sites of bleeding
Structural uterine pathology	Fibroids, endometrial cancer, or hyperplasia	Dysmenorrhea ± pelvic mass on exam; menorrhagia or intermenstrual bleeding
Hormonal medications (eg, OCPs)		Intermenstrual spotting, amenorrhea, postmenopausal bleeding
Dysfunctional uterine bleeding	Idiopathic, often anovulatory	Irregular menstrual pattern without an identifiable underlying cause

- **Intermittent/postcoital bleeding:** Think cervical lesions, endometrial polyps, cervicitis, and endometritis.
- **Menorrhagia:** Prolonged and/or excessive uterine bleeding. Think fibroids, adenomyosis, and coagulopathy.
- **Menometrorrhagia:** Heavy bleeding at irregular intervals. Think anovulation, some myomas, adenomyosis, **hyperplasia, and cancer**.
- **Amenorrhea:** Absence of menses for  $\geq 3$  usual cycle lengths (see below).

### Symptoms/Exam

- **History:** Determine whether bleeding is anatomic or anovulatory (irregular cycles with no premenstrual symptoms).
- **Exam:** Check for signs of PCOS (hirsutism, acne, obesity). Pelvic exam; Pap smear and urine pregnancy test.

### Diagnosis

- **Labs:** May include TSH, prolactin, and CBC/coagulation studies. Always check **urine pregnancy** in childbearing-age women before sending other tests.
- **Additional testing:** Ultrasound (fibroids), hysteroscopy (endometrial polyps, some fibroids), and endometrial biopsy (endometrial polyps, hyperplasia, cancer). Women  $>35$  years of age should **routinely undergo endometrial biopsy** for irregular bleeding to rule out endometrial cancer.

### Management

Acute control of active heavy bleeding: Treat with combined estrogen/progestin OCPs. Give four pills per day for 1 or 2 days; then taper to one pill daily through day 20. Early on, bleeding should stop, and after the process, withdrawal bleeding should occur.

Treat the underlying cause:

- **Ovulatory, heavy bleeding:** NSAIDs and OCPs  $\downarrow$  the amount of bleeding.
- **Anovulatory bleeding:** Hormonal treatment—OCPs, levonorgestrel IUDs, and cyclic progestins regularize cycles.
- **Profuse bleeding:** High-dose estrogen, dilation and curettage, endometrial ablation, hysterectomy.



### KEY FACT

**Dysfunctional uterine bleeding** refers to heavy and irregular bleeding due to anovulation and not to anatomic problems, leading to estrogen-induced stimulation of endometrium without progesterone to stabilize growth. It is a diagnosis of exclusion and should be considered in a woman with irregular bleeding in the absence of pelvic exam abnormalities or medical illness.



### QUESTION 1

A 30-year-old woman has 1 year of menorrhagia and dysmenorrhea. Her menses typically lasts 8 to 9 days and requires that she change her tampons as often as every hour. What is the most likely diagnosis?



### QUESTION 2

An 18-year-old marathon runner has irregular menstrual periods (monthly menses until 2 years ago, when it became irregular). Her last menses was 6 months ago. BMI is  $18 \text{ kg/m}^2$ . Urine pregnancy test is  $\ominus$ ; TSH, prolactin, and FSH are normal. She undergoes a progestin challenge test for 10 days, but has no withdrawal bleed. What could be the cause?

## AMENORRHEA

Amenorrhea may be 1° or 2°:

- 1°: Absence of menses by age 16, or by age 14 in the absence of 2° sexual characteristics.
- 2°: Previously normal menses; absence for three consecutive cycles or 6 months. The most common cause in women under 45 (with the exception of pregnancy) is PCOS, followed by hypothalamic hypoestrogenism, hyperprolactinemia, and premature ovarian failure.
- To understand amenorrhea and the workup, it helps to briefly review the menstrual physiology (Figure 17.2):
  - In the first half of the menstrual cycle, estrogen grows and matures the uterine lining as well as the egg prior to ovulation. In the second half of the cycle, ovulation triggers the synthesis of progesterone, which controls the buildup of the uterine lining and helps maintain it if there is a pregnancy. If there is no pregnancy, progesterone ↓ and the uterine lining is shed (menstrual bleeding occurs).
  - Thus, anovulation leads to progesterone deficiency, and menses cannot occur.

### KEY FACT

Consider Turner syndrome (karyotype XO) as a cause of 1° amenorrhea if the patient is short and has a webbed neck without 2° sexual characteristics (including no breast growth).

### Symptoms/Exam

- Ask about pregnancy symptoms, galactorrhea, headaches, visual changes, hirsutism, acne, stress or illness, medications, and menopausal symptoms. There may also be weight loss (eg, in eating disorders or exercise).
- Look for 2° sexual characteristics, virilization (male-pattern hair loss/growth, acne, clitoromegaly), galactorrhea, and pelvic exam abnormalities.

### Differential

Table 17.5 lists the differential diagnosis of amenorrhea.

- Hypothalamus-pituitary axis (HPA) dysfunction ( $\downarrow$  pulsatile GnRH activity of the hypothalamus leads to low estrogen levels): Physical or emotional stress, anorexia, heavy exercise; hyperprolactinemia and hypothyroidism.
- Hyperandrogenism (normal estrogen levels): PCOS, Cushing syndrome, prolactinoma, 21-hydroxylase deficiency.
- Uterine structural disorders: Endometrial scarring after a procedure or infection (Asherman syndrome).
- Premature ovarian failure: Autoimmune disease, Turner syndrome, postchemotherapy.
- Other: Pregnancy, menopause.

**A**

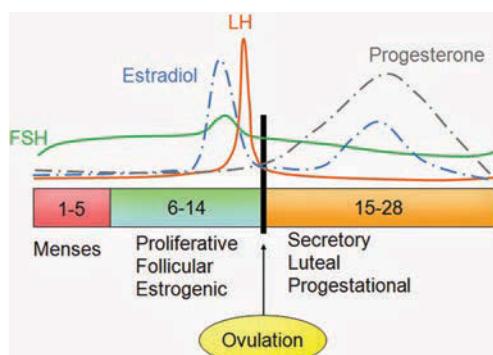
### ANSWER 1

Uterine fibroids though given her age pregnancy must be ruled out.

**A**

### ANSWER 2

Most likely due to either very low estrogen levels (HPA dysfunction from strenuous exercise and low BMI) or an outflow tract problem (uterine synechiae or cervical stenosis).



**FIGURE 17.2. Menstrual cycle stages and hormone levels.** (Reproduced with permission from USMLE-Rx.com.)

**TABLE 17.5. Differential Diagnosis of Amenorrhea**

	FSH	LH	PROLACTIN
HPA dysfunction	Normal or ↓	Normal or ↓	Normal or ↓
PCOS	↑	↑↑	Normal or ↑
Prolactinoma	Normal	Normal	↑
Premature ovarian failure	↑	↑	Normal or ↑

### Diagnosis

- To diagnose 2° amenorrhea: First rule out pregnancy.
- Consider pelvic ultrasound to assess for structural abnormality.
- Check TSH, FSH, LH, and prolactin:
  - Abnormal TSH: Thyroid dysfunction.
  - High prolactin: Hyperprolactinemia or pregnancy.
  - High FSH and LH: Premature ovarian failure.
  - Low FSH and LH: Low GnRH due to hypothalamus-pituitary axis dysfunction (“hypothalamic hypoestrogenism”), often due to stress, anorexia nervosa, or exercise.
  - ↑ LH-to-FSH ratio (>3:1): Suggests PCOS.
- If all tests are normal (particularly FSH), administer a progestin challenge test (medroxyprogesterone acetate daily for 5-10 days).
  - “Positive test” (withdrawal bleed after a progestin challenge): If the patient bleeds 2 to 7 days after the progesterone is withdrawn, there is adequate estrogen (estradiol level >40 mg/mL) allowing for buildup of endometrial lining, but there is no ovulation and thus no progesterone. The most common cause of anovulation is PCOS.
  - “Negative test” (no withdrawal bleed after progestin challenge): Indicates one of the following:
    - Very low estrogen levels (from low GnRH stemming from hypothalamus-pituitary axis dysfunction): Most commonly due to **stress, weight loss, anorexia, or heavy exercise**.
    - Abnormal outflow tract: Asherman syndrome (endometrial adhesions) or cervical stenosis. Proceed to **pelvic ultrasound** to rule out an anatomic defect.
    - Premature ovarian failure.

## Menopause

One year of amenorrhea after the final menstrual period. Average age is 45 to 55 years.

### Symptoms/Exam

- Irregularity of cycle length may begin during the perimenopause state (lasts ~4 years but can last up to 8).
- The most common complaints are vasomotor symptoms (hot flashes, night sweats) and vaginal atrophy/dryness.

### KEY FACT

For evaluation of 2° amenorrhea, a  $\oplus$  progestin challenge test (the presence of a withdrawal bleed after a course of progestin is given) suggests anovulation as a cause for amenorrhea. PCOS is the most common cause.

### KEY FACT

Amenorrhea and high FSH in young women indicate premature ovarian failure and put women at risk for osteoporosis from estrogen deficiency. Consider starting estrogen therapy. Women with 2° amenorrhea due to anorexia or heavy exercise can also be treated with estrogen though ideally weight gain is first intervention.



### QUESTION

A 70-year-old woman presents to your clinic with a 6-month history of intermittent vaginal spotting. What is the most appropriate diagnostic test?

### Differential

If indicated by the history and exam, consider thyroid disease, prolactinoma, and chronic medical conditions that cause night sweats (eg, TB, lymphoma).

### Diagnosis

Clinical diagnosis is generally adequate. A high FSH level is diagnostic but usually unnecessary.

### Management

- **Hormone replacement therapy (HRT):** First-line treatment of menopausal vasomotor and urogenital symptoms, but associated with an ↑ risk of VTE, breast cancer, stroke, and CAD. Current recommendations for HRT use are as follows:
  - Use the lowest dose for the shortest duration needed to treat symptoms (attempt to taper or discontinue every 6 months).
  - Do not use HRT to prevent chronic health conditions (ie, treatment/prevention of osteoporosis).
  - A history of breast/endometrial cancer, CAD, active pregnancy, or VTE are **absolute contraindications**.
  - Women with a uterus need to take **estrogen plus a progestin** to protect against endometrial cancer. Women who have undergone hysterectomy may take estrogen alone.
- **Other treatment options** for menopausal symptoms include:
  - Intravaginal estrogen (low dose), moisturizers, lubricants for **vaginal symptoms**.
  - **SSRIs** (paroxetine) are approved for symptom relief of **vasomotor instability** (eg, hot flashes) and are safe for women who cannot take estrogens.
  - Some evidence supports the efficacy of clonidine, venlafaxine, and gabapentin.
  - Complementary/alternative medications such as black cohosh and soy are not currently recommended as they show no evidence of benefit.

## Postmenopausal Bleeding

All women with postmenopausal bleeding should be evaluated for **endometrial carcinoma**. Other etiologies include endometrial atrophy (most common), exogenous hormones, nongynecologic sources, endometrial hyperplasia or polyps, and cervical cancer.

### Symptoms/Exam

- Patients may complain of “spotting” or of heavier, menses-like bleeding.
- Pelvic exam reveals vaginal atrophy, vaginal lesions, cervical polyps, or uterine masses.

### Diagnosis

- Pap smear to rule out cervical cancer. If normal, still need to rule out endometrial abnormalities.
- **Endometrial biopsy** is the gold standard for diagnosis.
- **Ultrasound** is an alternative first test (Figure 17.3); if the endometrial lining is <5 mm thick, endometrial biopsy may be deferred unless unexplained bleeding continues.

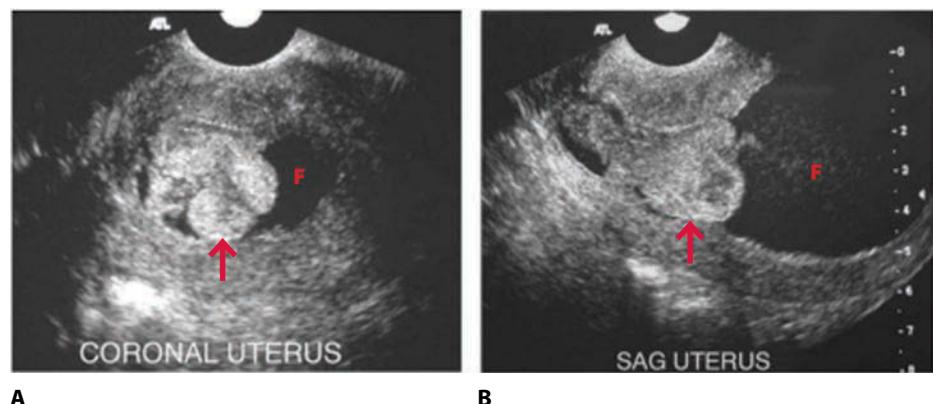
### Management

Bleeding is usually light and self-limited. Once malignancy has been ruled out, there is generally no need for treatment.

**A**

### ANSWER

Endometrial biopsy to rule out endometrial cancer.



**FIGURE 17.3. Endometrial cancer.** Transvaginal coronal (A) and sagittal (B) ultrasound images of the uterus demonstrate a large echogenic mass in the uterine cavity (arrow) with adjacent fluid or blood (F). (Reproduced with permission from USMLE-Rx.com.)

## Hirsutism

Hirsutism is due to excess androgen that can come from adrenal glands (Cushing syndrome, congenital adrenal hyperplasia, adrenal carcinoma), ovaries (ovarian tumors), exogenous sources (medications), other causes (PCOS).

### Symptoms/Exam

- ↑ hair growth in androgen-dependent areas such as the lip, chin, chest, abdomen, and back.
- May present with associated amenorrhea and signs of virilization (eg, deepening voice, male-pattern baldness, clitoromegaly, male body habitus).
- Look for obesity, male-pattern hair growth and/or androgenic alopecia, acne, signs of Cushing syndrome, and virilization.
- Conduct an abdominal and pelvic exam for mass lesions.

### Differential

PCOS is the most common medical condition associated with hirsutism but is **not** associated with virilization (see below). Other etiologies include the following:

- **Congenital adrenal hyperplasia** (late-onset 21-hydroxylase deficiency): Rare.
- **Medications:** Androgenic progestins in OCPs, danazol, minoxidil, cyclosporine.
- **Cushing syndrome:** Excess cortisol production; characterized by rapid weight gain, fat pads ("buffalo hump," "moon facies"), hypertension, and hyperglycemia.
- **Androgen-secreting ovarian tumors** (eg, Sertoli-Leydig tumor: very high testosterone but normal DHEAS).
- **Androgen-secreting adrenal neoplasm** (50% are malignant): Very high DHEAS.

Features associated with neoplastic causes of hirsutism are as follows:

- Abrupt onset, short duration (<1 year), or sudden progressive worsening.
- Onset in the third decade of life or later (not peripubertal).
- Virilization (acne, deepened voice, male-pattern baldness, clitoral hypertrophy, rare menses).

### Diagnosis

- No labs are indicated for patients with long-standing hirsutism who have regular menses and family members with similar hair growth patterns.
- Consider checking testosterone, androstenedione, and DHEAS (a precursor of adrenal androgens) to rule out ovarian or adrenal neoplasm.

### KEY FACT

Virilization and/or abrupt onset of hirsutism in an older woman may point to an androgen-secreting cancer in the ovaries or adrenal glands; check testosterone and DHEAS.



### QUESTION

A 26-year-old woman with diet-controlled type 2 DM presents with 6 months of irregular periods. BP is 150/76 mm Hg, BMI 32 kg/m<sup>2</sup>, and she has facial acne, hair in the chin area, and balding in a male pattern. Assuming she has PCOS, what is the best management strategy for her symptoms?

- Image the adrenals (CT) and ovaries (ultrasound or MRI) if androgen levels are significantly ↑. Mild elevations of testosterone levels are common in PCOS.

### Management

- Treat the underlying cause.
- **Nonpharmacologic treatment:** Shaving, depilatories, electrolysis, laser treatment, flormethine hydrochloride cream.
- **Antiandrogen therapy:** Try OCPs and/or spironolactone.

## Polycystic Ovarian Syndrome

PCOS is a syndrome characterized by menstrual irregularity (chronic anovulation) and hyperandrogenism (acne, hirsutism, balding). Diabetes and obesity are often present. Can present as 1° or 2° amenorrhea; onset is typically **peripubertal** and slowly progressive.

### Symptoms/Exam

- Patients seek treatment for **hirsutism, acne, oligomenorrhea/amenorrhea, or infertility**.
- Obesity, acne, hypertension, and acanthosis nigricans may be present. Enlarged, cystic ovaries may be found on bimanual exam.

### Differential

- **Irregular menses:** See the section on Menstrual Disorders.
- **Androgen excess:** Adrenal or ovarian tumor, congenital adrenal hyperplasia, Cushing syndrome.

### Diagnosis

- **Rotterdam criteria:** Requires two of the following: (1) anovulation or oligo-ovulation (leading to irregular menses); (2) hyperandrogenism by clinical or laboratory evidence; and (3) polycystic ovaries on ultrasound. Other characteristics may include infertility and insulin resistance.
- **Labs:** A serum LH-to-FSH ratio of  $>3:1$  is suggestive but not diagnostic of PCOS, and serum testosterone is **often mildly ↑**. Labs are most helpful for excluding other causes of amenorrhea or hirsutism (see the sections on those topics above). If androgens (testosterone, DHEAS) are very elevated, then look for tumors in ovaries or adrenal glands.
- **Imaging:** Ultrasound may reveal enlarged ovaries with numerous large cysts. However, such polycystic ovaries are seen in up to 25% of normal women, so their presence is not specific for PCOS.
- Many patients with PCOS have insulin resistance and are **at risk for type 2 DM and metabolic syndrome**. Fasting lipids and glucose should be measured periodically.

### Management

- Treatment depends on the target symptom, but **weight loss (in obese patients) and OCPs are best overall**. OCPs ↓ ovarian androgen secretion.
- Symptom-specific treatment is as follows:
  - **Insulin resistance:** Weight reduction. Metformin can be used but no strong data, may help with weight loss.
  - **Infertility:** Clomiphene induces ovulation.

### KEY FACT

PCOS is a clinical diagnosis; do not routinely order testosterone or DHEAS (for androgen-producing tumors) unless virilization is present. Serum testosterone is only mildly ↑ in PCOS, whereas stromal ovarian cancers have very high testosterone. Also note that the presence of polycystic ovaries is neither necessary nor sufficient to make the diagnosis of PCOS.

### KEY FACT

Consider these treatments in a patient with PCOS who may or may not desire pregnancy:

- **Desires pregnancy:** Clomiphene.
- **Hirsute and does not desire pregnancy:** Combined OCPs; add spironolactone if no improvement. Consider hair removal methods.
- **Not hirsute and does not desire pregnancy:** Periodic withdrawal bleeds with medroxyprogesterone or OCPs.

### A

### ANSWER

OCPs if not desiring to get pregnant.

- **Hirsutism, acne:** OCPs, spironolactone, other acne treatment, hair removal methods.
- **Endometrial hyperplasia:** OCPs or intermittent progestin therapy.

## Chronic Pelvic Pain

Chronic pelvic pain, or pain below the umbilicus lasting at least 6 months and severe enough to cause functional disability or require treatment. Often multifactorial and challenging to diagnose and treat. The most common underlying conditions leading to a chronic pelvic pain syndrome are as follows:

- **Gynecologic:** Endometriosis, chronic PID, adenomyosis, uterine fibroids, pelvic adhesions.
- **GI/renal:** IBS, interstitial cystitis (recurrent UTI-like symptoms without evidence of infection).
- **Musculoskeletal:** Fibromyalgia.
- **Other:** Depression, somatization, domestic violence, narcotic and other substance abuse.

### Diagnosis

- **Labs:** CBC, vaginal cultures/STI testing, UA, pregnancy testing.
- **Imaging:** Pelvic ultrasound, laparoscopy.

### Management

- Treat the underlying cause when one is apparent.
- Effective treatment of idiopathic chronic pelvic pain requires a multidisciplinary approach, including psychological counseling.

## Domestic Violence

Domestic violence is the leading cause of injury in women. Abuse may be physical, mental (including denial of financial or health care access), or sexual. Affects all socioeconomic groups; may also occur in same-sex relationships and in men. **Pregnancy** may initiate or exacerbate abuse.

### Symptoms

- See the mnemonic **SAFE** for screening and follow-up questions.
- Patients may present with no symptoms or with a variety of clinical scenarios, including the following:
  - Multiple somatic complaints.
  - Chronic pain syndromes.
  - Depression.
  - Injuries unexplained by the history (especially multiple injuries in various stages of healing).
  - A possible delay in seeking care.

### Exam

Conduct a mental status exam, and look for signs of new, old, or chronic trauma. Ask the partner to leave the room so that the patient can be interviewed alone.

### Differential

Psychological illness, physical illness, somatization.



### MNEMONIC

#### **Domestic violence questions—SAFE**

**S**tress and **S**afety:

Do you feel safe in your relationship?

**A**fraid or **A**bused:

Have you ever been in a relationship where you were threatened, hurt, or afraid?

**F**riend or **F**amily awareness:

Are your friends or family aware that you have been hurt? Could you tell them, and would they be able to give you support?

**E**mergency **E**scape plan:

Do you have a safe place to go and the resources you need in an emergency?



### QUESTION

A 37-year-old G2P2 woman presents with 1 week of vaginal discomfort and an abnormal odor. A speculum exam reveals normal vaginal mucosa, and no discharge from the cervix. A wet mount has clue cells and whiff test is  $\oplus$  with KOH. What is the diagnosis?

### Management

- Conduct a risk assessment (frequency, weapons, substance abuse, threats of suicide or homicide).
- Determine if the patient has a safety plan.
- Refer to appropriate support services, and report the abuse to law enforcement. Accurate documentation of any injuries is important for potential future legal proceedings.

## Vaginitis

Vaginitis is a change in normal vaginal flora. This can be a bacterial overgrowth (bacterial vaginosis), fungal (candidiasis), or protozoan (trichomonad). Bacterial vaginosis and candidiasis are not considered STIs, while trichomoniasis is.

### Symptoms/Exam

May present with abnormal discharge (fishy odor; thin, grayish-white discharge) and symptoms such as itching, burning, soreness, pyuria, and dyspareunia.

Conduct a pelvic exam and note:

- Vulvar edema/erythema is more consistent with candidiasis (yeast infection).
- **Discharge:** Quantity, color, adherence, odor.
- **Cervicitis:** Friability, purulent discharge, “strawberry cervix” (petechiae in trichomonad infection).

### Differential

UTI, normal (physiologic) discharge, noninfectious/irritants (spermicide, douching), atrophy.

### Diagnosis

- Wet mount (pH and microscopy in saline and KOH) (see Table 17.6 and Figure 17.4).
- Consider UA and/or STI.

### Management

Treat the underlying cause:

- **Bacterial vaginosis:** Metronidazole (PO 500 mg BID × 7 days or single 2-g dose, or topical × 5 days) or clindamycin (PO or topical × 7 days). May resolve spontaneously; recurrence is common.
- **Candidiasis:** Fluconazole 150 mg PO × 1 or various topical azoles (several are available OTC).
- **Trichomoniasis:** Oral metronidazole at the same doses as for bacterial vaginosis.

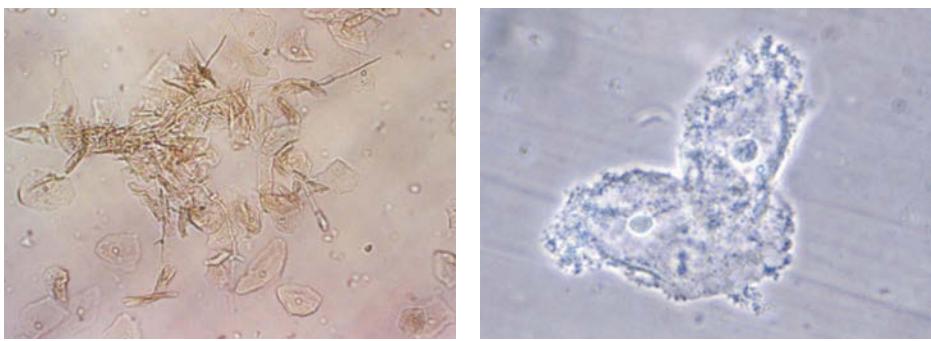
**TABLE 17.6. Wet Mount Criteria in Diagnosing Vaginitis**

DIAGNOSIS	DISCHARGE	CELLS	PH	"WHIFF TEST"
Bacterial vaginosis	Grayish-white, thin, fishy odor	Clue cells	>4.5	⊕ with KOH
Yeast	Thick, white, clumpy, adherent (“cottage cheese”)	Pseudohyphae with KOH	3.5-4.5	⊖
Trichomoniasis	Profuse, yellow-green, frothy, malodorous	Motile trichomonads	>4.5	⊕

A

### ANSWER

Bacterial vaginosis.



**FIGURE 17.4. Causes of vaginitis.** (A) Candidal vaginitis. *Candida albicans* organisms are evident on KOH wet mount. (B) *Gardnerella vaginalis*. Note the granular epithelial cells (“clue cells”) and indistinct cell margins. (Image A source: Centers for Disease Control and Prevention/Dr. Stuart Brown. Image B source: Centers for Disease Control and Prevention/M. Rein.)

## NOTES

## APPENDIX

## Abbreviations and Symbols

Abbreviation	Meaning	Abbreviation	Meaning
AA	Alcoholics Anonymous	ANC	absolute neutrophil count
A-a	alveolar-arterial (oxygen gradient)	ANCA	antineutrophil cytoplasmic antibody
AAA	abdominal aortic aneurysm	AP	anteroposterior
ABG	arterial blood gas	APL	acute promyelocytic leukemia
ABI	ankle-brachial index	APLA	antiphospholipid antibody (syndrome)
ABPA	allergic bronchopulmonary aspergillosis	APO	apolipoprotein
ABPA-CB	allergic bronchopulmonary aspergillosis with central bronchiectasis	AR	autosomal recessive
ABPA-S	allergic bronchopulmonary aspergillosis—seropositive	ARB	angiotensin receptor blocker
ACA	anterior cerebral artery	ARDS	acute respiratory distress syndrome
ACC	American College of Cardiology	5ASA	5-aminosalicylic acid
ACD	anemia of chronic disease	ASA	acetylsalicylic acid
ACEI	angiotensin-converting enzyme inhibitor	ASCA	anti- <i>Saccharomyces cerevisiae</i> antibody
ACh	acetylcholine	ASD	atrial septal defect
AChE	acetylcholinesterase	ASMA	anti-smooth muscle antibody
ACL	anterior cruciate ligament	ASO	antistreptolysin O
ACLS	advanced cardiac life support (protocol)	AST	aspartate aminotransferase
ACTH	adrenocorticotrophic hormone	AT	angiotensin, atrial tachycardia
AD	autosomal dominant	ATN	acute tubular necrosis
ADA	American Diabetes Association	ATP	adenosine triphosphate
ADH	antidiuretic hormone	ATP III	National Cholesterol Education Program
ADHD	attention-deficit hyperactivity disorder	ATRA	Adult Treatment Panel III
ADL	activities of daily living	AV	<i>all-trans</i> retinoic acid
ADPKD	autosomal dominant polycystic kidney disease	AVF	arteriovenous, atrioventricular
AED	automated external defibrillator	AVM	arteriovenous fistula
AF	atrial fibrillation	AVN	arteriovenous malformation
AFB	acid-fast bacillus	AVNRT	avascular necrosis
AFP	$\alpha$ -fetoprotein	AVP	atrioventricular nodal reentrant tachycardia
AGMA	anion-gap metabolic acidosis	AVRT	arginine vasopressor
AHA	American Heart Association	AXR	atrioventricular reentrant tachycardia
AI	adrenal insufficiency	AZT	abdominal x-ray
AIDS	acquired immunodeficiency syndrome	BAL	azidothymidine (zidovudine)
AIN	acute interstitial nephritis	BCC	bronchoalveolar lavage
AKI	acute kidney injury	BCG	basal cell carcinoma
ALI	acute lung injury	BG	bacille Calmette-Guérin
ALL	acute lymphoblastic leukemia	BID	blood glucose
ALS	amyotrophic lateral sclerosis	BiPAP	twice daily
ALT	alanine aminotransferase	BIW	bilevel positive airway pressure
AMA	antimitochondrial antibody	BMD	biweekly
AMD	age-related macular degeneration	BMI	bone mineral density
AML	acute myeloid leukemia	BNP	body mass index
ANA	antineutrophil antibody	BP	brain natriuretic peptide
		BPH	blood pressure
		BPPV	benign prostatic hyperplasia
			benign paroxysmal positional vertigo

Abbreviation	Meaning	Abbreviation	Meaning
BRAT	bran, rice, applesauce, toast (diet)	CRH	corticotropin-releasing hormone
BUN	blood urea nitrogen	CRP	C-reactive protein
BV	bleomycin and vincristine	CRPS	complex regional pain syndrome
C1-INH	C1-inhibitor	CSA	central sleep apnea
CABG	coronary artery bypass graft	CSF	cerebrospinal fluid
CaCO <sub>3</sub>	calcium carbonate	CTEPH	chronic thromboembolic pulmonary hypertension
CAD	coronary artery disease	CT	computed tomography
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody	CTCL	cutaneous T-cell lymphoma
CAP	community-acquired pneumonia	CTP	Child-Turcotte-Pugh (scoring)
CBC	complete blood cell count	CT-PA	CT pulmonary angiography
CBE	clinical breast examination	CVD	cardiovascular disease
CBT	cognitive behavioral therapy	CVA	cerebrovascular accident, costovertebral angle
CCB	calcium channel blocker	CVID	common variable immunodeficiency
CCK	cholecystokinin	CXR	chest x-ray
CCP	cyclic citrullinated peptide	D <sub>2</sub>	ergocalciferol
CD	cluster of differentiation	D <sub>3</sub>	cholecalciferol
CDC	Centers for Disease Control and Prevention	d4T	didehydrodeoxythymidine (stavudine)
CEA	carcinoembryonic antigen	D5W	dextrose 5% in water
CF	cystic fibrosis	DASH	Dietary Approaches to Stop Hypertension
CFS	chronic fatigue syndrome	DBP	diastolic blood pressure
CFTR	cystic fibrosis transmembrane regulator	DCIS	ductal carcinoma in situ
CHF	congestive heart failure	DDAVP	1-deamino (8-D-arginine) vasopressin
CHOP	cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisone	ddI	dideoxynosine
CI	confidence interval	DEET	N,N-diethyl-meta-toluamide
CIDP	chronic inflammatory demyelinating polyneuropathy	DES	diethylstilbestrol
CIWA	Clinical Institute Withdrawal Assessment	DEXA	dual-energy x-ray absorptiometry
CK	creatinine kinase	DF	discriminant function
CKD	chronic kidney disease	DFA	direct fluorescent antibody
CK-MB	creatine kinase, MB fraction	1,25-DHD	1,25-dihydroxyvitamin D
CLL	chronic lymphocytic leukemia	DHEAS	dehydroepiandrosterone sulfate
CMC	carpometacarpal (joint)	DI	diabetes insipidus
CML	chronic myelogenous leukemia	DIC	disseminated intravascular coagulation
CMMI	chronic myelomonocytic leukemia	DIP	distal interphalangeal (joint)
CMV	cytomegalovirus	DKA	diabetic ketoacidosis
CN	cranial nerve	DLCO	diffusing capacity for carbon monoxide
CNS	central nervous system	DM	diabetes mellitus
COMT	catechol-O-methyltransferase	DMARD	disease-modifying antirheumatic drug
COPD	chronic obstructive pulmonary disease	DNA	deoxyribonucleic acid
COX	cyclooxygenase	DNase	deoxyribonuclease
CP	ceruloplasmin	DNR	do not resuscitate
CPAP	continuous positive airway pressure	DOC	deoxycorticosterone
CPPD	calcium pyrophosphate dihydrate deposition	2,3-DPG	2,3-diphosphoglycerate
CPR	cardiopulmonary resuscitation	DPOA-HC	durable power of attorney for health care
Cr	creatinine	DPP-4	dipeptidyl peptidase-4
CrAg	cryptococcal antigen	DRE	digital rectal examination
CRBSI	catheter-related bloodstream infection	DRESS	drug reaction with eosinophilia and systemic symptoms
CrCl	creatinine clearance	dsDNA	double-stranded DNA
CREST	calcinoses, Raynaud phenomenon, esophageal involvement, sclerodactyly, telangiectasia (syndrome)	DTRs	deep tendon reflexes
		DTs	delirium tremens
		DVT	deep venous thrombosis
		DWI	diffusion-weighted imaging
		EBNA	Epstein-Barr nuclear antigen

Abbreviation	Meaning	Abbreviation	Meaning
EBV	Epstein-Barr virus	GBS	Guillain-Barré syndrome
ECG	electrocardiography	GCA	giant cell arteritis
ECT	electroconvulsive therapy	G-CSF	granulocyte colony-stimulating factor
ED	erectile dysfunction, emergency department	GDM	gestational diabetes mellitus
EEG	electroencephalography	GERD	gastroesophageal reflux disease
EF	ejection fraction	GFR	glomerular filtration rate
EFWC	electrolyte free water clearance	GGT	$\gamma$ -glutamyltransferase
EGD	esophagogastroduodenoscopy	GH	growth hormone
EGFR	epidermal growth factor receptor	GHRH	growth hormone-releasing hormone
EHEC	enterohemorrhagic <i>E coli</i>	GI	gastrointestinal
EIA	enzyme immunoassay	GIST	gastrointestinal stromal tumor
EIEC	enteroinvasive <i>E coli</i>	GLP-1	glucagon-like peptide-1
ELISA	enzyme-linked immunosorbent assay	GM-CSF	granulocyte-macrophage colony-stimulating factor
EM	electron microscopy, erythema multiforme	GnRH	gonadotropin-releasing hormone
EMG	electromyography	GOLD	Global Initiative for [Chronic Obstructive] Lung Disease
ENT	ears, nose, and throat	GU	genitourinary
EP	evoked potential	H&P	history and physical
ER	estrogen receptor	HAART	highly active antiretroviral therapy
ERCP	endoscopic retrograde cholangiopancreatography	HACEK	<i>Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella</i>
ERV	expiratory reserve volume	HAEM	herpes simplex-associated erythema multiforme
ES	elastic stockings	HAV	hepatitis A virus
ESR	erythrocyte sedimentation rate	Hb	hemoglobin
ESRD	end-stage renal disease	HbA <sub>1c</sub>	hemoglobin A <sub>1c</sub>
ETEC	enterotoxigenic <i>E coli</i>	HBeAg	hepatitis B early antigen
EtOH	ethanol	HBIG	hepatitis B immune globulin
EUS	endoscopic ultrasound	HBsAg	hepatitis B surface antigen
EVH	esophageal variceal hemorrhage	HbS	sickle hemoglobin
FAP	familial adenomatous polyposis	HBV	hepatitis B virus
FCH	familial combined hyperlipidemia	HCAP	health care-associated pneumonia
FDA	Food and Drug Administration	HCC	hepatocellular carcinoma
F-dUMP	5-fluorodeoxyuridine monophosphate	hCG	human chorionic gonadotropin
Fe <sub>Na</sub>	fractional excretion of sodium	HCM	hypertrophic cardiomyopathy
FEV <sub>1</sub>	forced expiratory volume in one second	HCO <sub>3</sub> <sup>-</sup>	bicarbonate
FFP	fresh frozen plasma	HCTZ	hydrochlorothiazide
FH	familial hypercholesterolemia	HCV	hepatitis C virus
FIO <sub>2</sub>	fraction of inspired oxygen	25-HD	25-hydroxyvitamin D
FLAIR	fluid-attenuated inversion recovery (imaging)	HDL	high-density lipoprotein
FNA	fine-needle aspiration	HDV	hepatitis D virus
FOBT	fecal occult blood test	HELLP	hemolysis, elevated LFTs, low platelets (syndrome)
FRC	functional reserve capacity	HEV	hepatitis E virus
FSH	follicle-stimulating hormone	HGA	human granulocytic anaplasmosis
FT <sub>3</sub>	free triiodothyronine	HHV	human herpesvirus
FT <sub>4</sub>	free thyroxine	5-HIAA	5-hydroxyindole acetic acid
5-FU	5-fluorouracil	HIDA	hepato-iminodiacetic acid (scan)
FUO	fever of unknown origin	HIPAA	Health Insurance Portability and Accountability Act
FVC	forced vital capacity	HIT	heparin-induced thrombocytopenia
G6PD	glucose-6-phosphate dehydrogenase	HIV	human immunodeficiency virus
GABA	gamma-aminobutyric acid	HL	hearing loss
GABHS	group A $\beta$ -hemolytic streptococcus	HLA	human leukocyte antigen
GAD	glutamic acid decarboxylase		
GBM	glomerular basement membrane		

Abbreviation	Meaning	Abbreviation	Meaning
HME	human monocytic ehrlichiosis	LAM	lymphangioleiomyomatosis
HNPPCC	hereditary nonpolyposis colorectal cancer	LBBC	left bundle branch block
HOCM	hypertrophic obstructive cardiomyopathy	LBP	lower back pain
HPV	human papillomavirus	LCIS	lobular carcinoma in situ
HR	heart rate	LDH	lactate dehydrogenase
HRCT	high-resolution computed tomography	LDL	low-density lipoprotein
HRS	hepatorenal syndrome	LDUH	low-dose unfractionated heparin
HRT	hormone replacement therapy	LES	lower esophageal sphincter
HSCT	hematopoietic stem cell transplantation	LFT	liver function test
HSV	herpes simplex virus	LGIB	lower GI bleeding
5-HT	5-hydroxytryptamine	LH	luteinizing hormone
HTLV-1	human T-cell leukemia virus type 1	LKM	liver/kidney microsomal (antibody)
HTN	hypertension	LLQ	left lower quadrant
HUS	hemolytic-uremic syndrome	LMN	lower motor neuron
IABP	intraaortic balloon pump	LMWH	low-molecular-weight heparin
IAHG	International Autoimmune Hepatitis Group	LP	lumbar puncture
IBD	inflammatory bowel disease	LR	likelihood ratio
IBS	irritable bowel syndrome	LT <sub>4</sub>	levothyroxine
ICA	internal carotid artery	LTBI	latent tuberculosis infection
ICD	implantable cardioverter-defibrillator	LTOT	long-term oxygen therapy
ICH	intracranial hemorrhage	LUQ	left upper quadrant
ICP	intracranial pressure	LVH	left ventricular hypertrophy
ICS	inhaled corticosteroid	MAC	<i>Mycobacterium avium</i> complex
ICU	intensive care unit	MAHA	microangiopathic hemolytic anemia
IF	intrinsic factor	MALT	mucosa-associated lymphoid tissue
IFE	immunofixation electrophoresis	MAOI	monoamine oxidase inhibitor
Ig	immunoglobulin	MCA	middle cerebral artery
IGF-1	insulin-like growth factor 1	MCL	midclavicular line
IL	interleukin	MCP	metacarpophalangeal (joint)
ILD	interstitial lung disease	MCTD	mixed connective tissue disease
IM	intramuscular	MCV	mean corpuscular volume
INH	isoniazid	MDI	metered-dose inhaler
INR	international normalized ratio	MDMA	3,4-methylene-dioxymethamphetamine ("ecstasy")
IPC	intermittent pneumatic compression	MDR	multidrug-resistant
IPF	idiopathic pulmonary fibrosis	MDS	myelodysplastic syndrome
IPSS	inferior petrosal sinus sampling	MELD	Model for End-stage Liver Disease
IRIS	immune reconstitution inflammatory syndrome	MEN	multiple endocrine neoplasia
ITP	idiopathic thrombocytopenic purpura	MG	myasthenia gravis
IUD	intrauterine device	MGUS	monoclonal gammopathy of undetermined significance
IUGR	intrauterine growth retardation	MI	myocardial infarction
IV	intravenous	MIBG	metaiodobenzylguanidine (scan)
IVC	inferior vena cava	MMA	methylmalonic acid
IVF	in vitro fertilization	MMI	methimazole
IVIG	intravenous immunoglobulin	MMR	measles, mumps, rubella (vaccine)
IVP	intravenous pyelography	MMSE	mini-mental status exam
JNC 7	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure	6-MP	6-mercaptopurine
JVD	jugular venous distention	MPA	microscopic polyangiitis
JVP	jugular venous pressure	MPGN	membranoproliferative glomerulonephritis
KOH	potassium hydroxide	MPO	myeloperoxidase
KS	Kaposi sarcoma	MR	magnetic resonance
LAD	left anterior descending (artery)	MRA	magnetic resonance angiography
		MRCP	magnetic resonance cholangiopancreatography

Abbreviation	Meaning	Abbreviation	Meaning
MRI	magnetic resonance imaging	P <sub>Cr</sub>	plasma creatinine
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>	PCR	polymerase chain reaction
MS	multiple sclerosis	PCT	porphyria cutanea tarda
MSM	men who have sex with men	PCV13	13-valent pneumococcal conjugate vaccine
mTOR	mammalian target of rapamycin	PCWP	pulmonary capillary wedge pressure
MTP	metatarsophalangeal (joint)	PDA	patent ductus arteriosus
MTX	methotrexate	PDE5	phosphodiesterase type 5
MUGA	multigated acquisition (scan)	PE	pulmonary embolism
MV	minute ventilation	PEEP	positive end-expiratory pressure
MVP	mitral valve prolapse	PEF	peak expiratory flow
NA	Narcotics Anonymous	PEG	polyethylene glycol
NAAT	nucleic acid amplification test	PET	positron emission tomography
nAChR	nicotinic acetylcholine receptor	PF4	platelet factor 4
NAEPP	National Asthma Education and Prevention Program	PFO	patent foramen ovale
NAGMA	non-anion gap metabolic acidosis	PFT	pulmonary function test
NaHCO <sub>3</sub>	sodium bicarbonate	PHN	postherpetic neuralgia
NCS	nerve conduction study	PICA	posterior inferior cerebellar artery
NF	neurofibromatosis	PID	pelvic inflammatory disease
NG	nasogastric	PIP	posterior interphalangeal (joint)
NHL	non-Hodgkin lymphoma	P <sub>K+</sub>	plasma potassium
NMS	neuroleptic malignant syndrome	PLEX	plasma exchange
NNT	number needed to treat	PLMS	periodic limb movements of sleep
NPO	nil per os (nothing by mouth)	PMI	point of maximal insertion
NPPV	noninvasive positive pressure ventilation	PMN	polymorphonuclear (leukocyte)
NPV	negative predictive value	PMR	polymyalgia rheumatica
NREM	non–rapid eye movement	P <sub>Na</sub>	plasma sodium
NS	normal saline	PNH	paroxysmal nocturnal hemoglobinuria
NSAID	nonsteroidal anti-inflammatory drug	PO	per os (by mouth)
NSCLC	non–small cell lung cancer	Po <sub>2</sub>	partial pressure of oxygen
NSIP	nonspecific interstitial pneumonia	P <sub>osm</sub>	plasma osmolality
NSTEMI	non-ST-elevation myocardial infarction	PPD	purified protein derivative (of tuberculin)
NVE	native valve endocarditis	PPI	proton pump inhibitor
NYHA	New York Heart Association	PPN	peripheral parenteral nutrition
O&P	ova and parasites	PPSV23	23-valent pneumococcal polysaccharide vaccine
OA	osteoarthritis	PPV	positive predictive value
OCD	obsessive-compulsive disorder	PR	progesterone receptor
OCP	oral contraceptive pill	PRA	plasma renin activity
OGTT	oral glucose tolerance test	PRCA	pure red cell aplasia
OSA	obstructive sleep apnea	PRN	pro re nata (as needed)
OTC	over the counter	PSA	prostate-specific antigen
PA	pernicious anemia, posteroanterior	PSVT	paroxysmal supraventricular tachycardia
PAC	plasma aldosterone concentration	PT	prothrombin time
Paco <sub>2</sub>	partial pressure of carbon dioxide in arterial blood	PTT	partial thromboplastin time
PAN	polyarteritis nodosa	PTA	percutaneous transluminal angioplasty
p-ANCA	perinuclear antineutrophil cytoplasmic antibody	PTH	parathyroid hormone
Pao <sub>2</sub>	partial pressure of oxygen in arterial blood	PTHC	percutaneous transhepatic cholangiography
PCI	percutaneous coronary intervention	PTHrP	parathyroid hormone-related protein
Pco <sub>2</sub>	partial pressure of carbon dioxide	PTSD	posttraumatic stress disorder
PCOP	pulmonary capillary occlusion pressure	PTT	partial thromboplastin time
PCOS	polycystic ovarian syndrome	PTU	propylthiouracil
PCP	phencyclidine, <i>Pneumocystis carinii</i> (now <i>jiroveci</i> ) pneumonia	PUD	peptic ulcer disease
		PUVA	psoralen and ultraviolet A
		PVC	premature ventricular contraction

Abbreviation	Meaning	Abbreviation	Meaning
PVD	peripheral vascular disease	SNRI	serotonin-norepinephrine reuptake inhibitor
PVE	prosthetic valve endocarditis	SOD	superoxide dismutase
PVT	portal vein thrombosis	SPEP	serum protein electrophoresis
QD	once daily	SQ	subcutaneous
QHS	at bedtime	SSPE	subacute sclerosing panencephalitis
QID	four times daily	SSRI	selective serotonin reuptake inhibitor
QOD	every other day	STARI	southern tick-associated rash illness
RA	refractory anemia, rheumatoid arthritis	STEMI	ST-elevation myocardial infarction
RADS	reactive airway dysfunction syndrome	STI	sexually transmitted infection
RAEB	refractory anemia with excess blasts	SVC	superior vena cava
RAI	radioactive iodine	SVR	systemic vascular resistance
RAIU	radioactive iodine uptake	SVT	supraventricular tachycardia
RARS	refractory anemia with ringed sideroblasts	T <sub>3</sub>	triiodothyronine
RAST	radioallergosorbent test	T <sub>4</sub>	thyroxine
RBBB	right bundle branch block	TB	tuberculosis
RBC	red blood cell	3TC	dideoxycytidine (lamivudine)
RCT	randomized clinical trial	TC	total cholesterol
RDW	red cell distribution width	TCA	tricyclic antidepressant
REM	rapid eye movement	Td	tetanus and diphtheria (vaccine)
RF	rheumatoid factor	Tdap	tetanus, diphtheria, acellular pertussis (vaccine)
RIBA	recombinant immunoblot assay	TEDS	thromboembolic disease stockings
RICe	rest, ice, compression, and elevation	TEE	transesophageal echocardiography
RLQ	right lower quadrant	TEN	toxic epidermal necrolysis
RLS	restless leg syndrome	TFT	thyroid function test
RNA	ribonucleic acid	TG	triglyceride
RNV	radionuclide ventriculogram	TIA	transient ischemic attack
ROM	range of motion	TIBC	total iron-binding capacity
RPGN	rapidly progressive glomerulonephritis	TID	three times daily
RPR	rapid plasma reagins	TIPS	transjugular intrahepatic portosystemic shunt
RR	respiratory rate	TLC	therapeutic lifestyle changes, total lung capacity
RSV	respiratory syncytial virus	TMP-SMX	trimethoprim-sulfamethoxazole
RTA	renal tubular acidosis	TNF	tumor necrosis factor
RUQ	right upper quadrant	tPA	tissue plasminogen activator
RV	residual volume	TPN	total parenteral nutrition
RVH	right ventricular hypertrophy	TPO	thyroperoxidase
SAAG	serum-ascites albumin gradient	TRALI	transfusion-related acute lung injury
SADNI	selective antibody deficiency with normal immunoglobulins	TRH	thyrotropin-releasing hormone
SAH	subarachnoid hemorrhage	T <sub>sat</sub>	transferrin saturation
SAMe	S-adenosyl-methionine	TSH	thyroid-stimulating hormone
SARS	severe acute respiratory syndrome	TSI	thyroid-stimulating immunoglobulin
SBP	spontaneous bacterial peritonitis, systolic blood pressure	TSS	toxic shock syndrome
SCA	superior cerebellar artery	TSST	toxic shock syndrome toxin
SCC	squamous cell carcinoma	TTE	transthoracic echocardiography
SCD	sequential compression device	TTG	tissue transglutaminase
SCLC	small cell lung cancer	TTKG	transtubular K <sup>+</sup> gradient
SERM	selective estrogen receptor modulator	TTP	thrombotic thrombocytopenic purpura
SIADH	syndrome of inappropriate secretion of antidiuretic hormone	TURP	transurethral resection of the prostate
SIRS	systemic inflammatory response syndrome	TV	tidal volume
SJS	Stevens-Johnson syndrome	TZD	thiazolidinedione
SLE	systemic lupus erythematosus	UA	urinalysis
SMA	smooth muscle antibody	UAG	urine anion gap

Abbreviation	Meaning	Abbreviation	Meaning
$U_{Cr}$	urine creatinine	VATS	video-assisted thoracoscopy
UFH	unfractionated heparin	VBI	vertebrobasilar insufficiency
UGIB	upper GI bleeding	VC	vital capacity
$U_{K^+}$	urine potassium	VDRL	Venereal Disease Research Laboratory
UKPDS	United Kingdom Prospective Diabetes Study	VEGF	vascular endothelial growth factor
ULN	upper limit of normal	VF	ventricular fibrillation
UMN	upper motor neuron	VIP	vasoactive intestinal peptide
$U_{Na}$	urine sodium	VMA	vanillylmandelic acid
UNOS	United Network for Organ Sharing	V/Q	ventilation-perfusion (ratio)
$U_{osm}$	urine osmolality	VSD	ventricular septal defect
UPEP	urinary protein electrophoresis	VT	ventricular tachycardia
URTI	upper respiratory tract infection	VTE	venous thromboembolism
USPSTF	United States Preventive Services Task Force	vWD	von Willebrand disease
UTI	urinary tract infection	vWF	von Willebrand factor
UV	ultraviolet	VZV	varicella-zoster virus
VAP	ventilator-associated pneumonia	WBC	white blood cell
		WHO	World Health Organization
		WPW	Wolff-Parkinson-White (syndrome)

## NOTES

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